Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-61824

54. **TÍTULO** COMPUESTOS DE TROPANO

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** EXELIXIS, INC.

DOMICILIO SOUTH SAN FRANCISCO, CALIFORNIA, U.S.A.

74. **APODERADO** LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de Usaquén

22. **BOGOTÁ, D.C.,**

(FORMA P-10)

Titular Cuw
25-05-2010

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-061824- -00000-0000
Fecha: 2010-05-24 15:37:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1362

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

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

2 SOLICITANTE (71)

Nombre: **EXELIXIS, INC.**
Sociedad constituida y existente bajo las leyes del Estado de Delaware, Estados Unidos de América.

Dirección: 210 East Grand Avenue,
P.O. Box 511,
South San Francisco,
California 94083-0511,
Estados Unidos de América

Domicilio: South San Francisco,
California,
Estados Unidos de América

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3 REPRESENTANTE O APODERADO

Nombre: LUZ CLEMENCIA DE PAEZ
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 35.456.344 T.P 23.555

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21. **Longcheng WANG**
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California 94306,
Estados Unidos de América

5 **PCT (86)**
Solicitud Internacional No. PCT/US2008/012221 Fecha: 27 de octubre de 2008
Publicación Internacional No. WO 2009/055077 A1 Fecha: 30 de abril de 2009

6 **Título (54)**
COMPUESTOS DE TROPANO (Folio ~~166~~ 1366)

7 **Clasificación Internacional (51)** C07D 451/002 A61P 35/00 A61K 31/46

8 **Prioridad** SI ☒ NO ☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	25 de octubre de 2007	61/000,687

9 **Comprobante de pago No.:** 10-34,601 **Fecha:** 04 de mayo de 2010
Comprobante de pago No.: 10-24,645 **Fecha:** 05 de abril de 2010
Comprobante de pago No.: 10-34,573 **Fecha:** 04 de mayo de 2010

10

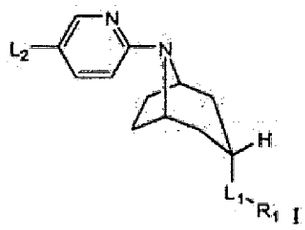
Anexos:

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 554.000.oo.
- [x] Comprobante de pago por 24 reivindicaciones adicionales después de la décima reivindicación por $624.000.oo.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] 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.
- [x] 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.
- [x] Otros: VER HOJA DE DOCUMENTOS ANEXOS

4

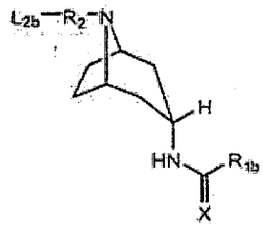
11

FIGURA CARACTERÍSTICA



(I)

or



(II)

12 Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PAEZ

FIRMA : Luz Clemencia de Paez

C.C. 35.456.344 de Usaquén T.P. 23.555

SCT

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2009/055077 A1

   Descripción:

   Páginas 473 en el idioma original

   Páginas 749 en español

   Reivindicaciones: Número (s) 34

   Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

6

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 – COLOMBIA

193

Representación, Ratificación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation, ratification and Power-of-Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION, RATIFICACION Y PODER

REPRESENTATION, RATIFICATION AND POWER-OF-ATTORNEY

75397
5579

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

EXELIXIS, INC

domiciliado (s) en/of

170 Harbor Way
P.O. Box 511
South San Francisco
California 94083-0511
United States of America

Por el presente ratificamos la solicitud de patente No. 06.063.447 presentada por EMILIO FERRERO

como agente oficioso ante la División de Nuevas Creaciones

en Bogotá, Colombia
el 29 de junio de 2006

y por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y DANIEL PEÑA, tpa. 65620 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,

Hereby ratify the patent application No. 06.063.447

filed without a Power of Attorney by EMILIO FERRERO

before the Patent Office

in Bogotá, Colombia
on June 29, 2006

and do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and DANIEL PEÑA, tpa. 65620, domiciled at Carrera 4ª Nº 72-35, Bogotá, Colombia, in due compliance with the terms of Paragraph 1st. of Article 543 of the Commercial Code, 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 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 [illegible] such time.

In addition, we grant Power of Attorney in [illegible] the above-named

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C.: HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
20 MAYO 2010
AMPARO QUINTERO ACUARO
NOTARIA

© CAVELIER ABOGADOS

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, nombres de dominio, 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 o 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.

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, domain names, 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.

Dado y firmado hoy/Given and signed this 11 July 2006

en/in South San Francisco California, USA

por/by Pamela A. Simonton, Senior Vice President, Patents & Licensing

Firma Signature

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA

20 MAYO 2010

AMPARO QUINTERO ARTEAGA
NOTARIA

© CAVÉLIER ABOGADOS
WPPODE01-193 (MINUTA 12.1.1.2.9.r USA)

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____

de 200 ___ ante mí, Notario Público o Funcionario Autorizado de

_____

compareció(eron) personalmente _____

_____

_____

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

NOTARIAL CERTIFICATION (INDIVIDUAL)

On this _____ day of _____

200 ___ before me, a Notary Public or Attesting Official of

_____

personally appeared See attached Notary Certificate

_____

_____

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.

--- NOTARIO PÚBLICO O FUNCIONARIO AUTORIZADO --- NOTARY PUBLIC OR ATTESTING OFICIAL ---

CERTIFICACIÓN NOTARIAL (SOCIEDAD)

A los _____ días del mes de _____

de 200 _____ compareció(eron) ante mí,

_____

_____

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

_____

Certifico:

1. Que he visto los siguientes documentos:*

2.Que dichos documentos prueban lo siguiente:

2.1.Que es una Sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes del Estado de

2.2.Que el domicilio de dicha Sociedad/Compañía es

_____

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.) _____

_____

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

Ciudad _____

Estado _____

Hoy _____ de 200 __

NOTARIAL CERTIFICATION (CORPORATION)

On this _____ day of _____

200 ___ appeared before me

_____

_____

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

_____

I certify:

1.That I have seen the following documents:*
Statement of Information from the Secretary of State of the State of California; on July 6, 2006
Certificate of Good Standing from the Secretary of State of the State of Delaware; on July 6, 2006

2. That the above documents duly prove the following:

2.1.That Exelixis, Inc. is a Corporation/Company legally constituted and in existence in accordance with the laws of the State of Delaware

2.2.That the domicile of said Corporation/Company is California

2.3. That the purpose or 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.) Pamela A. Simonton

_____

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

City: South San Francisco
State: California, United States of America
This 12th day of July 2006

--- NOTARIO PÚBLICO O FUNCIONARIO AUTORIZA

ATTESTING OFFICIAL
Christop
Vice Pres

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. DIGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA
20 MAYO 2010
AMPARO QUINTERO MUÑOZ
NOTARIA

* Los documentos deben identificarse con fecha y origen

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WPC15199-ID 006

9

State of California

SECRETARY OF STATE

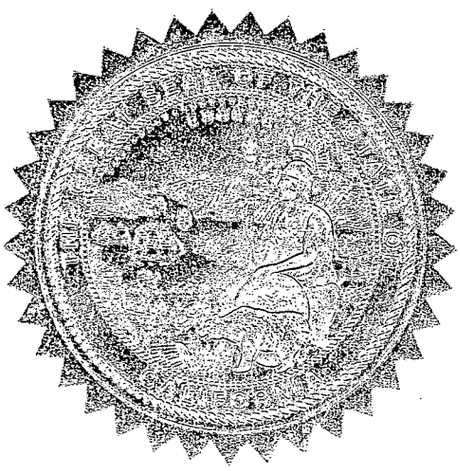
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

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

CERTIFIED

5. *At Sacramento, California*
6. *the 8th day of September 2006*
7. *by Deputy Secretary of State, State of California*
8. *No. 302336*
9. *Seal/Stamp:*



10. *Signature*

Secretary of State

NP-24 A (REV. 4-05)

BY

OSP 05 90772

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA, CERTIFICO QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA

20 MAYO 2010

AMPARO QUINTERO LOZANO
NOTARIA

10

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of San Mateo } ss.

On 11 July 2006 (Date), before me, J. Cohen, Notary Public (Name and Title of Officer (e.g., "Jane Doe, Notary Public")),
personally appeared Pamela A. Simonton (Name(s) of Signer(s)),

☑ personally known to me
☐ proved to me on the basis of satisfactory evidence

J. COHEN
Commission # 1417900
Notary Public - California
San Mateo County
My Comm. Expires Jun 11, 2007

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.

J Cohen
Signature of Notary Public

Place Notary Seal Above

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, Ratification and Power of Attorney 980049.4030 1Co.
Document Date: _____ Number of Pages: _____

Signer(s) Other Than Named Above: _____

Capacity(ies) Claimed by Signer
Signer's Name: Pamela A. Simonton
☐ Individual
☑ Corporate Officer — Title(s): Senior Vice President Patents & Licensing
☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____

Signer Is Representing: Exelixis, Inc.

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

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20 MAYO 2010
AMPARO QUINTERO ARTURO
NOTARIA

11

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of San Mateo } ss.

On 12 July 2006 (Date), before me, J. Cohen, Notary Public (Name and Title of Officer (e.g., "Jane Doe, Notary Public")),
personally appeared Christoph Pereira (Name(s) of Signer(s)),

☑ personally known to me
☐ proved to me on the basis of satisfactory evidence

J. COHEN
Commission # 1417900
Notary Public - California
San Mateo County
My Comm. Expires Jun 11, 2007

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.

J Cohen
Signature of Notary Public

Place Notary Seal Above

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, Ratification and Power-of-Attorney
Document Date: _____ Number of Pages: _____

Signer(s) Other Than Named Above: _____

Capacity(ies) Claimed by Signer
Signer's Name: Christoph Pereira
☐ Individual
☑ Corporate Officer — Title(s): Vice President, Legal Affairs and Secretary
☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____

Signer Is Representing: Exelixis, Inc.

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

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BOGOTA D.C. REPUBLICA DE COLOMBIA
20 MAYO 2010
AMPARO QUINTERO ARTURO
NOTARIA

TRADUCCIÓN OFICIAL No. 24/09.06 preparada por María Elvira Martelo, traductora oficial aprobada por el Ministerio de Justicia mediante Resolución No. 2879 de 1995 y reconocida por el Ministerio de Relaciones Exteriores.

A continuación se traducen los sellos y legalizaciones de un documento escrito en inglés y español, por el cual **EXELIXIS, INC.**, sociedad domiciliada en 170 Harbor Way, P.O. Box 511, South San Francisco, California 94083-0511, Estados Unidos de América, ratifica la solicitud de patente No. 06063447 presentada por Emilio Ferrero ante la División de Nuevas Creaciones el 29 de junio de 2006 y a su vez otorga poder a **EMILIO FERRERO, GONZALO PERDOMO, LUZ CLEMENCIA DE PAEZ Y DANIEL PEÑA**).

Dado y firmado el 11 de julio de 2006

En South San Francisco, California, EUA

Por Pamela A. Simonton, Vicepresidente Principal de Patentes y Licencias

---

CALIFORNIA - RECONOCIMIENTO PARA TODO EFECTO

Estado de California }

Condado de San Mateo }ss.

El 11 de julio de 2006, ante mí, **J. Cohen**, Notario Público, compareció personalmente **Pamela A Simonton**,

[✓] conocida personalmente por mí

[ ] quien con base en evidencia satisfactoria comprobó ser la persona cuyo nombre suscribe el instrumento adjunto y reconoció ante mí haber ejecutado el mismo en su capacidad autorizada y que con su firma la persona o entidad en nombre de quien actuó la persona, ejecutó el instrumento.

CERTIFICAN mi firma y sello oficial.
[Firma Ilegible].

Sello: J. COHEN
Comisión # 1417900
Notario Público – California
Condado de San Mateo
Mi comisión expira el 11 de junio de 2007

----------*OPCIONAL*---------

Aunque la ley no exige la información que se solicita a continuación, puede resultar valiosa para las personas que dependen del documento y puede evitar que este formato se elimine y adjunte a otro documento.

Descripción del documento anexo

Título o tipo de documento: Representación, Ratificación y Poder 980049.40301 CO

Fecha del documento: _____

Firmantes además del arriba mencionado: _____

Capacidad del/de los firmante(s)

Nombre del firmante: Pamela A Simonton

__ Persona natural

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPÚBLICA DE COLOMBIA
20 MAYO 2010
AMPARO QUINTERO ARTUZ
NOTARIA

✓ Funcionario de la compañía–Cargo(s): Vicepresidente Principal Patentes y Licencias

__ Socio) __ limitado __ general

__ Apoderado

__ Fideicomisario

__ Custodio o curador

__ Otros: Vicepresidente de Asuntos Comerciales y Jurídicos

El firmante representa a: Exelixis, Inc.

CERTIFICACIÓN NOTARIAL (SOCIEDAD) en inglés y español referente a la existencia legal de Exelixis, Inc. y a la capacidad legal de Pamela A. Simonton para otorgar poder.

Ciudad: South San Francisco

Estado: California, Estados Unidos de América

12 de julio de 2006

[Firma ilegible], FUNCIONARIO DE CERTIFICACIÓN

Christoph Pereira

Vicepresidente, Asuntos Jurídicos y Secretario

CALIFORNIA - RECONOCIMIENTO PARA TODO EFECTO

Estado de California }

Condado de San Mateo }ss.

El 11 de julio de 2006, ante mí, **J. Cohen**, Notario Público, compareció personalmente **Christoph Pereira**,

[✓] conocida personalmente por mí
[ ] quien con base en evidencia satisfactoria comprobó ser la persona cuyo nombre suscribe el instrumento adjunto y reconoció ante mí haber ejecutado el mismo en su capacidad autorizada y que con su firma la persona o entidad en nombre de quien actuó la persona, ejecutó el instrumento.

CERTIFICAN mi firma y sello oficial.
[Firma llegible].

Sello: J. COHEN
Comisión # 1417900
Notario Público – California
Condado de San Mateo
Mi comisión expira el 11 de junio de 2007

----------*OPCIONAL*----------

Aunque la ley no exige la información que se solicita a continuación, puede ser útil para las personas que dependen del documento y puede evitar que este formato se elimine y adjunte a otro documento.

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C.: HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C., REPUBLICA DE COLOMBIA
20 MAYO 2010
AMPARO QUINTERO ARTURO
NOTARIA

Descripción del documento anexo

Título o tipo de documento: Representación, Ratificación y Poder 980049.40301-CO

Fecha del documento: _____ Número de páginas: ___

Firmantes además del arriba mencionado: _____

Capacidad del/de los firmante(s)

Nombre del firmante: Christoph Pereira

__ Persona natural

✓ Funcionario de la compañía–Cargo(s): Vicepresidente Asuntos Jurídicos y Secretario

__ Socio __ limitado __ general

__ Apoderado

__ Fideicomisario

__ Custodio o curador

__ Otros: Vicepresidente de Asuntos Comerciales y Jurídicos

El firmante representa a: Exelixis, Inc.

ESTADO DE CALIFORNIA

SECRETARIO DE ESTADO

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 J Cohen*
3. *en su capacidad de Notario Público, Estado* de California
4. *lleva el sello/timbre de J Cohen, Notario Público, Estado de California*

CERTIFICADO

5. *en Sacramento, California*
6. *el 8 de septiembre de 2006*
7. *por el Subsecretario de Estado, Estado de California*
8. *No.* **302336**
9. *Sello/Timbre*: EL GRAN SELLO DEL ESTADO
10. Firma (Firma Ilegible), Secretario de Estado
    Por: [Firma ilegible]

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA

20 MAYO 2010

AMPARO QUINTERO ARTURO
NOTARIA

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

COLO 15391-841-001-7

WPC 15391 - ID 10

SEP 27/06

María E. Martelo

TRADUCCION No.: 24/09.06

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

COINCIDE(N) CON LA FIRMA REGISTRADA POR EL (ELLOS) EN ESTA NOTARIA

SANTAFE DE BOGOTA. 02 OCT 2006

CODEX JURIS CIVILIS

REPUBLICA DE COLOMBIA
Juan Manuel
Notario Sexto
SANTAFE DE BOGOTA D.C.

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2006 OCT 2 A 11: 36

JEFE DE LEGALIZACIONES BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

RECE EN EL SEMPERA INDICADAS

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA

20 MAYO 2010

AMPARO QUINTERO ARTUNDUAGA
NOTARIA

15

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ABOGADOS

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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

Poderdante : EXELIXIS, INC

Poder conferido el : 11/07/2006

Yo, EMILIO FERRERO, obrando como apoderado principal del poderdante arriba mencionado, mediante el presente escrito sustituyo el poder a mi otorgado a la doctora LUZ CLEMENCIA DE PAEZ, identificada con cédula de ciudadanía No. 35.456.344 y Tarjeta Profesional N°23.555, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil.

EMILIO FERRERO
T.P.A. N° 31.929
C.C. N° 438.019 de Usaquén

Acepto:

LUZ CLEMENCIA DE PAEZ
T.P.A. N° 23.555
C.C. No. 35.456.344 de Usaquén

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
20 MAYO 2010
AMPARO QUINTERO ARTURO
NOTARIA

15391

NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

Bogotá, D.C.

Ante mi AMPARO QUINTERO ARTURO, 3 - NOV. 2009

NOTARIA SEXTA DEL CÍRCULO DE BOGOTÁ, D.C.

Compareció(eron) Emilio Ferro Williamson

Luz Clemencia Sánchez de Páez

Quien(es) exhibió(eron) la(s) C.C.

CC 438019 TP 31929

CC 35456344 TP 23555

Y declaró(aron) que la(s) firma(s) que s ece(n) en el presente documento es(aon) la(s) suya(s) y que el contenido del mismo es cierto.

En constancia se firma esta diligencia.

Emilio Ferro

Luz Clemencia Sánchez

REPÚBLICA DE COLOMBIA
Amparo Quintero Arturo
NOTARIA
NOTARIA SEXTA DE BOGOTÁ

NOTARIA SEXTA DEL CÍRCULO DE BOGOTÁ D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTÁ D.C., REPÚBLICA DE COLOMBIA

20 MAYO 2010

AMPARO QUINTERO ARTURO
NOTARIA

17

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 April 2009 (30.04.2009)

PCT

(10) International Publication Number
WO 2009/055077 A1

(51) International Patent Classification:
C07D 451/02 (2006.01) *A61P 35/00* (2006.01)
A61K 31/46 (2006.01)

(21) International Application Number:
PCT/US2008/012221

(22) International Filing Date: 27 October 2008 (27.10.2008)

(25) Filing Language: English

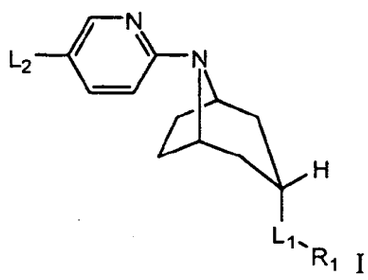
(26) Publication Language: English

(30) Priority Data:
61/000,687 25 October 2007 (25.10.2007) US

(71) Applicant *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; Post Office Box 511, 210 East Grand Avenue, South San Francisco, CA 94083-0511 (US).

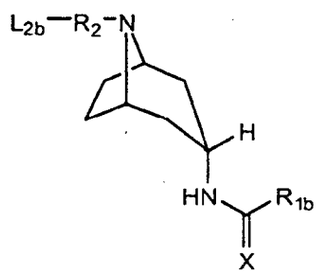
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **RICE, Kenneth D.** [US/US]; 444 Monticello Road, San Rafael, CA 94903 (US). **AAY, Naing** [US/US]; 112 North Rochester Street, San Mateo, CA 94401 (US). **ANAND, Neel Kumar** [GB/US]; 977 El Camino Real, #303, Burlingame, CA 94010 (US). **ARCALAS, Arlyn** [US/US]; 434 Brosnan Court, South San Francisco, CA 94080 (US). **BAIK, Tae-Gon** [KR/US]; 124 Albacore Lane, Foster City, California 94404 (US). **BLAZEY, Charles M.** [US/US]; 171 Randall Street, San Francisco, California 94031 (US). **BOWLES, Owen Joseph** [CA/US]; 468 Manor Drive, Apt. D3, Pacifica, California 94044 (US). **BUHR, Chris A.** [US/US]; 355 Belmont Avenue, Redwood City, California 94061 (US). **BUSSENIUS, Joerg** [DE/US]; 223 Bonita Lane, Foster City, CA 94404 (US). **COSTANZO, Simona** [IT/US]; 215 North El Monte Avenue, Los Altos, CA 94022 (US). **CURTIS, Jeffry Kimo** [US/US]; 310 Redwood Road, San Anselmo, CA 94960 (US). **DEFINA, Steven Charles** [US/US]; 1232 Floribunda Avenue, #6, Burlingame, CA 94010 (US). **DUBENKO, Larisa** [US/US]; 584 46th Avenue, San Francisco, CA 94121 (US). **KENNEDY, Abigail R.** [US/US]; 2417 East 28th Street, Oakland, CA 94601 (US). **KIM, Angie Inyoung** [US/US]; 928 Shoal Drive, San Mateo, CA 94404 (US). **LARA, Katherine** [US/US]; 3133 Casa de Campo, #211, San Mateo, California 94403 (US). **MA, Sunghoon** [KR/US]; 802 Spruance Lane, Foster City, California 94404 (US). **MANALO, Jean-Claire Limun** [US/US]; 4159 Callan Boulevard, Daly City, CA 94015 (US). **PETO, Csaba J.** [US/US]; 9 Christensen Court, Alameda, CA 94502 (US). **TSANG, Tsze H.** [US/US];
[Continued on next page]

(54) Title: TROPANE COMPOUNDS



(I)

or



(II)

(57) Abstract: A compound according to Formula I or II: (I) or (II) wherein R_1, R_{1b}, R_2, L_1, and L_2 and L_{2b} are as defined in the specification, pharmaceutical compositions thereof, and methods of use thereof.

WO 2009/055077 A1

18.

8367 Kent Drive, El Cerrito, CA 94530 (US). WANG, **Longcheng** [CN/US]; 4294 Wilkie Way, Apt. L, Palo Alto, California 94306 (US).

(74) **Agents: BERNSTEIN, Robert L.** et al.; EXELIXIS, Inc., 210 East Grand Avenue Post Office Box 511, South San Francisco, CA 94083-0511 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

TROPANE COMPOUNDS

FIELD OF THE INVENTION

[0001] This disclosure relates to certain tropane compounds. In particular, this disclosure relates to certain tropane compounds useful as inhibitors of HSP90.

BACKGROUND OF THE INVENTION

[0002] HSP90 (heat shock protein 90) is one of the most abundant cellular proteins. There are at least four HSP90 family members in the human genome: the stress-inducible HSP90 (HSP90α or HSP90AA1), the constitutive cytosolic HSP90β (HSP90AB1), the endoplasmic reticulum-localized GRP94 (HSP90B), and the mitochondrial TRAP1 [2]. HSP90 contains approximately 730 amino acids arranged as 3 major domains: an N-terminal ATP-binding domain, a central domain and a C-terminal dimerization domain. HSP90 acts primarily as molecular chaperone, promoting the folding and stabilization of many labile cellular proteins. In general, HSP90 acts in concert with the HSP70 chaperone machinery, and also recruits multiple co-chaperone proteins to regulate its activity. Over 100 HSP90 substrates ("client proteins") have been described in the art. HSP90 constitutes ~1-2% of total protein in normal cells and this concentration can double under stress conditions, reflecting its importance in maintaining cellular homeostasis.

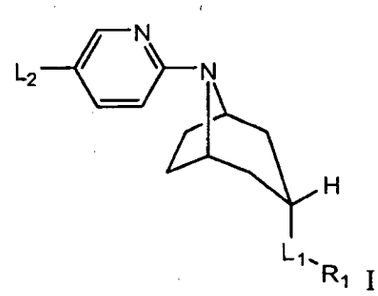
[0003] HSP90 expression and activity is frequently upregulated in tumor cells and is particularly associated with poor prognosis in breast cancer. Furthermore, HSP90 in tumor cells appears to exist in a hyperactivated state with elevated ATPase activity which is highly sensitive to HSP90 inhibition, compared to the largely latent form found in normal cells. This hyperactivated state suggests that HSP90 inhibitors can selectively target tumor cells, with relatively low impact on normal tissues. Many HSP90 client proteins are involved in various aspects of tumor growth and progression. HSP90 promotes the folding and/or stabilization of many oncogenic proteins that confer autonomous growth on cells (eg, EGFR and ErbB2, B-Raf and steroid hormone receptors, and also regulates multiple proteins that promote tumor cell survival (eg, IGF-1 receptor, PDK1 and Akt, RIP, IκB and survivin. HSP90 can also promote aberrant cell cycle progression by stabilizing Cdk4, Cdk6 and cyclin D, Cdk2, and Plk1. Conversely, HSP90 inhibitors can downregulate the cell cycle

checkpoint kinase Chk1 and sensitize tumors to various forms of chemotherapy. HSP90 inhibition can also blunt tumor angiogenesis, since hypoxia-inducible factor (HIF-1α) and the vascular endothelial growth factor (VEGF) receptor tyrosine kinases are HSP90 clients. The receptor tyrosine kinase Met, which stimulates cellular motility, migration and invasion, is also downregulated in response to HSP90 inhibition, both directly and via inhibition of HIF-1α. Apart from its role as a cellular chaperone, HSP90α has also been implicated in extracellular matrix degradation and tumor cell invasion, via activation (and possibly stabilization) of the matrix metalloproteinase MMP2. HSP90 depletion or inhibition promotes telomere erosion and apoptosis, and can also enable the evolution of heterogenous, metastatic and drug-resistant phenotypes by allowing propagation of metastable mutations. HSP90 has been implicated in activation of the unfolded protein response (UPR,). Failure of the UPR (for example, via inhibition of HSP90) leads to an ER stress signal and apoptosis. Therefore, HSP90 inhibitors can promote tumor cell death indirectly by disrupting the UPR, as well as by directly targeting pro-survival factors.

[0004] Accordingly, there is a need for new compounds that can inhibit HSP90.

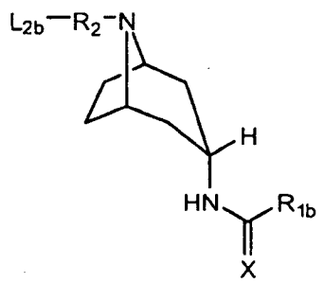
SUMMARY OF THE INVENTION

[0005] One aspect of the disclosure relates to a compound according to Formula I or II:



I

or



II

wherein R_1, R_{1b}, R_2, L_1, and L_2 and L_{2b} are as defined in the specification.

[0006] Another aspect of this disclosure relates to a method of inhibiting HSP90 in a cell, comprising contacting the cell, in which inhibition of HSP90 is desired, with a compound according to Formula I or II.

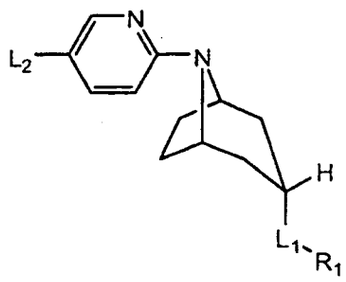
[0007] Another aspect of this disclosure relates to a method of inhibiting HSP90 in a cell, comprising contacting a cell in which inhibition of HSP90 is desired with a pharmaceutical composition, comprising the compound according Formula I or II, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0008] Another aspect of this disclosure relates to a method of treating one of the diseases or conditions disclosed herein that involves HSP90, comprising administering to an animal, in need of said treatment, the compound according to Formula I or II, optionally in combination with the one or more additional therapeutic agents or therapies disclosed hererin.

DETAILED DESCRIPTION OF THE INVENTION

[0009] There are many different aspects of the disclosure described hereinbelow, and each aspect is non-limiting in regard to the scope of the disclosure. The terms "aspects" and "embodiments" are meant to be non-limiting regardless of where the terms "aspect" or "embodiment" appears in this specification. The transitional term "comprising" as used herein, which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

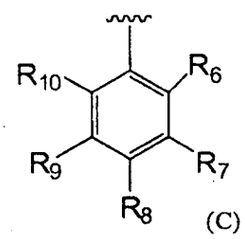
[0010] One aspect of the disclosure relates to a compound according to Formula I:



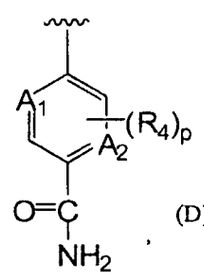
I

or a pharmaceutically acceptable salt thereof, wherein:

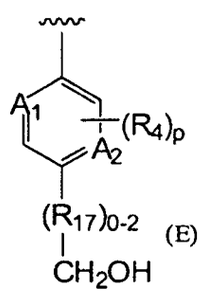
R_1 is selected from



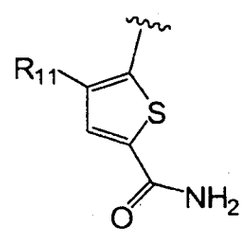
(C) ,



(D) ,



(E) and



(Q) ;

R_3 is selected from hydrogen, $-CF_3$, $-NH_2$, -OH, alkyl optionally substituted with 1, 2 or 3 R_5, alkoxy, dialkylaminoalkyl, cycloalkyl optionally substituted with arylalkoxy, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy and heterocycloalkyl optionally substituted with alkyl or aryl, alkenyl, alkynyl, heterocycloalkyl optionally substituted with a group selected from alkyl, -C(O)O-alkyl and arylalkyl, arylalkyl optionally substituted with alkylheterocycloalkyl at any ring position of the aryl group, and heteroaryl;

R_4, R_7, R_8, R_9 and R_{11} are each independently selected from hydrogen, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hydroxy, alkenyl, alkynyl, hydroxyalkynyl, halogen, hydroxyalkyl, dihydroxyalkyl, $-O-C(O)-NH_2$, amino(imino)alkyl, $-C(O)-NH_2$, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkyl optionally substituted with 1-8 halogen, dialkylamino, -N(H)alkylheterocycloalkyl, alkylsulfonylheterocycloalkylamino,

cycloalkylalkylamino, cycloalkoxy, $-NH_2$, -O-alkyl-heterocycloalkyl, dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl optionally substituted with 1, 2 or 3 groups selected from alkyl, alkoxy and halogen;

R_5 is selected from halogen, cycloalkyl, cycloalkylalkylamino, heteroaryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl and alkoxy, alkylthio, heterocycloalkyl optionally substituted with 1, 2, or 3 groups selected from alkyl, halogen, phenyl and oxo, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy, and heterocycloalkyl optionally substituted with alkyl, alkoxy, dialkylamino, -OH, $-C(O)-NH_2$, $-C(O)-O-CH_3$, $-C(O)-N(H)(C_1-C_3)$alkyl, heteroarylamino optionally substituted with halogen, and $-OCF_3$;

R_6 and R_{10} are each selected from hydrogen, alkyl optionally substituted with 1-8 halogens, alkylthio, alkenyl, alkynyl, hydroxyalkynyl, halogen, hydroxyalkyl, dihydroxyalkyl, amino(imino)alkyl, $-C(O)-NH_2$, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkylamino optionally substituted with 1-8 halogens, dialkylamino, alkoxyalkylamino, -N(H)alkylheterocycloalkyl, cycloalkylalkylamino, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkylamino optionally substituted with a group selected form -OH, alkyl, $-CF_3$ and heterocycloalkyl, -N(H)cycloalkyl optionally substituted with -OH or $-NH_2$, $-NH_2$, -N(H)-heteroaryl, -N(H)-aryl optionally substituted with 1, 2 or 3 groups selected from alkoxy, heterocycloalkylalkoxy and dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl;

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, alkyl, heterocycloalkyl, and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkyl, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl;

R_{17}, when present, is $-CH_2-$ or -CH(OH)-;

each of A_1 or A_2 is N or C(H), wherein A_1 and A_2 can be the same or different, provided that A_1 can be substituted with R_4 only when A_1 is C(H), and provided that A_2 can be substituted with R_4 only when A_2 is C(H);

L_1 is selected from -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, $-(CH_2)_nC(O)NH-$,

$-(CH_2)_nNHC(O)-$, $-(CH_2)_mNH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)_nNHSO_2-$, $-(CH_2)_mC(O)-$, $-(CH_2)_mO-$, and $-(CH_2)_mNH-(CH_2)_n-$;

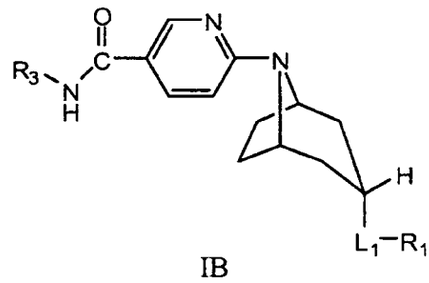
L_2 is $-C(O)-NH-R_3$, -CN, $-C(O)-N(CH_3)-OCH_3$, or $-C(O)-R_3$;

n is 0 or 1;

m is 0, 1 or 2; and

each p is independently 0, 1, 2, 3 or 4.

[0011] In another embodiment, the compound of Formula I is a compound of Formula IB:

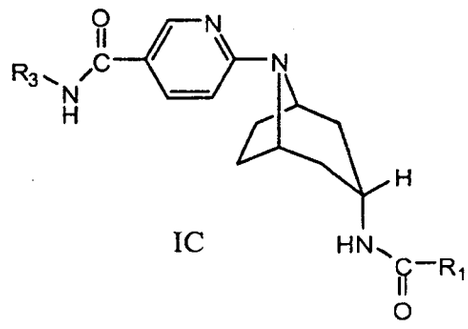


IB

or a pharmaceutically acceptable salt thereof,

wherein L_1, R_1 and R_3 are as defined in Formula I.

[0012] In another embodiment, the compound of Formula I is a compound of Formula IC:

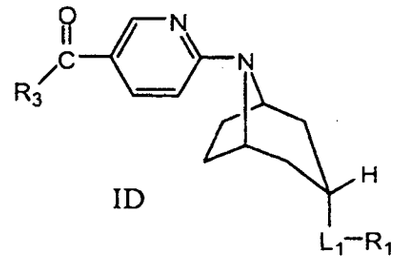


IC

or a pharmaceutically acceptable salt thereof,

wherein R_1 and R_3 are as defined in Formula I.

[0013] Another embodiment of Formula I is the compound of Formula ID:

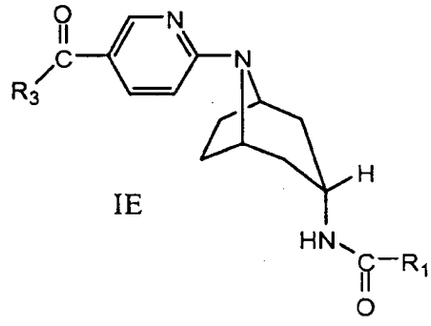


ID

or a pharmaceutically acceptable salt thereof,

wherein R_1, R_3 and L_1 are as defined in Formula I.

[0014] Another embodiment of Formula I is the compound of Formula IE:



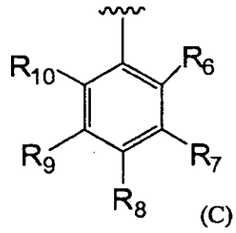
IE

or a pharmaceutically acceptable salt thereof,

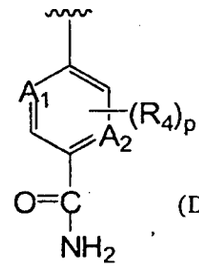
wherein R_1 and R_3 are as defined in Formula I.

[0015] Another embodiment relates to any one of Formula I, IB, IC, ID or IE as defined above, or a pharmaceutically acceptable salt thereof.

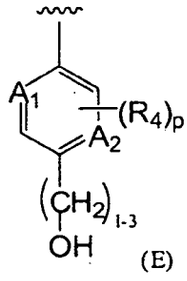
[0016] Another embodiment relates to a compound of Formula I, wherein R_1 is selected from



(C)

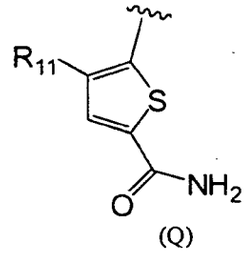


(D)



(E)

and



(Q) ;

R_3 is selected from hydrogen, $-CF_3$, $-NH_2$, -OH, alkyl optionally substituted with 1, 2 or 3 R_5, alkoxy, dialkylaminoalkyl, cycloalkyl optionally substituted with arylalkoxy, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy and heterocycloalkyl optionally substituted with alkyl or aryl, alkenyl, alkynyl, heterocycloalkyl optionally substituted with a group selected from alkyl, -C(O)O-alkyl and arylalkyl, arylalkyl optionally substituted with alkylheterocycloalkyl at any ring position of the aryl group, and heteroaryl;

R_4, R_7, R_8 , R_9 and R_{11} are each independently selected from hydrogen, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hydroxy, alkenyl, alkynyl, hydroxyalkynyl, alkoxy, halogen, hydroxyalkyl, dihydroxyalkyl, $-O-C(O)-NH_2$, amino(imino)alkyl, $-C(O)-NH_2$, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkyl optionally substituted with 1-8 halogen, dialkylamino, -N(H)alkylheterocycloalkyl, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkoxy, $-NH_2$, -O-alkyl-heterocycloalkyl, dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl optionally substituted with 1, 2 or 3 groups selected from alkyl, alkoxy and halogen;

R_5 is selected from halogen, cycloalkyl, cycloalkylalkylamino, heteroaryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl and alkoxy, alkylthio, heterocycloalkyl optionally substituted with 1, 2, or 3 groups selected from alkyl, halogen, phenyl and oxo, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy, and heterocycloalkyl (optionally substituted with alkyl), alkoxy, dialkylamino, -OH, $-C(O)-NH_2$, $-C(O)-O-CH_3$, $-C(O)-N(H)(C_1-C_3)$alkyl, heteroarylamino optionally substituted with halogen, and $-OCF_3$;

R_6 and R_{10} are each selected from hydrogen, alkyl optionally substituted with 1-8 halogens, alkylthio, alkenyl, alkynyl, hydroxyalkynyl, halogen, hydroxyalkyl, dihydroxyalkyl, amino(imino)alkyl, $-C(O)-NH_2$, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkylamino optionally substituted with 1-8 halogens, dialkylamino, alkoxyalkylamino, -N(H)alkylheterocycloalkyl, cycloalkylalkylamino, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkylamino

optionally substituted with a group selected form -OH, alkyl, $-CF_3$ and heterocycloalkyl, -N(H)cycloalkyl optionally substituted with -OH or $-NH_2$), $-NH_2$, -N(H)-heteroaryl, -N(H)-aryl optionally substituted with 1, 2 or 3 groups selected from alkoxy, heterocycloalkylalkoxy and dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl;

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, alkyl, heterocycloalkyl, and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkoxy, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkoxy;

each of A_1 or A_2 is –N= or –CH=, wherein A_1 and A_2 can be the same or different;

L_1 is selected from -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)_nC(O)NH-$, $-(CH_2)_nNHC(O)-$, $-(CH_2)_mNH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)_nNHSO_2-$, $-(CH_2)_mC(O)-$, $-(CH_2)_mO-$, and $-(CH_2)_mNH-$;

L_2 is $-C(O)-NH-R_3$, -CN or $-C(O)-R_3$;

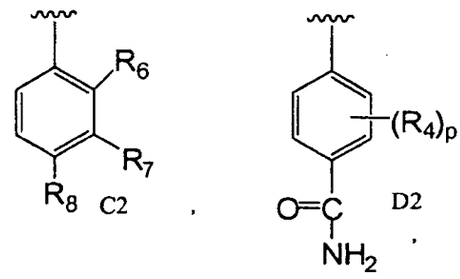
n is 0 or 1;

m is 0, 1 or 2; and

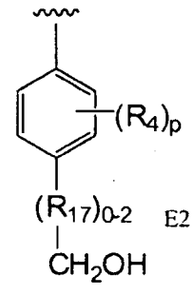
each p is independently 0, 1, 2, 3 or 4.

[0017] Another embodiment relates to a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from



and



;

R_3 is selected from CF_3, cyclopropyl, cyclobutyl, cyclohexyl optionally substituted with hydroxyl, cyclopropylmethyl, N-propyl, 3-methylbutyl, (1S)-2-hydroxy-1-methylethyl, (2S)-2-hydroxypropyl, methoxyethyl, ethoxyethyl, methylphenyl, phenyl, dimethylphenyl, methoxyphenyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminoethyl, diethylaminopropyl, cyclopentyl, halophenyl, phenylmethyl, phenylethyl optionally substituted with hydroxyl at the ethyl position of phenylethyl, phenylpropyl, phenylpiperidinyl, diethylaminoethyloxyphenylmethyl, diethylaminoethyloxyphenylethyl, pyrrolidinylphenylmethyl, diethylaminoethyloxy-2-fluorophenylethyl, phenyl(C_1-C_3)alkyl optionally substituted at the phenyl position of phenyl(C_1-C_3)alkyl with 1-3 groups selected from methoxy, halo and methyl, methylphenyl(C_1-C_4)alkyl wherein the (C_1-C_4)alkyl portion of methylphenyl(C_1-C_4)alkyl is optionally substituted with -C(O)NH_2, -C(O)$NHCH_3$ or -C(O)$NHCH_2CH_3$, thienylmethyl, furanylmethyl, pyridinylethyl, pyridinylmethyl, methylpyrazinylmethyl, methyl, ethyl, methylpropyl, 2-methylpropyl, 2,3-dihydroxypropyl, (1S)-1-methylpropyl, (1S)-1,2-dimethylpropyl, (1R)-1,2-dimethylpropyl, methyloxypropyl, ethyloxypropyl, (1S)-1-methyl-2-(methyloxy)ethyl, 1,3-benzodioxolyl, 1,3-benzodioxolylmethyl, N-prop-2-yn-1-yl, N-[3-(4-methylpiperazin-1-yl)propyl, N-[2-(ethylthio)ethyl], (1S,2S)-2-[(phenylmethyl)oxy]cyclopentyl, 6-chloropyridinylmethyl, 2-chloro-6-fluorophenylmethyl, methylthioethyl, N-butyl, 1-methylethyloxyethyl, 1-methylethyloxypropyl, 4,4-bismethyloxybutyl, methylpyrazinylmethyl, propyloxypropyl, trifluoromethyloxyphenylmethyl, methyloxyphenylethyl, (2,2-

dimethyl-1,3-dioxolan-4-yl)methyl, phenylmethylpyrrolidinyl, oxopyrrolidinylpropyl, pyrrolidinylethyl, methylpyrrolidinylethyl, ethylpyrrolidinylmethyl, N-(1R,2R,4S)-bicyclo[2.2.1]hept-2-yl, 3,3-dimethylbutyl, ethyloxyphenylmethyl, phenylmethylpiperidinyl, ethoxycarbonylpiperidinyl, trifluoromethylphenylmethyl, imidazolylpropyl, (3R)-pyrrolidin-3-yl, morpholinylethyl, morpholinylpropyl, piperidinylethyl, pyrrolidinyl, piperidinyl, pyrrolidinylmethyl, 1-methylethylpyrrolidinyl, ethylpyrrolidinyl, methylpyrrolidinyl, methylethylpiperidinyl, methylpiperidinyl, ethylpiperidinyl, ethylazetidinyl, azetidinyl, methylazetidinyl, 1-methylethylazetidinyl, methylpiperazinylphenylmethyl, piperazinylphenylmethyl, methylpiperazinylphenyl, methylpiperidinylphenyl, piperidinylphenyl(C_1-C_3)alkyl optionally substituted with 1-4 halo, methylpiperazinylphenyl(halo)methyl, methylpiperidinylphenylmethyl, methylpiperazinylphenylethyl, 2-methylpropylpiperazinylphenylmethyl, morpholinylphenylmethyl, piperazinylpyridinylethyl, -CH(CH_3)C(O)-NH_2, dimethylaminoethyloxyphenyl, isopropyl, (C_1-C_5)alkyl optionally substituted with 1-7 halo,-OH, -NH_2, cylcohexyl(C_1-C_5)alkyl optionally substituted with 1-2 hydroxyl groups, phenylaminoethyl optionally substituted with halo, morpholinylethyl, phenylpiperazinylethyl, and methylpiperazinylethyl;

each R_4, when present, is independently selected from halo, 1-ethylpropylamino, methyl, ethyl, cyclohexylamino optionally substituted with hydroxyl, cyclobutylamino, 1-methylpropyloxy, methoxyethoxy, -CF_3, piperidinyl or amino, mopholinylamino, dimethylaminobutyl, methylethylaminopropyl, methylethylaminopropylamino, cyclopentylamino, piperidinylamino, methylethylamino, ethylamino, 2-methylpropylamino, tetrahydraopyranylamino, ethylpiperidinylamino, 2,2-dimethylpropylamino, pyrrolidinylamino, 1-methylpropylamino, 2-methylpropylamino, amino, 1,1 dimethylethylamino, tetrahydropyranylmethylamino, piperidinylamino optionally substituted with methylsulfonyl, phenylamino optionally substituted with 1-3 groups selected from methoxy and dimethylaminoethyloxy, methylsulfonylethylamino, methoxyethylamino, morpholinylethyloxy, -N(H)C(O)CH_3, cyclobutylamino, methoxy, cyclobutyloxy, cyclobutylamino, pyridinylamino, ethylamino, 1-methylcyclopropylethylamino, methylethyloxyethylamino, butylamino, piperidinyl, pentylamino, azetinyl, 1,2-dimethylpropylamino, 1-methylethylpropylamino,

propylamino, 1-cyclopropylpropylamino, 1-propylbutylamino, 1-cyclopropylethylamino, dicyclopropylmethylamino, 1,2,2-trimethylpropylamino, tetrahydrofuranylamino, (C_1-C_5)alkylamino substituted with 1-7 halo, morpholinylethyloxy and cyclopropylmethylamino;

R_6 is selected from hydrogen, (C_1-C_4)alkyl optionally substituted with hydroxy, (C_1-C_3)alkylamino or dimethylamino, (C_1-C_4)alkynyl optionally substituted with hydroxyl, and halo;

R_7 is selected from hydrogen, -OH, -O(C_1-C_3)alkyl, -S(C_1-C_3)alkyl, -N(H)(C_1-C_3)alkyl, (C_5-C_6)cycloalkylamino optionally substituted with hydroxyl, (C_1-C_3)alkylamino or dimethylamino, -C(O)NH_2, and -O-C(O)NH_2;

R_8 is selected from hydrogen, -O(C_1-C_3)alkyl, -O-C(O)NH_2, and -C(=NH)-NH_2;

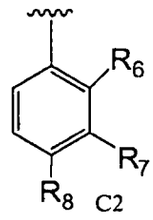
L_1 is -N(H)C(O)-;

L_2 is -C(O)-NH-R_3 or -C(O)-R_3; and

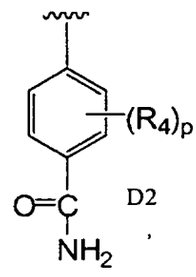
each p is independently 0, 1, 2 or 3.

[0018] Another embodiment relates to a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from

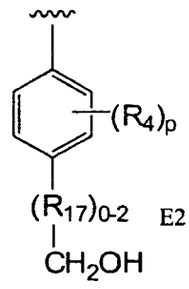


C2 ,



D2 ,

and



E2 ;

R_3 is selected from hydrogen, -CF_3, -NH_2, -OH, alkyl optionally substituted with 1, 2 or 3 R_5, alkoxy, diethylaminoethoxy, ethylmethylaminoethoxy, dimethylaminoethoxy, cylcopentyl optionally substituted with arylalkoxy, cyclobutyl optionally substituted with arylalkoxy, cyclopropyl optionally substituted with

arylalkoxy, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy, piperazinyl optionally substituted with alkyl or phenyl, morpholinyl optionally substituted with alkyl or phenyl, azetidinyl and piperidinyl optionally substituted with alkyl or phenyl, alkenyl, alkynyl, heterocycloalkyl selected from piperidinyl, pyrrolidinyl, morpholinyl and piperizinyl, wherein the heterocycloalkyl is optionally substituted with a group selected from alkyl, -C(O)O-alkyl and arylalkyl, arylalkyl optionally substituted with alkylheterocycloalkyl at any ring position of the aryl group, and heteroaryl;

R_6 is selected from hydrogen, $(C_1\text{-}C_4)$alkyl optionally substituted with hydroxy, $(C_1\text{-}C_3)$alkylamino or dimethylamino, $(C_1\text{-}C_4)$alkynyl optionally substituted with hydroxyl, and halo;

R_7 is selected from hydrogen, -OH, -O$(C_1\text{-}C_3)$alkyl, -S$(C_1\text{-}C_3)$alkyl, -N(H)$(C_1\text{-}C_3)$alkyl, $(C_5\text{-}C_6)$cycloalkylamino optionally substituted with hydroxyl, $(C_1\text{-}C_3)$alkylamino or dimethylamino, -C(O)NH_2, and -O-C(O)NH_2;

R_8 is selected from hydrogen, -O$(C_1\text{-}C_3)$alkyl, -O-C(O)NH_2, and -C(=NH)-NH_2;

each R_4, when present, is independently selected from methyl, 1-methylethylamino, ethylamino, 1-ethylpropylamino, 2-methylpropylamino, (2,2-dimethylpropyl)amino, (2-aminoethyl)amino, (2,2,3,3,3-pentafluoropropyl)amino, 1-methylpropylamino, (1S)-1-methylpropylamino, (2,2,2-trifluoroethyl)amino, 1-propylbutylamino, propylamino, 1,2-dimethylpropylamino, (3,3,3-trifluoropropyl)amino, (2,2,3,3,4,4,4-heptafluorobutyl)amino, butylamino, 1,2,2-trimethylpropylamino, 1-[(methyloxy)methyl]propylamino, 1-methylethyloxyethylamino, 1-methylpropylamino, pentylamino, (2,2,3,3,3-pentafluoropropyl)amino, butylamino, 2-[(1-methylethyl)oxy]ethylamino, (1S)-1-methylpropylamino, (1R)-1-methylpropylamino, (1S)-1,2-dimethylpropylamino, 1-cyclopropylethylamino, (1R)-1,2-dimethylpropylamino, 1-ethyl-2-methylpropylamino, and 3-[(1-methylethyl)amino]propylamino;

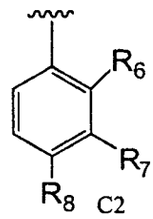
L_1 is -N(H)C(O)-;

L_2 is -C(O)-NH-R_3 or -C(O)-R_3; and

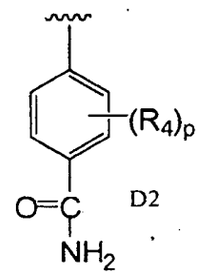
each p is independently 0, 1, 2 or 3.

[0019] Another embodiment relates to a compound of Formula IB or ID, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from

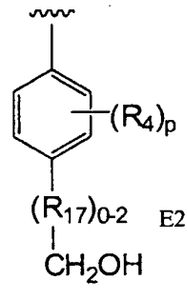


C2 ,



D2 ,

and



E2 ;

R_3 is selected from CF_3, cyclopropyl, cyclobutyl, cyclohexyl optionally substituted with hydroxyl, cyclopropylmethyl, N-propyl, 3-methylbutyl, (1S)-2-hydroxy-1-methylethyl, (2S)-2-hydroxypropyl, methoxyethyl, ethoxyethyl, methylphenyl, phenyl, dimethylphenyl, methoxyphenyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminoethyl, diethylaminopropyl, cyclopentyl, halophenyl, phenylmethyl, phenylethyl optionally substituted with hydroxyl at the ethyl position of phenylethyl, phenylpropyl, phenylpiperidinyl, diethylaminoethyloxyphenylmethyl, diethylaminoethyloxyphenylethyl, pyrrolidinylphenylmethyl, diethylaminoethyloxy-2-fluorophenylethyl, phenyl(C_1-C_3)alkyl optionally substituted at the phenyl position of phenyl(C_1-C_3)alkyl with 1-3 groups selected from methoxy, halo and methyl, methylphenyl(C_1-C_4)alkyl wherein the (C_1-C_4)alkyl portion of methylphenyl(C_1-C_4)alkyl is optionally substituted with -C(O)NH_2, -C(O)$NHCH_3$ or -C(O)$NHCH_2CH_3$, thienylmethyl, furanylmethyl, pyridinylethyl, pyridinylmethyl, methylpyrazinylmethyl, methyl, ethyl, methylpropyl, 2-methylpropyl, 2,3-dihydroxypropyl, (1S)-1-methylpropyl, (1S)-1,2-dimethylpropyl, (1R)-1,2-dimethylpropyl, methyloxypropyl, ethyloxypropyl, (1S)-1-methyl-2-(methyloxy)ethyl, 1,3-benzodioxolyl, 1,3-benzodioxolylmethyl, N-prop-2-yn-1-yl, N-[3-(4-methylpiperazin-1-yl)propyl, N-[2-(ethylthio)ethyl], (1S,2S)-2-[(phenylmethyl)oxy]cyclopentyl, 6-chloropyridinylmethyl, 2-chloro-6-fluorophenylmethyl, methylthioethyl, N-butyl, 1-methylethyloxyethyl, 1-methylethyloxypropyl, 4,4-bismethyloxybutyl, methylpyrazinylmethyl,

propyloxypropyl, trifluoromethyloxyphenylmethyl, methyloxyphenylethyl, (2,2-dimethyl-1,3-dioxolan-4-yl)methyl, phenylmethylpyrrolidinyl, oxopyrrolidinylpropyl, pyrrolidinylethyl, methylpyrrolidinylethyl, ethylpyrrolidinylmethyl, N-(1R,2R,4S)-bicyclo[2.2.1]hept-2-yl, 3,3-dimethylbutyl, ethyloxyphenylmethyl, phenylmethylpiperidinyl, ethoxycarbonylpiperidinyl, trifluoromethylphenylmethyl, imidazolylpropyl, (3R)-pyrrolidin-3-yl, morpholinylethyl, morpholinylpropyl, piperidinylethyl, pyrrolidinyl, piperidinyl, pyrrolidinylmethyl, 1-methylethylpyrrolidinyl, ethylpyrrolidinyl, methylpyrrolidinyl, methylethylpiperidinyl, methylpiperidinyl, ethylpiperidinyl, ethylazetidinyl, azetidinyl, methylazetidinyl, 1-methylethylazetidinyl, methylpiperazinylphenylmethyl, piperazinylphenylmethyl, methylpiperazinylphenyl, methylpiperidinylphenyl, piperidinylphenyl(C_1-C_3)alkyl optionally substituted with 1-4 halo, methylpiperazinylphenyl(halo)methyl, methylpiperidinylphenylmethyl, methylpiperazinylphenylethyl, 2-methylpropylpiperazinylphenylmethyl, morpholinylphenylmethyl, piperazinylpyridinylethyl, -CH(CH_3)C(O)-NH_2, dimethylaminoethyloxyphenyl, isopropyl, (C_1-C_5)alkyl optionally substituted with 1-7 halo,-OH, -NH_2, cylcohexyl(C_1-C_5)alkyl optionally substituted with 1-2 hydroxyl groups, phenylaminoethyl optionally substituted with halo, morpholinylethyl, phenylpiperazinylethyl, and methylpiperazinylethyl;

each R_4, when present, is independently selected from halo, 1-ethylpropylamino, methyl, ethyl, cyclohexylamino optionally substituted with hydroxyl, cyclobutylamino, 1-methylpropyloxy, methoxyethoxy, -CF_3, piperidinyl or amino, mopholinylamino, dimethylaminobutyl, methylethylaminopropyl, methylethylaminopropylamino, cyclopentylamino, piperidinylamino, methylethylamino, ethylamino, 2-methylpropylamino, tetrahydraopyranylamino, ethylpiperidinylamino, 2,2-dimethylpropylamino, pyrrolidinylamino, 1-methylpropylamino, 2-methylpropylamino, amino, 1,1 dimethylethylamino, tetrahydropyranylmethylamino, piperidinylamino optionally substituted with methylsulfonyl, phenylamino optionally substituted with 1-3 groups selected from methoxy and dimethylaminoethyloxy, methylsulfonylethylamino, methoxyethylamino, morpholinylethyloxy, -N(H)C(O)CH_3, cyclobutylamino, methoxy, cyclobutyloxy, cyclobutylamino, pyridinylamino, ethylamino, 1-methylcyclopropylethylamino, methylethyloxyethylamino, butylamino, piperidinyl,

pentylamino, azetinyl, 1,2-dimethylpropylamino, 1-methylethylpropylamino, propylamino, 1-cyclopropylpropylamino, 1-propylbutylamino, 1-cyclopropylethylamino, dicyclopropylmethylamino, 1,2,2-trimethylpropylamino, tetrahydrofuranylamino, (C_1-C_5)alkylamino substituted with 1-7 halo, morpholinylethyloxy and cyclopropylmethylamino;

R_6 is selected from hydrogen, (C_1-C_4)alkyl optionally substituted with hydroxy, (C_1-C_3)alkylamino or dimethylamino, (C_1-C_4)alkynyl optionally substituted with hydroxyl, and halo;

R_7 is selected from hydrogen, -OH, -O(C_1-C_3)alkyl, -S(C_1-C_3)alkyl, -N(H)(C_1-C_3)alkyl, (C_5-C_6)cycloalkylamino optionally substituted with hydroxyl, (C_1-C_3)alkylamino or dimethylamino, -C(O)NH_2, and -O-C(O)NH_2;

R_8 is selected from hydrogen, -O(C_1-C_3)alkyl, -O-C(O)NH_2, and -C(=NH)-NH_2;

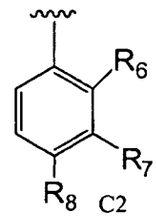
L_1 is -N(H)C(O)-;

L_2 is -C(O)-NH-R_3 or -C(O)-R_3; and

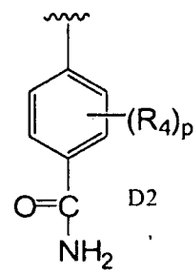
each p is independently 0, 1, 2 or 3.

[0020] Another embodiment relates to a compound of Formula IC or IE, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from

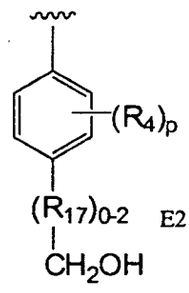


C2 ,



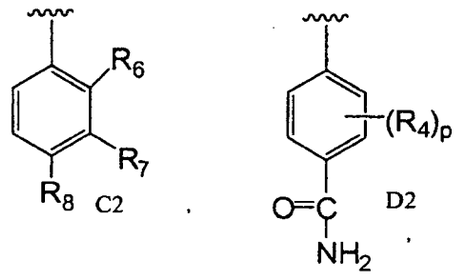
D2 ,

and



E2 ;

R_1 is selected from



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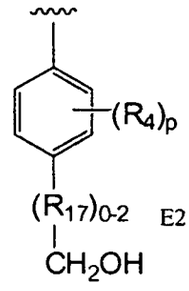


;

R_3 is selected from CF_3, cyclopropyl, cyclobutyl, cyclohexyl optionally substituted with hydroxyl, cyclopropylmethyl, N-propyl, 3-methylbutyl, (1S)-2-hydroxy-1-methylethyl, (2S)-2-hydroxypropyl, methoxyethyl, ethoxyethyl, methylphenyl, phenyl, dimethylphenyl, methoxyphenyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminoethyl, diethylaminopropyl, cyclopentyl, halophenyl, phenylmethyl, phenylethyl optionally substituted with hydroxyl at the ethyl position of phenylethyl, phenylpropyl, phenylpiperidinyl, diethylaminoethyloxyphenylmethyl, diethylaminoethyloxyphenylethyl, pyrrolidinylphenylmethyl, diethylaminoethyloxy-2-fluorophenylethyl, phenyl(C_1-C_3)alkyl optionally substituted at the phenyl position of phenyl(C_1-C_3)alkyl with 1-3 groups selected from methoxy, halo and methyl, methylphenyl(C_1-C_4)alkyl wherein the (C_1-C_4)alkyl portion of methylphenyl(C_1-C_4)alkyl is optionally substituted with -C(O)NH_2, -C(O)$NHCH_3$ or -C(O)$NHCH_2CH_3$, thienylmethyl, furanylmethyl, pyridinylethyl, pyridinylmethyl, methylpyrazinylmethyl, methyl, ethyl, methylpropyl, 2-methylpropyl, 2,3-dihydroxypropyl, (1S)-1-methylpropyl, (1S)-1,2-dimethylpropyl, (1R)-1,2-dimethylpropyl, methyloxypropyl, ethyloxypropyl, (1S)-1-methyl-2-(methyloxy)ethyl, 1,3-benzodioxolyl, 1,3-benzodioxolylmethyl, N-prop-2-yn-1-yl, N-[3-(4-methylpiperazin-1-yl)propyl, N-[2-(ethylthio)ethyl], (1S,2S)-2-[(phenylmethyl)oxy]cyclopentyl, 6-chloropyridinylmethyl, 2-chloro-6-fluorophenylmethyl, methylthioethyl, N-butyl, 1-methylethyloxyethyl, 1-methylethyloxypropyl, 4,4-bismethyloxybutyl, methylpyrazinylmethyl, propyloxypropyl, trifluoromethyloxyphenylmethyl, methyloxyphenylethyl, (2,2-

dimethyl-1,3-dioxolan-4-yl)methyl, phenylmethylpyrrolidinyl, oxopyrrolidinylpropyl, pyrrolidinylethyl, methylpyrrolidinylethyl, ethylpyrrolidinylmethyl, N-(1R,2R,4S)-bicyclo[2.2.1]hept-2-yl, 3,3-dimethylbutyl, ethyloxyphenylmethyl, phenylmethylpiperidinyl, ethoxycarbonylpiperidinyl, trifluoromethylphenylmethyl, imidazolylpropyl, (3R)-pyrrolidin-3-yl, morpholinylethyl, morpholinylpropyl, piperidinylethyl, pyrrolidinyl, piperidinyl, pyrrolidinylmethyl, 1-methylethylpyrrolidinyl, ethylpyrrolidinyl, methylpyrrolidinyl, methylethylpiperidinyl, methylpiperidinyl, ethylpiperidinyl, ethylazetidinyl, azetidinyl, methylazetidinyl, 1-methylethylazetidinyl, methylpiperazinylphenylmethyl, piperazinylphenylmethyl, methylpiperazinylphenyl, methylpiperidinylphenyl, piperidinylphenyl(C_1-C_3)alkyl optionally substituted with 1-4 halo, methylpiperazinylphenyl(halo)methyl, methylpiperidinylphenylmethyl, methylpiperazinylphenylethyl, 2-methylpropylpiperazinylphenylmethyl, morpholinylphenylmethyl, piperazinylpyridinylethyl, -CH(CH_3)C(O)-NH_2, dimethylaminoethyloxyphenyl, isopropyl, (C_1-C_5)alkyl optionally substituted with 1-7 halo,-OH, -NH_2, cylcohexyl(C_1-C_5)alkyl optionally substituted with 1-2 hydroxyl groups, phenylaminoethyl optionally substituted with halo, morpholinylethyl, phenylpiperazinylethyl, and methylpiperazinylethyl;

each R_4, when present, is independently selected from halo, 1-ethylpropylamino, methyl, ethyl, cyclohexylamino optionally substituted with hydroxyl, cyclobutylamino, 1-methylpropyloxy, methoxyethoxy, -CF_3, piperidinyl or amino, mopholinylamino, dimethylaminobutyl, methylethylaminopropyl, methylethylaminopropylamino, cyclopentylamino, piperidinylamino, methylethylamino, ethylamino, 2-methylpropylamino, tetrahydraopyranylamino, ethylpiperidinylamino, 2,2-dimethylpropylamino, pyrrolidinylamino, 1-methylpropylamino, 2-methylpropylamino, amino, 1,1 dimethylethylamino, tetrahydropyranylmethylamino, piperidinylamino optionally substituted with methylsulfonyl, phenylamino optionally substituted with 1-3 groups selected from methoxy and dimethylaminoethyloxy, methylsulfonylethylamino, methoxyethylamino, morpholinylethyloxy, -N(H)C(O)CH_3, cyclobutylamino, methoxy, cyclobutyloxy, cyclobutylamino, pyridinylamino, ethylamino, 1-methylcyclopropylethylamino, methylethyloxyethylamino, butylamino, piperidinyl, pentylamino, azetinyl, 1,2-dimethylpropylamino, 1-methylethylpropylamino,

propylamino, 1-cyclopropylpropylamino, 1-propylbutylamino, 1-cyclopropylethylamino, dicyclopropylmethylamino, 1,2,2-trimethylpropylamino, tetrahydrofuranylamino, (C_1-C_5)alkylamino substituted with 1-7 halo, morpholinylethyloxy and cyclopropylmethylamino;

R_6 is selected from hydrogen, (C_1-C_4)alkyl optionally substituted with hydroxy, (C_1-C_3)alkylamino or dimethylamino, (C_1-C_4)alkynyl optionally substituted with hydroxyl, and halo;

R_7 is selected from hydrogen, -OH, -O(C_1-C_3)alkyl, -S(C_1-C_3)alkyl, -N(H)(C_1-C_3)alkyl, (C_5-C_6)cycloalkylamino optionally substituted with hydroxyl, (C_1-C_3)alkylamino or dimethylamino, -C(O)NH_2, and -O-C(O)NH_2;

R_8 is selected from hydrogen, -O(C_1-C_3)alkyl, -O-C(O)NH_2, and -C(=NH)-NH_2;

L_1 is -N(H)C(O)-;

L_2 is -C(O)-NH-R_3 or -C(O)-R_3; and

each p is independently 0, 1, 2 or 3.

[0021] In other embodiments, R_1 of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is aryl optionally substituted with 1, 2 or 3 groups independently selected from (1) -C(O)NH_2, (2) methoxy, (3) alkyl, such as methyl as a non-limiting example, (4) alkylamino, such as ethylpropylamino, methylpropylamino or cyclopropylpropylpropylamino as non-limiting examples, (5) cycloalkylamino optionally substituted with OH, such as cyclohexylamino or cyclopentylamino as non-limiting examples, and (6) heterocycloalkylamino, such as furanyl or tetrahydro-2H-pyran as non-limiting examples.

[0022] In another embodiment of the compound of Formula I, or a pharmaceutically acceptable salt thereof, L_1 is -NHC(O)-.

[0023] In another embodiment of the compound of Formula I, or a pharmaceutically acceptable salt thereof, L_1 is selected from -NHC(O)-, -NHSO_2-, -NHC(O)O-, -C(O)O-, -C(O)NH-, -C(O)NHSO_2-, -C(O)-, -(CH_2)C(O)NH-, -(CH_2)NHC(O)-, -(CH_2)NH-, -(CH_2)$_n$$SO_2$NH-, -($CH_2$)NH$SO_2$-, -($CH_2$)C(O)-, -($CH_2$)O-, and -NH-($CH_2$)-.

[0024] In another embodiment of the compound of Formula I, or a pharmaceutically acceptable salt thereof, L_2 is -C(O)-NH-cyclopropyl, -C(O)-NH-CH_3, -C(O)-cyclopropyl, or -C(O)-CH_3.

[0025] In another embodiment of the compound of Formula I, or a pharmaceutically acceptable salt thereof, L_2 is -C(O)-NH-cyclopropyl or -C(O)-NH-CH_3.

[0026] In another embodiment of the compound of Formula I, or a pharmaceutically acceptable salt thereof, L_2 is -C(O)-NH-CH_3.

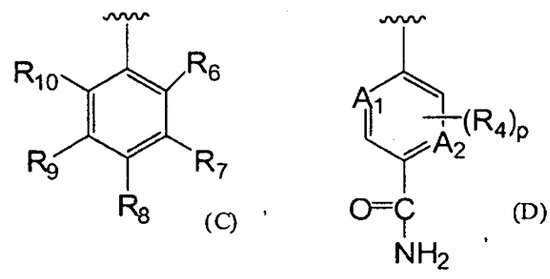
[0027] In another embodiment of the compound of Formula I, or a pharmaceutically acceptable salt thereof, L_2 is -C(O)-NH-cyclopropyl.

[0028] In another embodiment of the compound of Formula I, or a pharmaceutically acceptable salt thereof, L_2 is -C(O)-cyclopropyl or -C(O)-CH_3.

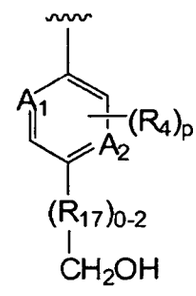
[0029] In another embodiment of the compound of Formula I, or a pharmaceutically acceptable salt thereof, L_2 is -C(O)-cyclopropyl.

[0030] In another embodiment of the compound of Formula I, or a pharmaceutically acceptable salt thereof, L_2 is -C(O)-CH_3.

[0031] In another embodiment of the compound of Formula I, IB, IC, ID, and IE, or a pharmaceutically acceptable salt thereof, R_1 is selected from:

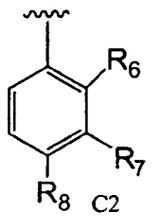


and

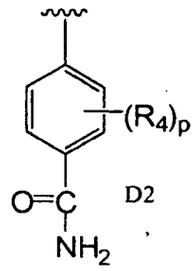


wherein A_1, A_2, R_4, R_6, R_7, R_8, R_9, R_{10}, R_{17}, and p are as defined above.

[0032] In another embodiment of the compound of Formula I, IB, IC, ID, and IE, or a pharmaceutically acceptable salt thereof, R_1 is selected from:

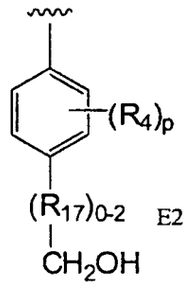


C2



D2

and

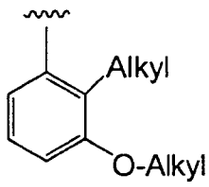


E2

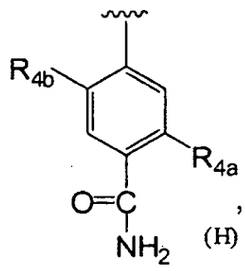
wherein R_4, R_6, R_7, R_8, R_{17}, and p are as defined above.

[0033] In another embodiment of the compound of Formula I, IB, IC, ID, or IE, R_1 is selected from one of the following of Group Z:

Group Z

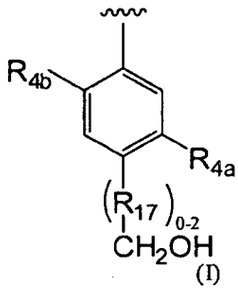


(G)



(H)

and



(I)

wherein R_{4a} is selected from hydrogen, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hydroxy, alkenyl, alkynyl, hydroxyalkynyl, alkoxy, halogen, hydroxyalkyl, dihydroxyalkyl, -O-C(O)-NH_2, amino(imino)alkyl, -C(O)-NH_2, -N(H)C(O)alkyl, alkylaminoalkyl,

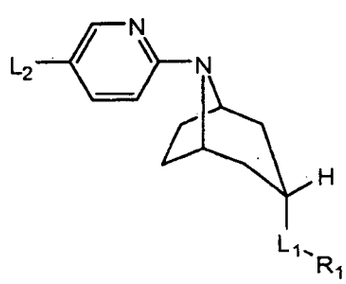
alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkyl optionally substituted with 1-8 halogens, dialkylamino, -N(H)alkylheterocycloalkyl, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkoxy, $-NH_2$, -O-alkyl-heterocycloalkyl, dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl optionally substituted with 1, 2 or 3 groups selected from alkyl, alkoxy and halogen;

R_{4b} is selected from H, halogen and methyl optionally substituted with 1-3 halogens;

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, alkyl, heterocycloalkyl, and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkyl, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalky; and

R_{17}, when present, is $-CH_2-$ or -CH(OH)-.

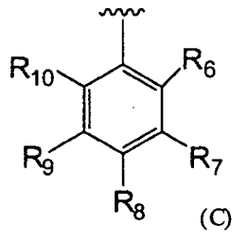
[0034] Another aspect of the disclosure relates to a compound according to Formula I:



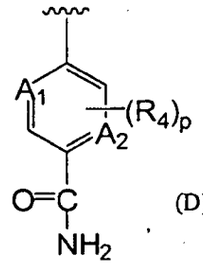
I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from:

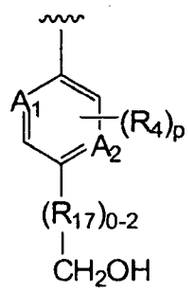


(C)



(D)

and



(E)

;

R_3 is selected from hydrogen, $-CF_3$, $-NH_2$, -OH, alkyl optionally substituted with 1, 2 or 3 R_5, alkoxy, dialkylaminoalkyl, cycloalkyl optionally substituted with arylalkoxy, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy and heterocycloalkyl optionally substituted with alkyl or aryl, alkenyl, alkynyl, heterocycloalkyl optionally substituted with a group selected from alkyl, -C(O)O-alkyl and arylalkyl, arylalkyl optionally substituted with alkylheterocycloalkyl at any ring position of the aryl group, and heteroaryl;

R_4, R_7, R_8, R_9 and R_{11} are each independently selected from hydrogen, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hydroxy, alkenyl, alkynyl, hydroxyalkynyl, alkoxy, halogen, hydroxyalkyl, dihydroxyalkyl, $-O-C(O)-NH_2$, amino(imino)alkyl, $-C(O)-NH_2$, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkyl optionally substituted with 1-8 halogen, dialkylamino, -N(H)alkylheterocycloalkyl, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkoxy, $-NH_2$, -O-alkyl-heterocycloalkyl, dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl optionally substituted with 1, 2 or 3 groups selected from alkyl, alkoxy and halogen;

R_5 is selected from halogen, cycloalkyl, cycloalkylalkylamino, heteroaryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl and alkoxy, alkylthio, heterocycloalkyl optionally substituted with 1, 2, or 3 groups selected from alkyl, halogen, phenyl and oxo, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy, and heterocycloalkyl

optionally substituted with alkyl, alkoxy, dialkylamino, -OH, -C(O)-NH_2, -C(O)-O-CH_3, -C(O)-N(H)(C_1-C_3)alkyl, heteroarylamino optionally substituted with halogen, and -OCF_3;

R_6 and R_{10} are each selected from hydrogen, alkyl optionally substituted with 1-8 halogens, alkylthio, alkenyl, alkynyl, hydroxyalkynyl, halogen, hydroxyalkyl, dihydroxyalkyl, amino(imino)alkyl, -C(O)-NH_2, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkylamino optionally substituted with 1-8 halogens, dialkylamino, alkoxyalkylamino, -N(H)alkylheterocycloalkyl, cycloalkylalkylamino, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkylamino optionally substituted with a group selected form -OH, alkyl, -CF_3 and heterocycloalkyl, -N(H)cycloalkyl optionally substituted with -OH or -NH_2, -NH_2, -N(H)-heteroaryl, -N(H)-aryl optionally substituted with 1, 2 or 3 groups selected from alkoxy, heterocycloalkylalkoxy and dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl;

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, -NH_2, alkyl, heterocycloalkyl, and -CF_3, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or -NH_2, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkyl, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl;

R_{17}, when present, is -CH_2- or -CH(OH)-;

each of A_1 or A_2 is N or C(H), wherein A_1 and A_2 can be the same or different, provided that A_1 can be substituted with R_4 only when A_1 is C(H), and provided that A_2 can be substituted with R_4 only when A_2 is C(H);

L_1 is selected from -NHC(O)-, -$NHSO_2$-, -NHC(O)O-, -C(O)O-, -C(O)NH-, -C(O)$NHSO_2$-, -C(O)-, -(CH_2)C(O)NH-, -(CH_2)NHC(O)-, -(CH_2)NH-, -$(CH_2)_nSO_2NH$-, -(CH_2)$NHSO_2$-, -(CH_2)C(O)-, -(CH_2)O-, and -NH-(CH_2)-;

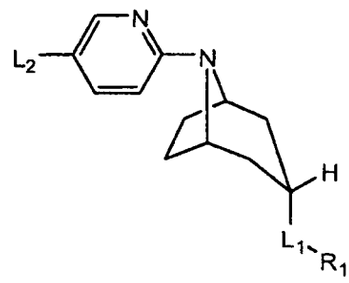
L_2 is -C(O)-NH-cyclopropyl or -NH-C(O)-CH_3;

n is 0 or 1;

m is 0, 1 or 2; and

each p is independently 0, 1, 2, 3 or 4.

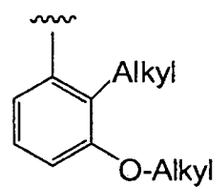
[0035] Another aspect of the disclosure relates to a compound according to Formula I:



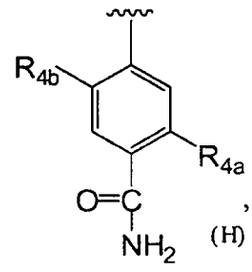
I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from:

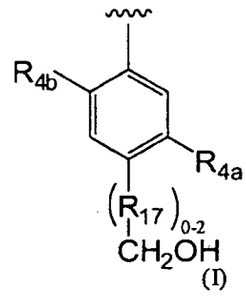


(G)



(H)

and



(I)

wherein R_{4a} is selected from hydrogen, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hydroxy, alkenyl, alkynyl, hydroxyalkynyl, alkoxy, halogen, hydroxyalkyl, dihydroxyalkyl, -O-C(O)-NH_2, amino(imino)alkyl, -C(O)-NH_2, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkyl optionally substituted with 1-8 halogens, dialkylamino, -N(H)alkylheterocycloalkyl, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkoxy, $-NH_2$, -O-alkyl-heterocycloalkyl, dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl optionally substituted with 1, 2 or 3 groups selected from alkyl, alkoxy and halogen;

R_{4b} is selected from H, halogen and methyl optionally substituted with 1-3 halogens;

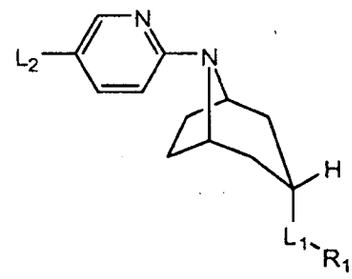
R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, alkyl, heterocycloalkyl, and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkyl, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl;

R_{17}, when present, is $-CH_2-$ or -CH(OH)-;

L_1 is selected from -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)C(O)NH-$, $-(CH_2)NHC(O)-$, $-(CH_2)NH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)NHSO_2-$, $-(CH_2)C(O)-$, $-(CH_2)O-$, and $-NH-(CH_2)-$; and

L_2 is -C(O)-NH-cyclopropyl or $-NH-C(O)-CH_3$.

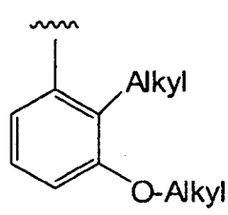
[0036] Another aspect of the disclosure relates to a compound according to Formula I:



I

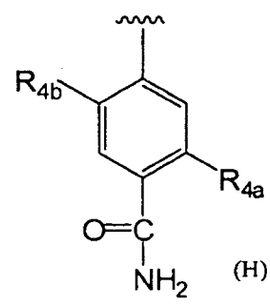
or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from:



(G)

and



(H)

wherein R_{4a} is selected from hydrogen, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hydroxy, alkenyl, alkynyl, hydroxyalkynyl, alkoxy, halogen, hydroxyalkyl, dihydroxyalkyl, $-O-C(O)-NH_2$, amino(imino)alkyl, $-C(O)-NH_2$, -N(H)C(O)alkyl, alkylaminoalkyl,

alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkyl optionally substituted with 1-8 halogens, dialkylamino, -N(H)alkylheterocycloalkyl, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkoxy, $-NH_2$, -O-alkyl-heterocycloalkyl, dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl optionally substituted with 1, 2 or 3 groups selected from alkyl, alkoxy and halogen;

R_{4b} is selected from H, halogen and methyl optionally substituted with 1-3 halogens;

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, alkyl, heterocycloalkyl, and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkyl, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl;

L_1 is selected from -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)C(O)NH-$, $-(CH_2)NHC(O)-$, $-(CH_2)NH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)NHSO_2-$, $-(CH_2)C(O)-$, $-(CH_2)O-$, and $-NH-(CH_2)-$; and

L_2 is -C(O)-NH-cyclopropyl or $-NH-C(O)-CH_3$.

[0037] For purposes of this specification, the language for the definition of R_{16}, as defined in Formula I, is meant to mean that R_{16} can be hydrogen, or R_{16} can be alkyl optionally substituted with 1-8 halogen groups, or R_{16} can be cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, alkyl, heterocycloalkyl, and $-CF_3$, or R_{16} can be cycloalkylalkyl, or R_{16} can be heterocycloalkyl optionally substituted with -OH or -NH, or R_{16} can be alkoxyalkyl, or R_{16} can be aryl optionally substituted with 1, 2 or 3 alkoxy, or R_{16} can be heterocycloalkylalkyl, or R_{16} can be heteroaryl, or R_{16} can be gem-dicycloalkylalkyl, or R_{16} can be dialkylaminoalkyl. This interpretation of the language for R_{16} is meant to be exemplary for the interpretation of the language in the definitions for the other variables listed in this specification.

[0038] When any of the embodiments in this specification refers to a compound of Formula I, IB, IC, ID or IE, this is meant to mean that this embodiment includes each of Formula I, IB, IC, ID or IE individually or in any combination of each other. For instance, when any of the embodiments in this specification refers to a compound of Formula I, IB, IC, ID or IE, this can be interpreted to include only compounds

having Formula I, or only compounds having Formula IB, or only compounds having Formula IC, or only compounds having Formula ID, or only compounds having Formula IE, or a combination of any two of Formula I, IB, IC, ID or IE, (such as, for example, a compound of Formula IB or IC, or a compound of Formula ID or IE, wherein all variables L_1, R_1 and R_3 are as defined in Formula I) or a combination of any three of Formula I, IB, IC, ID or IE, or a combination of any four of Formula I, IB, IC, ID or IE, or all of Formula I, IB, IC, ID and IE.

[0039] Unless otherwise specificed, the compounds disclosed herein are meant to include pharmaceutically acceptable salts of these compounds, whether this is exlicitely srated or not, as alternative embodiments to the free base forms of the compounds in this disclosure.

[0040] In another embodiment of the compound of Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, R_{4a} is selected from $-N(H)R_{16}$, $-OR_{16}$, and $-SR_{16}$;

R_{4b} is selected from H, alkyl optionally substituted with one or more halogens, and halogen; and

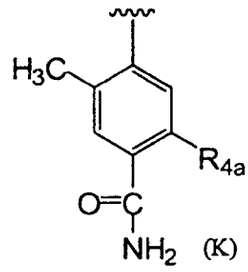
R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, $-CH_3$ and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with alkyl, -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkyl, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl.

[0041] In another embodiment of the compound of Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, R_{4a} is cyclohexylamino optionally substituted with -OH.

[0042] In another embodiment of the compound of Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, R_{4b} is alkyl optionally substituted with 1-8 fluoro.

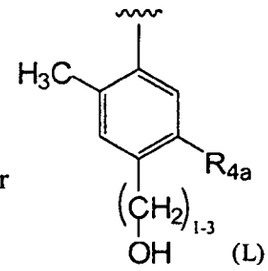
[0043] In another embodiment of the compound of Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, R_{16} is cyclopropyl, cyclopentyl or cyclohexyl, wherein each cyclopropyl, cyclopentyl or cyclohexyl can be optionally substituted with 1 or 2 -OH.

[0044] In another embodiment of the compound of Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, R_1 is



(K)

or

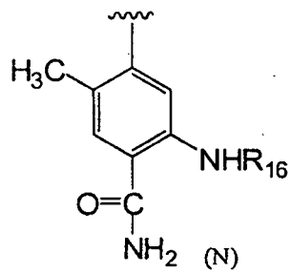


(L)

wherein R_{4a} is selected from $-N(H)R_{16}$, $-OR_{16}$, and $-SR_{16}$; and

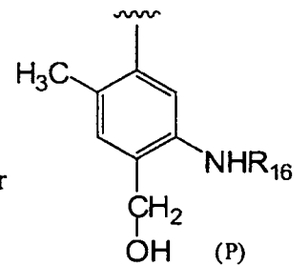
R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, $-CH_3$ and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl.

[0045] In another embodiment of the compound of Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, R_1 is



(N)

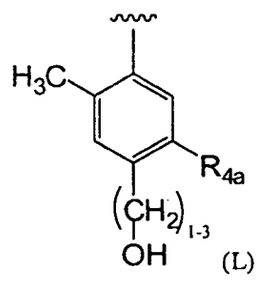
or



(P)

wherein R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, $-CH_3$ and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl.

[0046] In another embodiment of the compound of Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, R_1 is

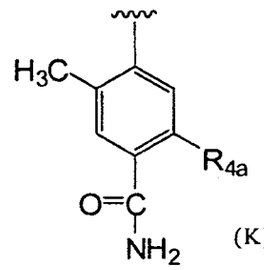


(L)

wherein R_{4a} is selected from $-N(H)R_{16}$, $-OR_{16}$, and $-SR_{16}$; and

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, $-CH_3$ and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl.

[0047] In another embodiment of the compound of Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, R_1 is

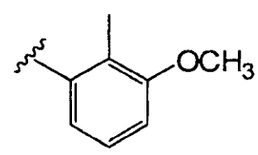


(K)

wherein R_{4a} is selected from $-N(H)R_{16}$, $-OR_{16}$, and $-SR_{16}$; and

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, $-CH_3$ and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl.

[0048] In another embodiment of the compound of Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, R_1 is



[0049] In another embodiment of the compound of Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, the heterocycloalkyl substituents of aryl in R_3 is piperazinyl, morpholinyl, azetidinyl or piperidinyl. In another embodiment, the heterocycloalkyl substituents of aryl in R_3 for Formula I, IB, IC, ID and IE is piperazinyl, morpholinyl or piperidinyl, wherein the piperazinyl, morpholinyl or piperidinyl is N-substituted with alkyl or phenyl. In other embodiments, the heterocycloalkyl substituents of aryl in R_3 for Formula I, IB, IC, ID or IE is piperazinyl, morpholinyl, azetidinyl or piperidinyl, and R_1 is of Formula (G), (H), (I), (K), (L), (N) or (P).

[0050] When any of the embodiments in this specification refers to a compound of Formula (G), (H), (I), (K), (L), (N) or (P), this is meant to mean that this embodiment includes each of Formula (G), (H), (I), (K), (L), (N) or (P) individually or in any combination of each other. For instance, when any of the embodiments in this specification refers to a compound of Formula (G), (H), (I), (K), (L), (N) or (P), this can be interpreted to include only compounds having Formula (G), or only compounds having Formula (H), or only compounds having Formula (I), or only compounds having Formula (K), or only compounds having Formula (L), or only compounds having Formula (N), or only compounds having Formula (P), or a combination of any two of Formula (G), (H), (I), (K), (L), (N) or (P), or a combination of any three of Formula (G), (H), (I), (K), (L), (N) or (P), or a combination of any four of Formula (G), (H), (I), (K), (L), (N) or (P), or a combination of any five of Formula (G), (H), (I), (K), (L), (N) or (P), or a combination of any six of Formula (G), (H), (I), (K), (L), (N) or (P), or all of Formula (G), (H), (I), (K), (L), (N) and (P).

[0051] Non-limiting examples of the heterocycloalkyl for Formula I, IB, IC, ID or IE, when R_3 is heterocycloalkyl, include piperidinyl, pyrrolidinyl, morpholinyl and piperizinyl. In another embodiment, this heterocycloalkyl group is piperidinyl or pyrrolidinyl. In another embodiment, this heterocycloalkyl group is piperidinyl. In another embodiment, this heterocycloalkyl group is pyrrolidinyl. In other embodiments, the heterocycloalkyl for Formula I, IB, IC, ID or IE, when R_3 is heterocycloalkyl, include piperidinyl, pyrrolidinyl, morpholinyl and piperizinyl, and R_1 is of Formula (G), (H), (I), (K), (L), (N) or (P).

[0052] Non-limiting examples of the dialkylaminoalkoxy in R_3 for Formula I, IB, IC, ID and IE include diethylaminoethoxy, ethylmethylaminoethoxy and dimethylaminoethoxy.

[0053] In other embodiments, the dialkylaminoalkoxy in R_3 for Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, is diethylaminoethoxy, ethylmethylaminoethoxy or dimethylaminoethoxy, and R_1 is of Formula (G), (H), (I), (K), (L), (N) or (P).

[0054] Non-limiting examples of the heterocycloalkyl for Formula I, IB, IC, ID and IE, or a pharmaceutically acceptable salt thereof, when R_5 is heterocycloalkyl, include piperidinyl or piperizinyl, In another embodiment, the piperidinyl or

piperizinyl is N-substituted with methyl. In other embodiments, the heterocycloalkyl for Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, when R_5 is heterocycloalkyl, is piperidinyl or piperizinyl, and R_1 is of Formula (G), (H), (I), (K), (L), (N) or (P).

[0055] Non-limiting examples of the heterocycloalkyl substituents of aryl in R_5 for Formula I, IB, IC, ID and IE, or a pharmaceutically acceptable salt thereof, include piperazinyl, morpholinyl and piperidinyl. In other embodiments, the heterocycloalkyl substituent of aryl in R_5 for Formula I, IB, IC, ID and IE, or a pharmaceutically acceptable salt thereof, is piperazinyl, morpholinyl or piperidinyl, and R_1 is of Formula (G), (H), (I), (K), (L), (N) or (P).

[0056] In other embodiments, R_3 for the compound of Formula I, IB, IC, ID or IE.or a pharmaceutically acceptable salt thereof, is cycloalkyl, such as cylcopentyl, cyclobutyl or cyclopropyl as non-limiting examples. In other embodiments, R_3 for the compound of Formula I, IB, IC, ID or IE is cylcopentyl, cyclobutyl or cyclopropyl, and R_1 is of Formula (G), (H), (I), (K), (L), (N) or (P).

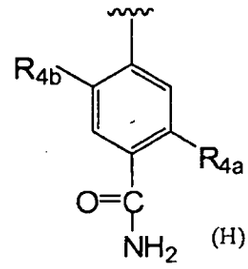
[0057] In other embodiments, R_3 for the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, is heterocycloalkyl, such as pyrrolidinyl, piperidinyl or azetidinyl as non-limiting examples. In other embodiments, R_3 for the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, is cylcopentyl, cyclobutyl or cyclopropyl, and R_1 is of Formula (G), (H), (I), (K), (L), (N) or (P).

[0058] In other embodiments, R_3 for the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, is heteroaryl. In other embodiments, R_3 for the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, is heteroaryl, and R_1 is of Formula (G), (H), (I), (K), (L), (N) or (P).

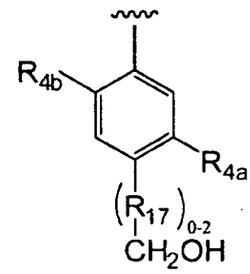
[0059] In other embodiments, R_3 for the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, is H. In other embodiments, R_3 for the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, is H, and R_1 is of Formula (G), (H), (I), (K), (L), (N) or (P).

[0060] In other embodiments, R_3 for the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, is arylalkyl, such as phenylmethyl as a non-limiting example. In other embodiments, R_3 for the compound of Formula I, IB, IC, ID or IE is arylalkyl, and R_1 is of Formula (G), (H), (I), (K), (L), (N) or (P).

[0061] In other embodiments of the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, R_1 is



(H) or



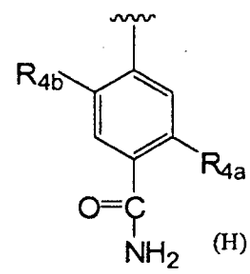
(I)

wherein R_{4a} is cycloalkylamino optionally substituted with -OH, alkyl, $-CF_3$, or heterocycloalkyl;

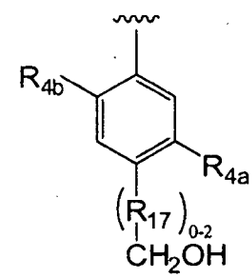
R_{4b} is selected from H, halo and methyl optionally substituted with 1-3 halogens; and R_{17}, when present, is $-CH_2-$ or -CH(OH)-. In this embodiment, L_1 can be -N(H)C(O)-.

[0062] Non-limiting examples of R_{4a} for any of the above embodiments include trans-4-hydroxycyclohexylamino, cyclohexylamino, cyclopentylamino, cyclopropylamino, cis-4-hydroxy-4-methylcyclohexylamino, 4-(trifluoromethyl)cyclohexylamino and trans-4-piperidin-1-ylcyclohexylamino.

[0063] In other embodiments of the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, R_1 is



(H) or



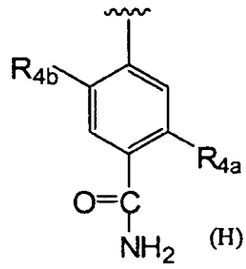
(I)

wherein R_{4a} is trans-4-hydroxycyclohexylamino, cyclohexylamino, cyclopentylamino, cyclopropylamino, cis-4-hydroxy-4-methylcyclohexylamino, 4-(trifluoromethyl)cyclohexylamino or trans-4-piperidin-1-ylcyclohexylamino;

R_{4b} is selected from H, halo and methyl optionally substituted with 1-3 halogens; and

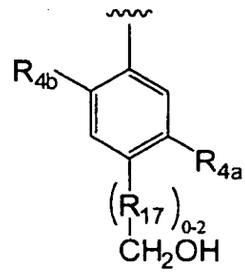
R_{17}, when present, is $-CH_2-$ or -CH(OH)-.

[0064] In other embodiments of the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, R_1 or a pharmaceutically acceptable salt thereof, is



(H)

or



(I)

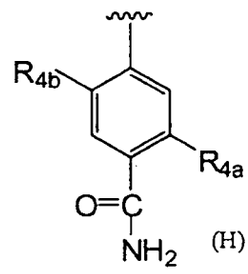
wherein R_{4a} is cycloalkylalkylamino;

R_{4b} is selected from H, halo and methyl optionally substituted with 1-3 halogens. In this embodiment, L_1 can be -N(H)C(O)-; and

R_{17}, when present, is $-CH_2-$ or -CH(OH)-.

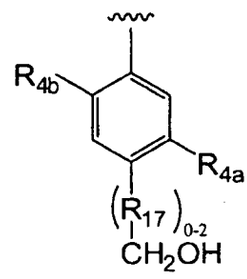
[0065] A non-limiting example of R_{4a} for any of the above embodiments includes cyclopropylmethylamino.

[0066] In other embodiments of the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, R_1 is



(H)

or



(I)

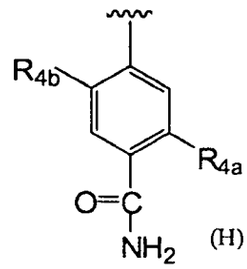
wherein R_{4a} is alkylamino optionally substituted with 1-8 halo;

R_{4b} is selected from H, halo and methyl optionally substituted with 1-3 halogens; and R_{17}, when present, is $-CH_2-$ or -CH(OH)-. In this embodiment, L_1 can be -N(H)C(O)-.

[0067] Non-limiting examples of R_{4a} for any of the above embodiments include 1-methylethylamino, ethylamino, 1-ethylpropylamino, 2-methylpropylamino, (2,2-dimethylpropyl)amino, (2-aminoethyl)amino, (2,2,3,3,3-pentafluoropropyl)amino, 1-methylpropylamino, (1S)-1-methylpropylamino, (2,2,2-trifluoroethyl)amino, 1-propylbutylamino, propylamino, 1,2-dimethylpropylamino, (3,3,3-trifluoropropyl)amino, (2,2,3,3,4,4,4-heptafluorobutyl)amino, butylamino, 1,2,2-trimethylpropylamino, 1-[(methyloxy)methyl]propylamino, 1-methylethyloxyethylamino, 1-methylpropylamino, pentylamino, (2,2,3,3,3-pentafluoropropyl)amino, butylamino, 2-[(1-methylethyl)oxy]ethylamino, (1S)-1-methylpropylamino, (1R)-1-methylpropylamino, (1S)-1,2-dimethylpropylamino, 1-

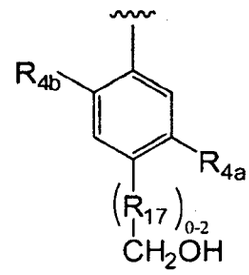
cyclopropylethylamino, (1R)-1,2-dimethylpropylamino, 1-ethyl-2-methylpropylamino, and 3-[(1-methylethyl)amino]propylamino.

[0068] In other embodiments of the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, R_1 is



(H)

or

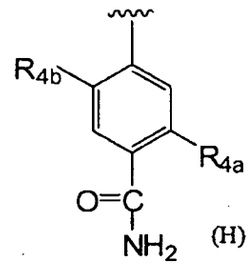


(I)

wherein R_{4a} is heterocycloalkylamino optionally substituted with alkyl; R_{4b} is selected from H, halogen and methyl optionally substituted with 1-3 halogens; and R_{17}, when present, is $-CH_2-$ or -CH(OH)-. In this embodiment, L_1 can be -N(H)C(O)-.

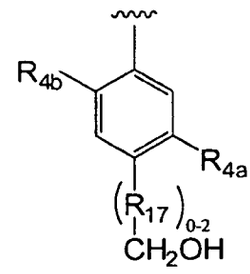
[0069] Non-limiting examples of R_{4a} for any of the above embodiments include tetrahydrofuran-3-ylamino, piperidin-4-ylamino, tetrahydro-2H-pyran-4-ylamino, (1-ethylpiperidin-4-yl)amino, (tetrahydrofuran-2-ylmethyl)amino, pyrrolidin-3-ylamino, (piperidin-3-ylmethyl)amino, (pyrrolidin-3-ylmethyl)amino, (3S)-tetrahydrofuran-3-ylamino, (3R)-tetrahydrofuran-3-ylamino, azetidin-1-yl, piperidin-1-ylamino, and (3S)-tetrahydrofuran-3-ylamino.

[0070] In other embodiments of the compound of Formula I, IB, IC, ID or IE, R_1 is



(H)

or



(I)

wherein R_{4a} is -N(H)-aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkoxy or dialkylaminoalkoxy;

R_{4b} is selected from H, halogen and methyl optionally substituted with 1-3 halogens; and

R_{17}, when present, is $-CH_2-$ or -CH(OH)-.

In this embodiment, L_1 can be -N(H)C(O)-.

[0071] Non-limiting examples of R_{4a} for any of the above embodiments include phenylamino, (phenylmethyl)amino, (3-{[2-(dimethylamino)ethyl]oxy}phenyl)amino, 3-{[2-(dimethylamino)-4-(methyloxy)ethyl]oxy}phenyl)amino and {4-(methyloxy)-3-[(2-morpholin-4-ylethyl)oxy]phenyl}amino.

[0072] In another embodiment, R_1 in Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, is selected from one of Group Z; R_{4a} is (2,2,3,3,3-pentafluoropropyl)amino, butylamino, 2-[(1-methylethyl)oxy]ethylamino, (1S)-1-methylpropyl]amino, (1-methylpropyl)amino, (1R)-1-methylpropyl]amino, 2-(propylamino), (1S)-1,2-dimethylpropyl]amino, (1-cyclopropylethyl)amino, (1R)-1,2-dimethylpropyl]amino or 2,2-dimethylpropylamino; and R_{4b} is H.

[0073] In another embodiment, R_1 in Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, is selected from one of Group Z; R_{4a} is1-ethylpropylamino; and R_{4b} is chloro, fluoro, bromo, or methyl.

[0074] In other embodiments, R_1 in Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, s selected from one of Group Z; R_{4a} is 1-ethyl-2-methylpropyl)amino, (1R)-1-methylpropylamino, 1-cyclopropylethylamino, 1-cyclopropylpropylamino, (1R)-1,2,2-trimethylpropylamino, (1R)-1,2-dimethylpropylamino, 3,3,3-trifluoro-1-methylpropylamino, 2-methyl-1-trifluoromethylpropylamino, 2-methyl-1-(1-methylethyl)propylamino, 1-methylethylamino, dicyclopropylmethylamino, cyclopentylamino, trifluoromethylpropylamino, 2-methylpropylamino, cyclopentylmethylamino, cyclobutylamino, (1S)-1-methylpropylamino, 3,3,3-trifluoropropylamino, propylamino or 2-fluoro-1-(fluoromethyl)ethylamino; and R_{4b} is methyl.

[0075] In other embodiments, R_1 in Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, is selected from one of Group Z; R_{4a} is 1-ethylpropylamino or (1R)-1-methylpropylamino; and R_{4b} is CF_3.

[0076] In other embodiments, R_1 in Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, is selected from one of Group Z; R_{4a} is (1R)-1-methylpropylamino, 1-methylethylamino, cyclopentylamino, 2-methylpropylamino, 2,2-dimethylpropylamino, (1R)-1,2-dimethylpropylamino, propylamino, (3,3,3-trifluoropropyl)amino or cyclobutylamino; and R_{4b} is Br.

[0077] In other embodiments, R_1 in Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, is selected from one of Group Z; R_{4a} is

SS

(cyclopropylmethyl)amino, (1-ethylpropyl)amino, (cis-4-hydroxy-4-methylcyclohexyl)amino or (trans-4-piperidin-1-ylcyclohexyl)amino; and R_{4b} is H.

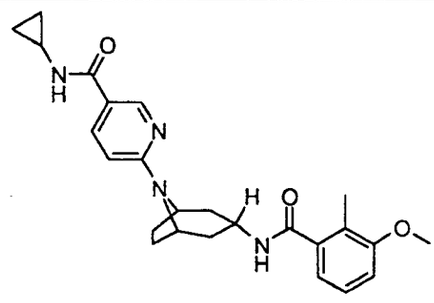
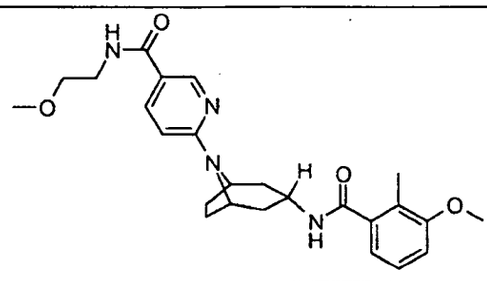
[0078] In other embodiments, R_1 in Formula I, IB, IC, ID, or IE is selected from one of Group Z; R_{4a} is cyclopropylmethylamino or 1-(1-methylcyclopropyl)ethylamino; and R_{4b} is methyl.

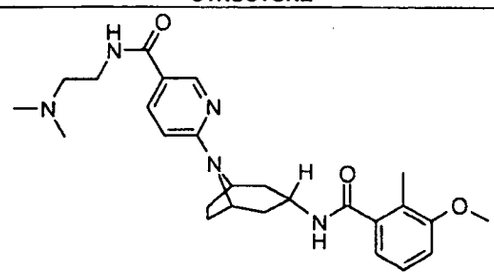
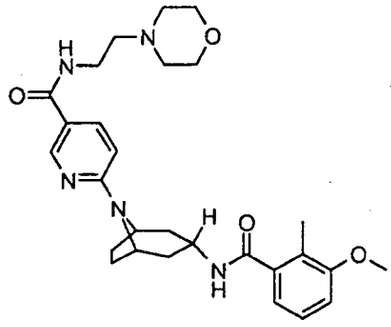
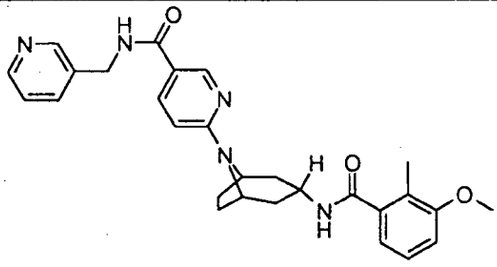
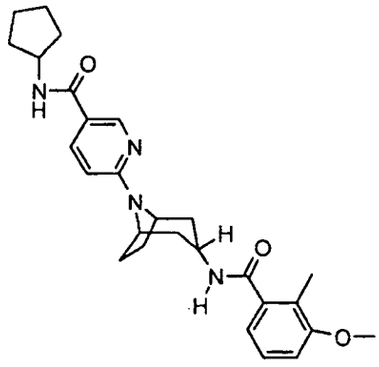
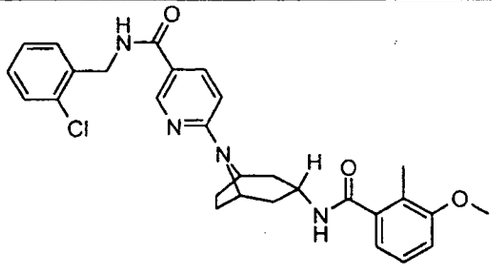
[0079] In other embodiments, R_1 in Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, is selected from one of Group Z; R_{4a} is pyridin-4-ylamino; and R_{4b} is H.

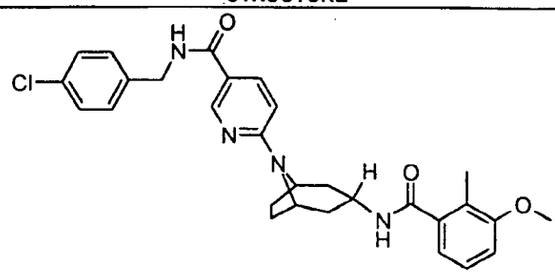
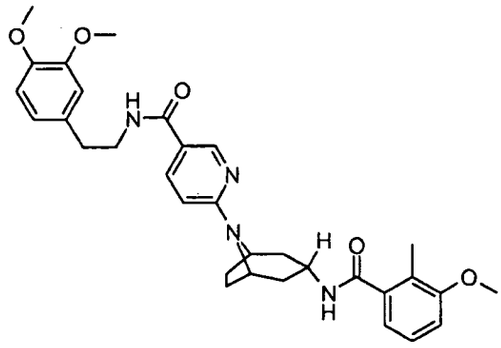
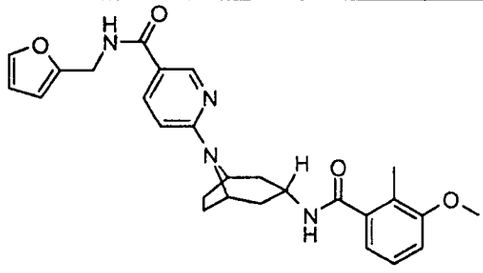
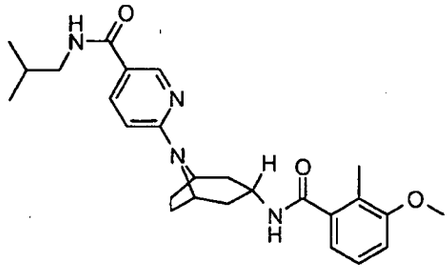
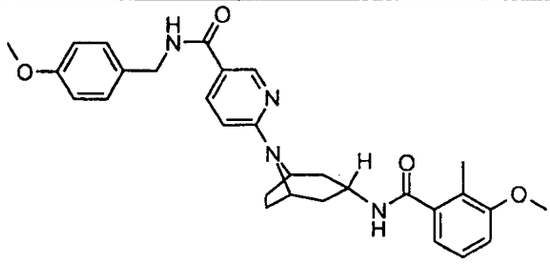
[0080] In another embodiment, R_1 in Formula I, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof, is selected from one of Group Z; R_{4a} is (3S)-tetrahydrofuran-3-ylamino; and R_{4b} is methyl.

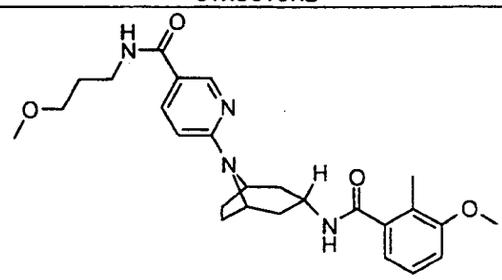
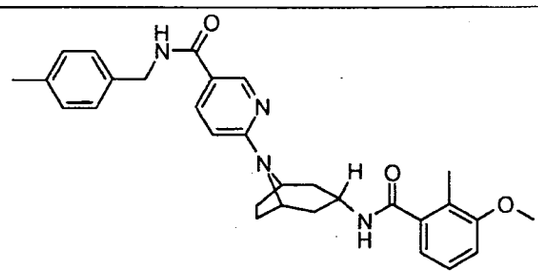
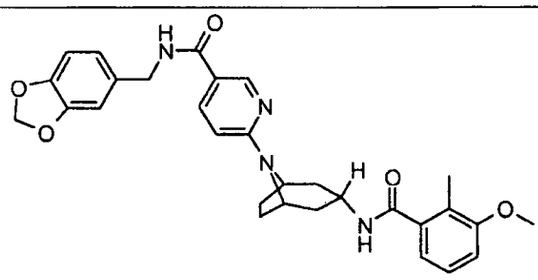
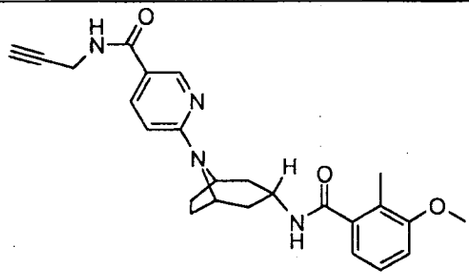
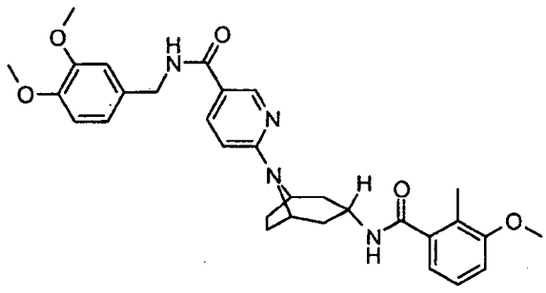
[0081] In another embodiment, the compound of Formula I is selected from one of the following compounds from Table I, or a pharmaceutically acceptable salt of any of the compounds in Table I:

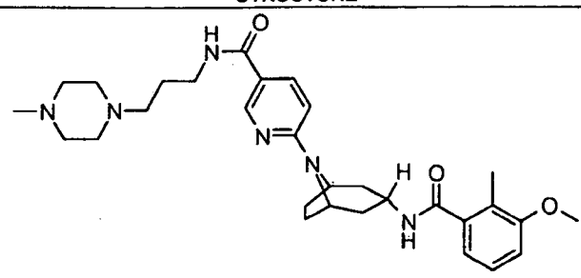
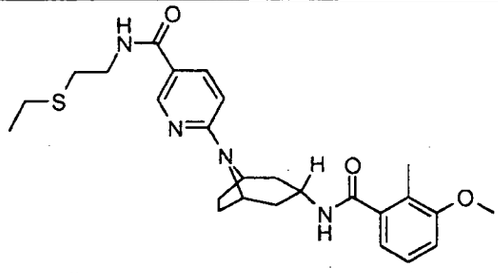
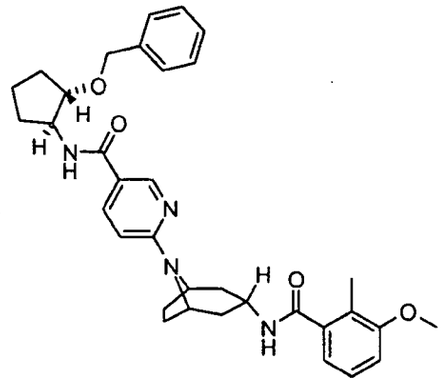
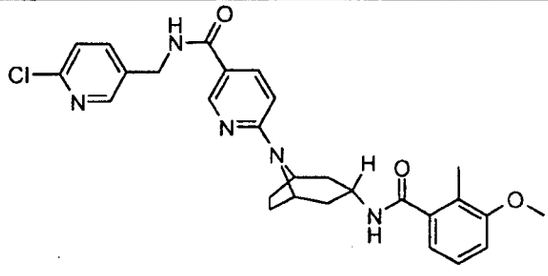
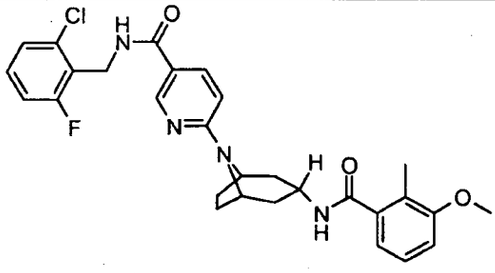
TABLE I

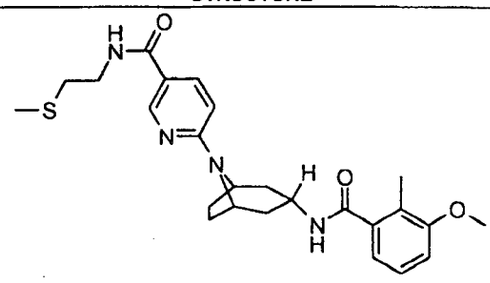
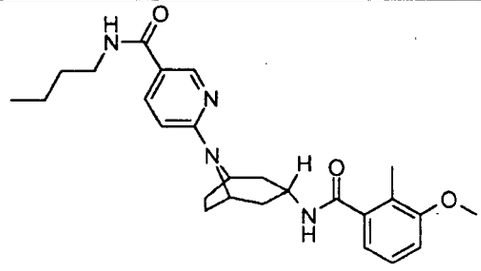
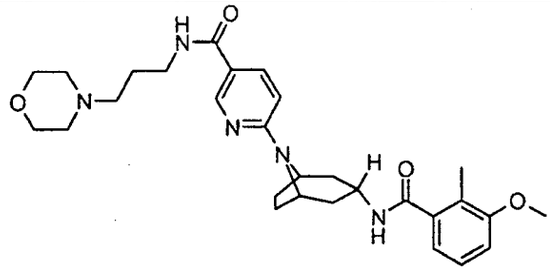
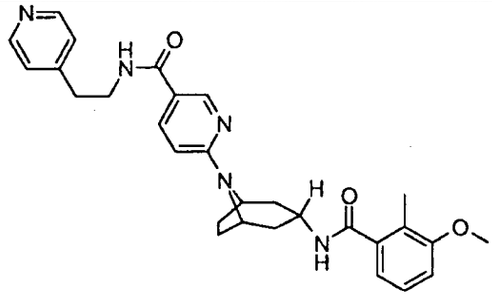
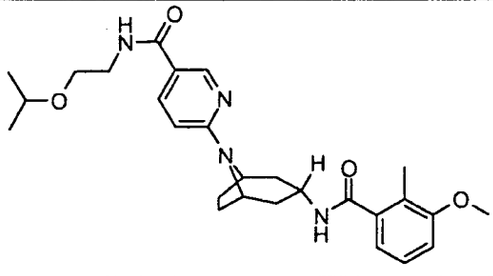
STRUCTURE	NAME & ACTIVITY
	N-cyclopropyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide ACTIVITY = C
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(methyloxy)ethyl]pyridine-3-carboxamide ACTIVITY = D

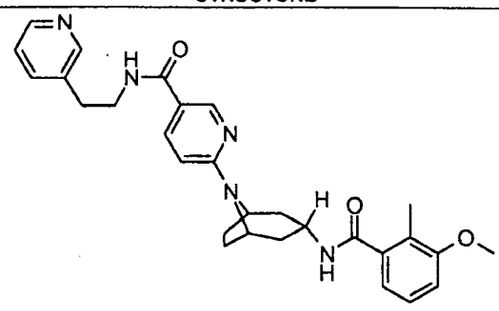
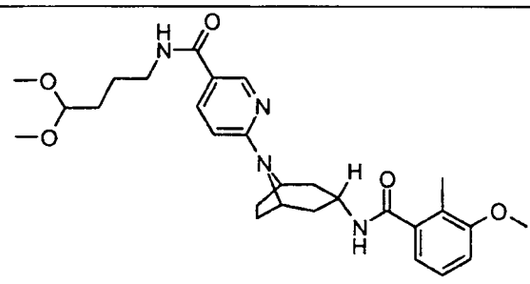
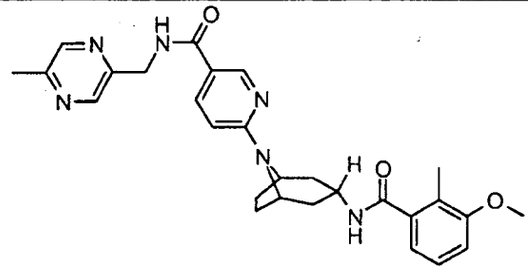
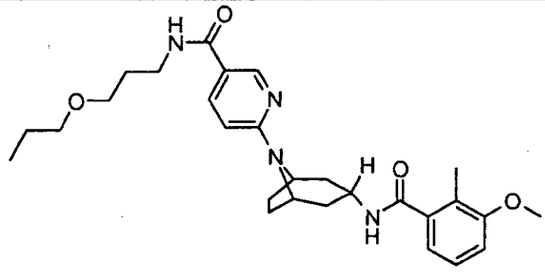
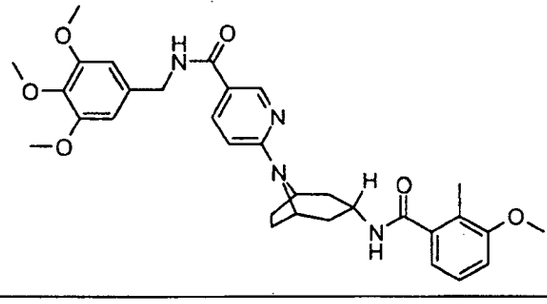
STRUCTURE	NAME & ACTIVITY
	N-[2-(dimethylamino)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-morpholin-4-ylethyl)pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyridin-3-ylmethyl)pyridine-3-carboxamide **ACTIVITY = A**
	N-cyclopentyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-[(2-chlorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**

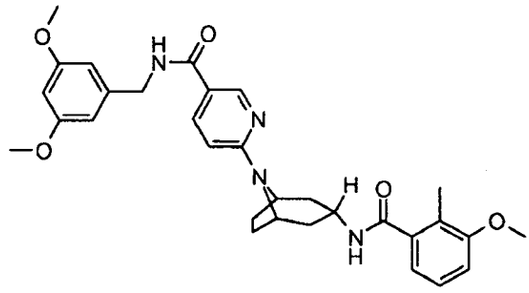
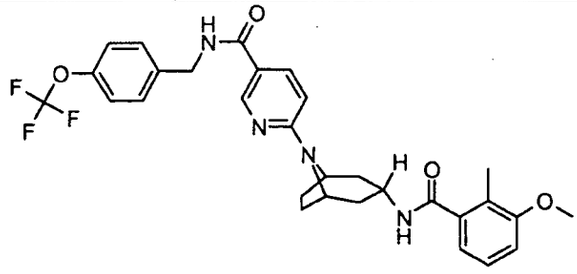
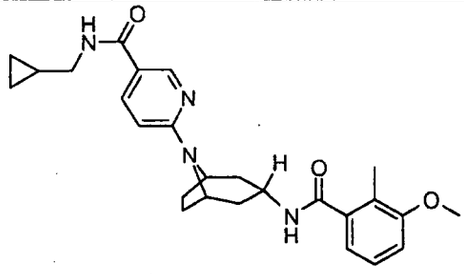
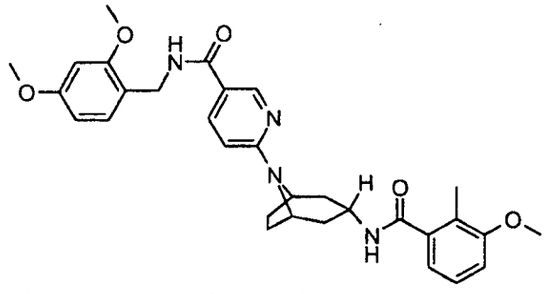
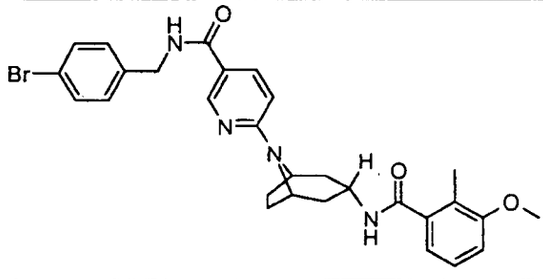
STRUCTURE	NAME & ACTIVITY
	N-[(4-chlorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-{2-[3,4-bis(methyloxy)phenyl]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	N-(furan-2-ylmethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-methylpropyl)pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(methyloxy)phenyl]methyl}pyridine-3-carboxamide **ACTIVITY = A**

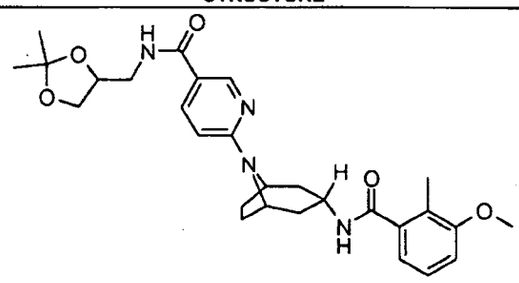
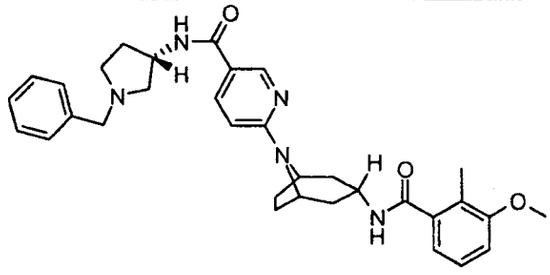
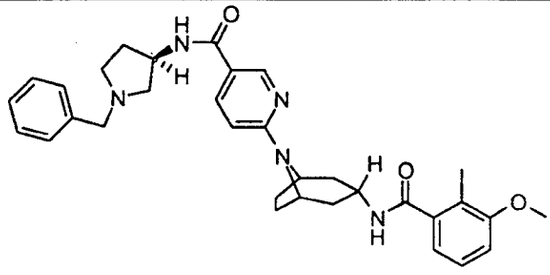
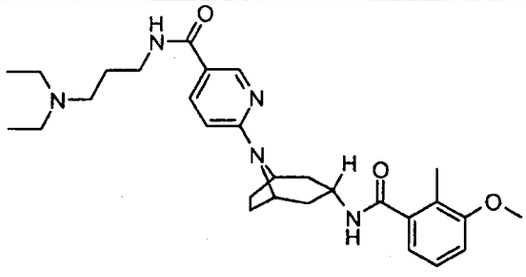
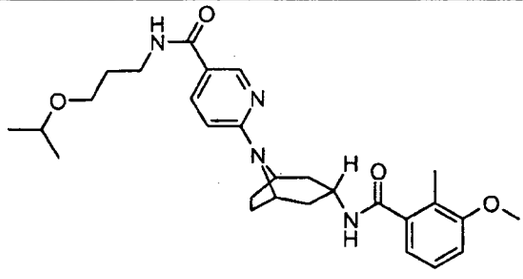
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(methyloxy)propyl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-methylphenyl)methyl]pyridine-3-carboxamide **ACTIVITY = A**
	N-(1,3-benzodioxol-5-ylmethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-prop-2-yn-1-ylpyridine-3-carboxamide **ACTIVITY = C**
	N-{[3,4-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY =**

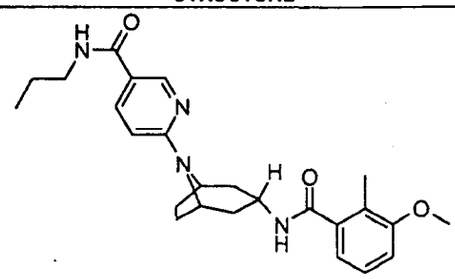
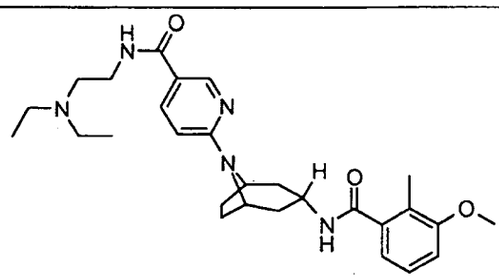
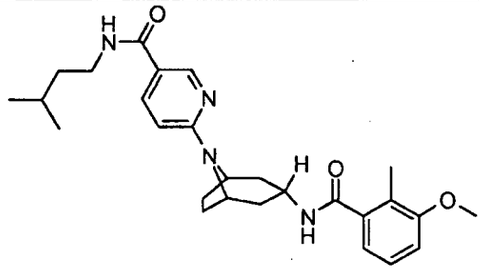
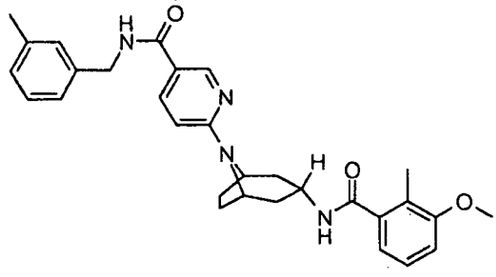
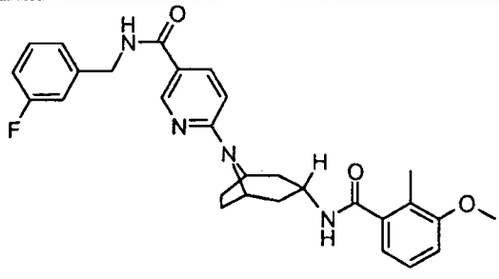
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(4-methylpiperazin-1-yl)propyl]pyridine-3-carboxamide **ACTIVITY = B**
	N-[2-(ethylthio)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S,2S)-2-[(phenylmethyl)oxy]cyclopentyl}pyridine-3-carboxamide **ACTIVITY = D**
	N-[(6-chloropyridin-3-yl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-[(2-chloro-6-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**

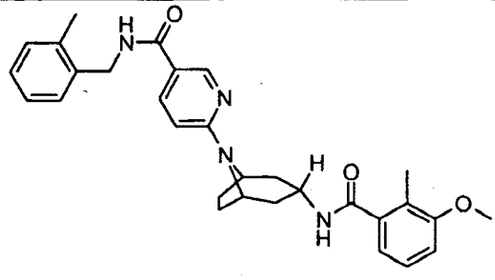
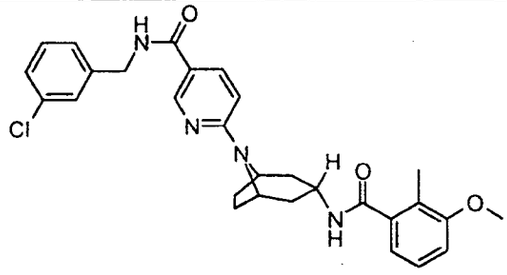
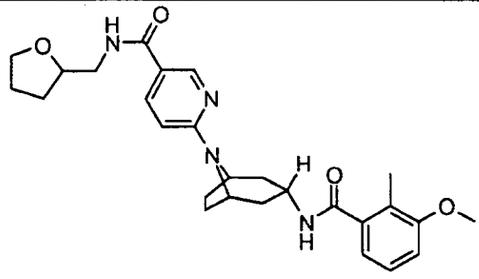
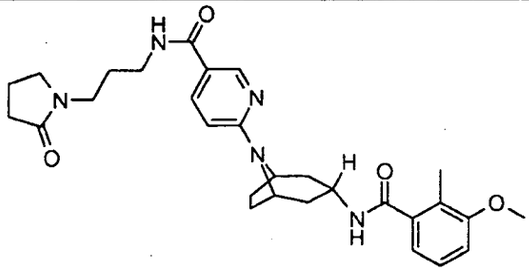
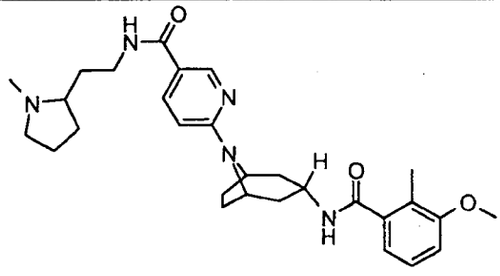
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(methylthio)ethyl]pyridine-3-carboxamide **ACTIVITY = C**
	N-butyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(3-morpholin-4-ylpropyl)pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-pyridin-4-ylethyl)pyridine-3-carboxamide **ACTIVITY = C**
	N-{2-[(1-methylethyl)oxy]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**

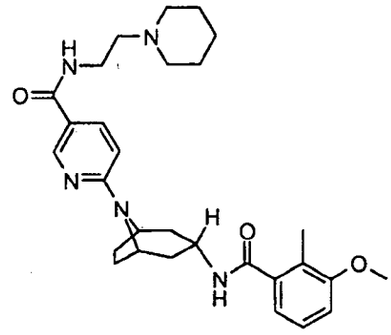
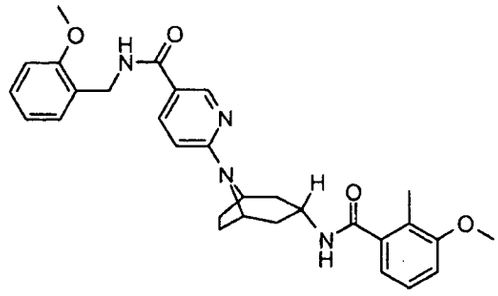
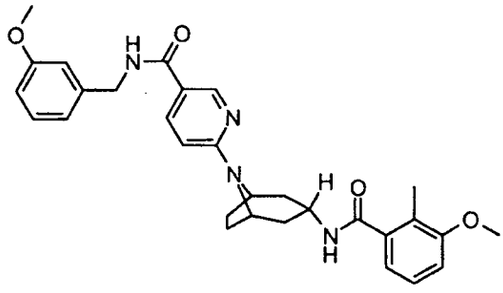
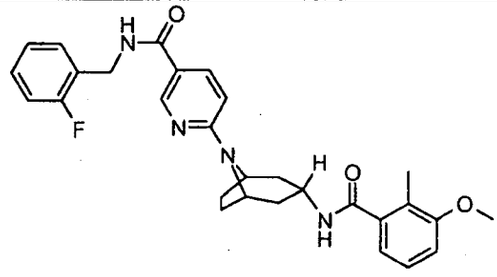
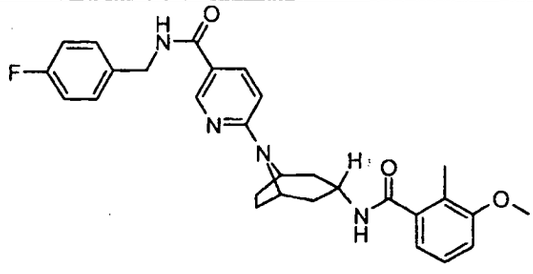
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-pyridin-3-ylethyl)pyridine-3-carboxamide **ACTIVITY = C**
	N-[4,4-bis(methyloxy)butyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(5-methylpyrazin-2-yl)methyl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-endo-(propyloxy)propyl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[3,4,5-tris(methyloxy)phenyl]methyl}pyridine-3-carboxamide **ACTIVITY = C**

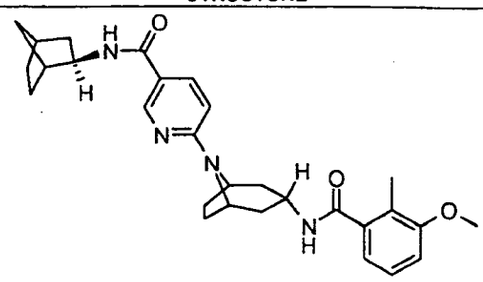
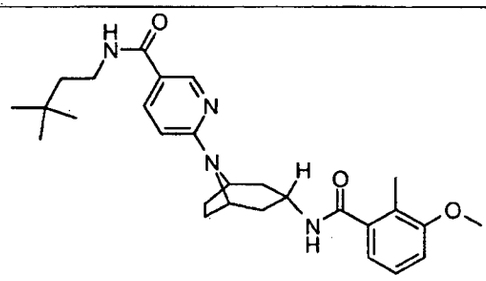
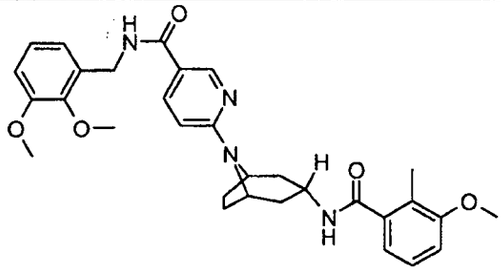
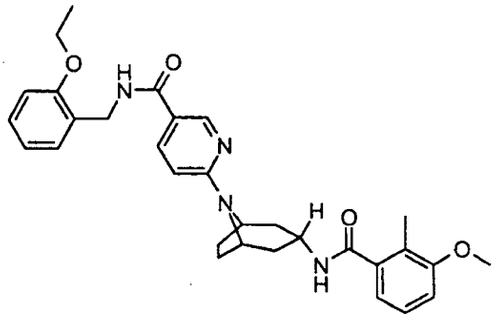
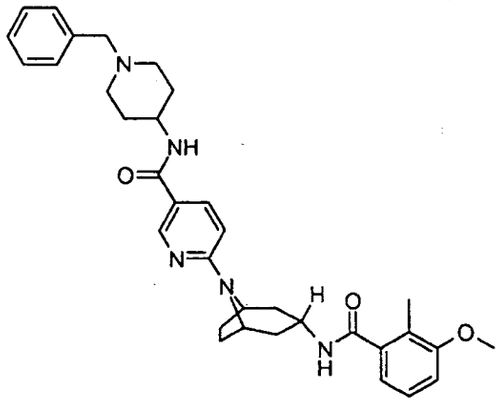
STRUCTURE	NAME & ACTIVITY
	N-{[3,5-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-({4-[(trifluoromethyl)oxy]phenyl}methyl)pyridine-3-carboxamide **ACTIVITY = D**
	N-(cyclopropylmethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-{[2,4-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-[(4-bromophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**

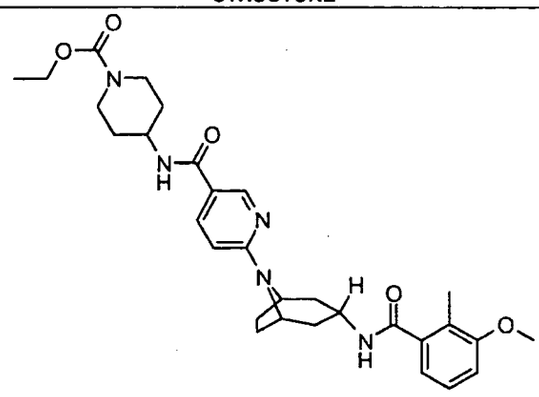
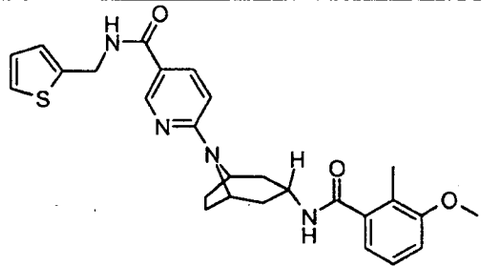
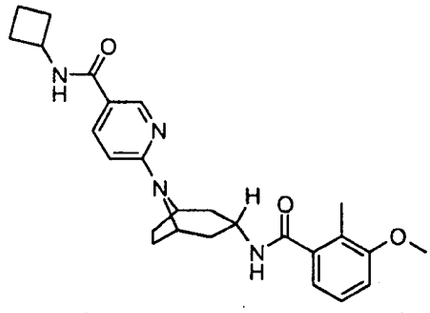
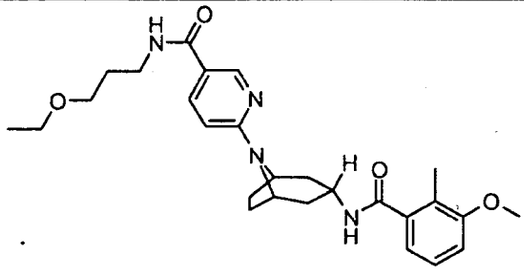
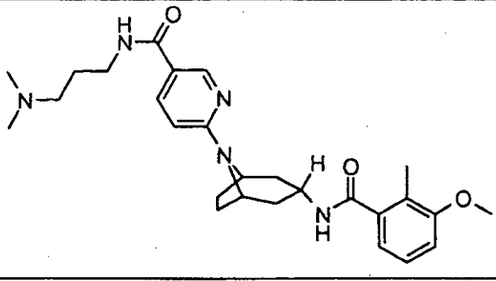
STRUCTURE	NAME & ACTIVITY
	N-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3S)-1-(phenylmethyl)pyrrolidin-3-yl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3R)-1-(phenylmethyl)pyrrolidin-3-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-[3-(diethylamino)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-{3-[(1-methylethyl)oxy]propyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**

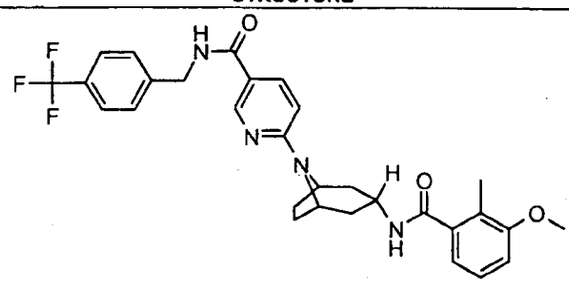
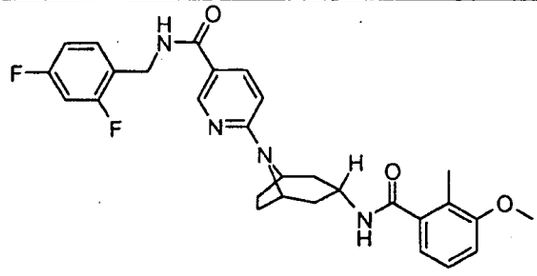
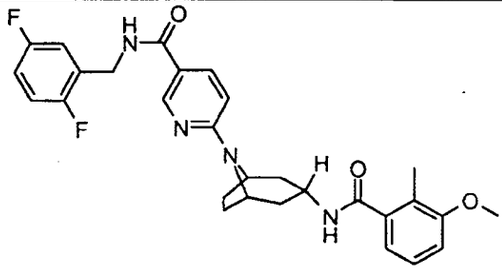
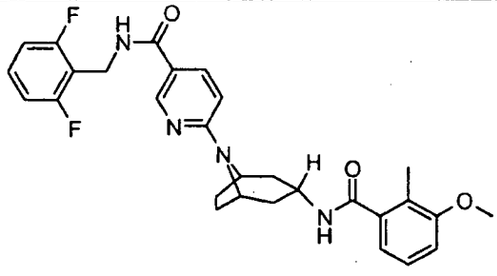
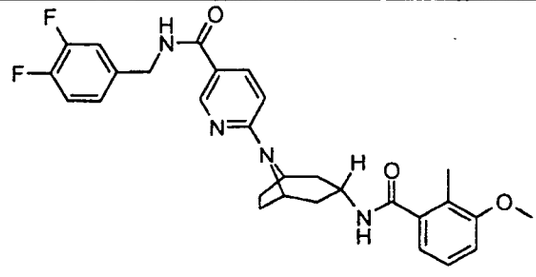
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-propylpyridine-3-carboxamide **ACTIVITY = C**
	N-[2-(diethylamino)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-(3-methylbutyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3-methylphenyl)methyl]pyridine-3-carboxamide **ACTIVITY = D**
	N-[(3-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**

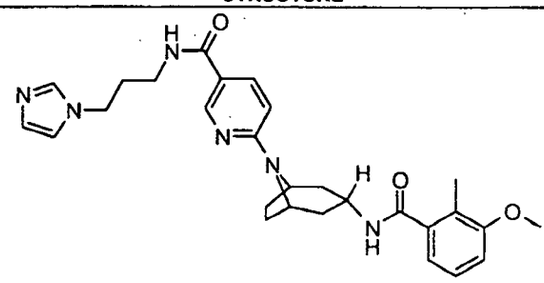
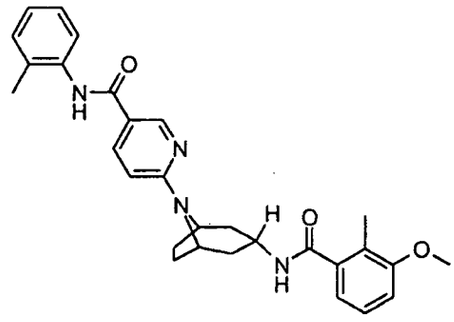
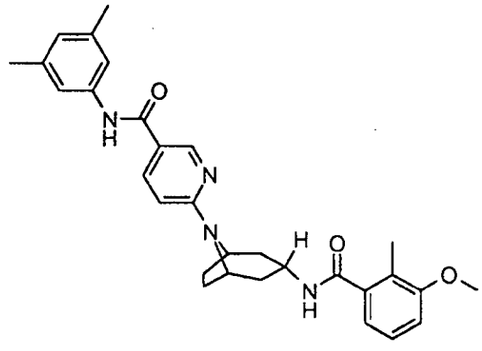
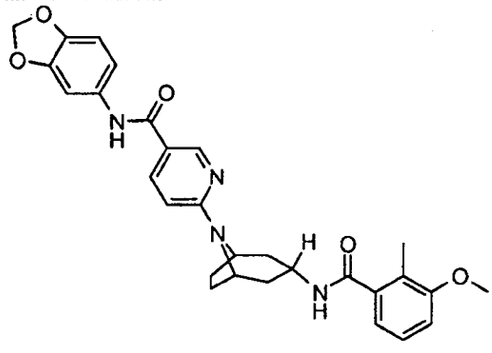
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2-methylphenyl)methyl]pyridine-3-carboxamide **ACTIVITY = A**
	N-[(3-chlorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(tetrahydrofuran-2-ylmethyl)pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(1-methylpyrrolidin-2-yl)ethyl]pyridine-3-carboxamide **ACTIVITY = B**

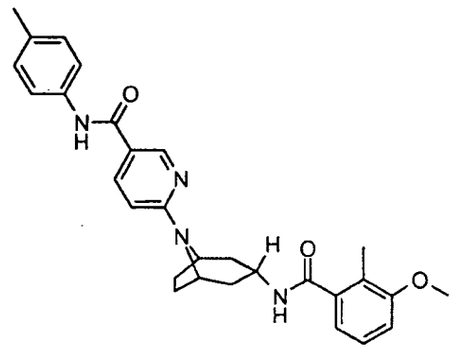
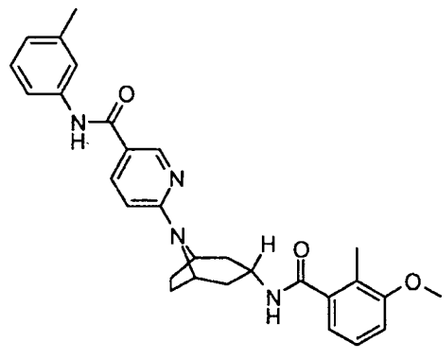
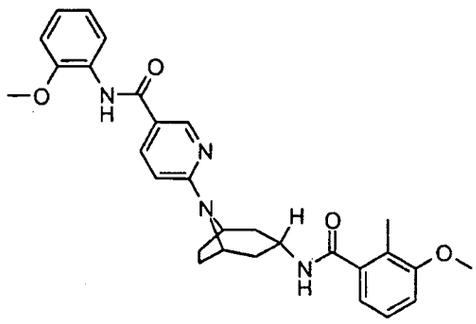
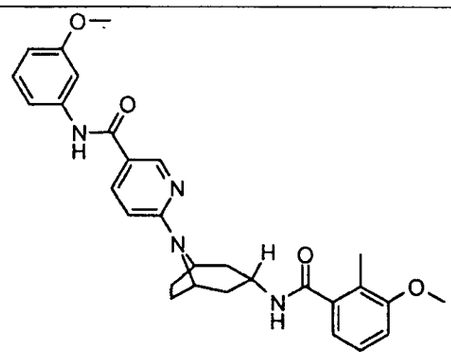
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-piperidin-1-ylethyl)pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[2-(methyloxy)phenyl]methyl}pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[3-(methyloxy)phenyl]methyl}pyridine-3-carboxamide **ACTIVITY = D**
	N-[(2-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-[(4-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**

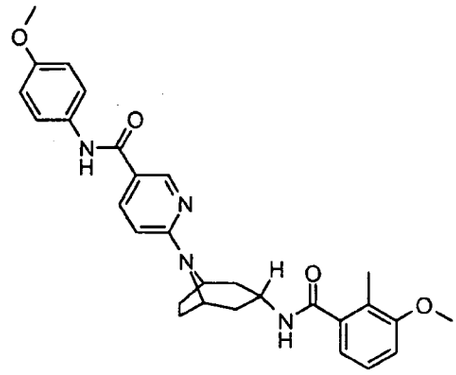
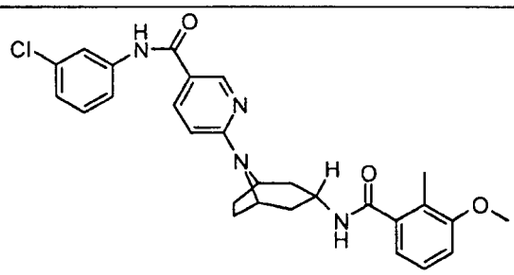
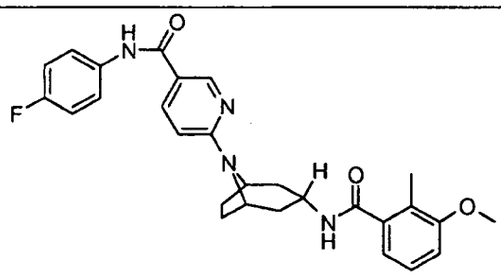
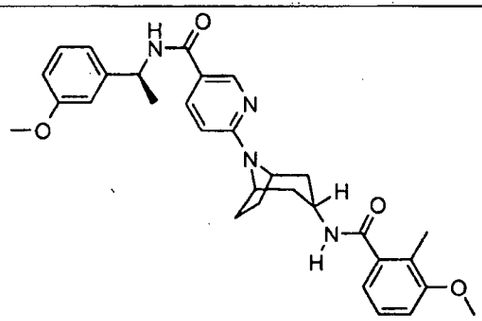
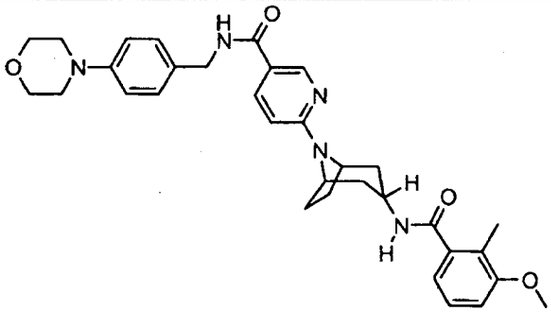
STRUCTURE	NAME & ACTIVITY
	N-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-yl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	N-(3,3-dimethylbutyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	N-{[2,3-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	N-{[2-(ethyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[1-(phenylmethyl)piperidin-4-yl]pyridine-3-carboxamide **ACTIVITY = A**

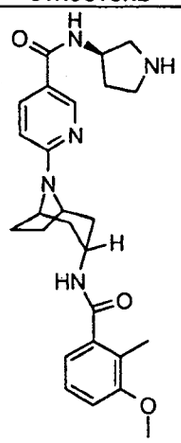
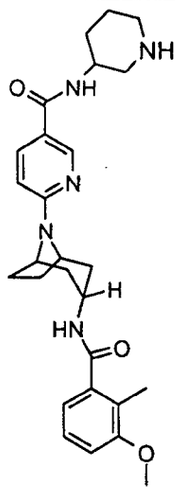
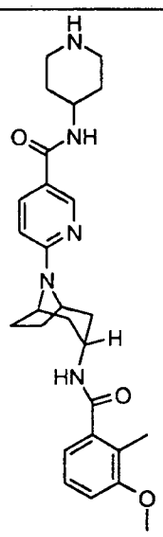
STRUCTURE	NAME & ACTIVITY
	ethyl 4-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino]piperidine-1-carboxylate **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-thienylmethyl)pyridine-3-carboxamide **ACTIVITY = A**
	N-cyclobutyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-[3-(ethyloxy)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	N-[3-(dimethylamino)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**

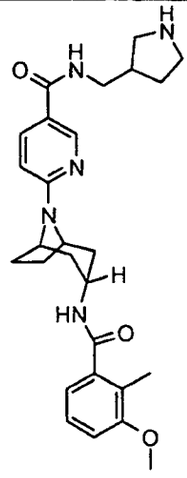
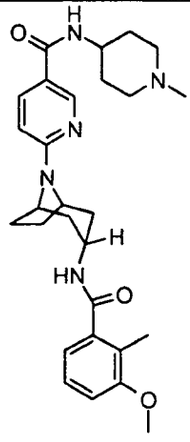
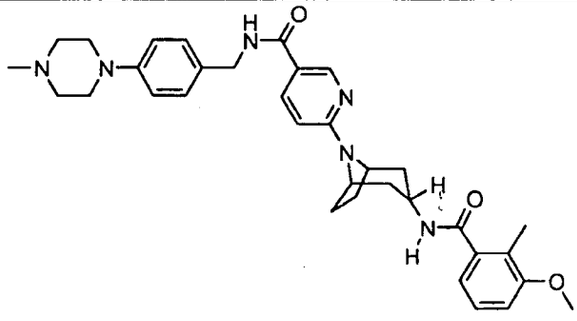
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(trifluoromethyl)phenyl]methyl}pyridine-3-carboxamide **ACTIVITY = C**
	N-[(2,4-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-[(2,5-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-[(2,6-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-[(3,4-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**

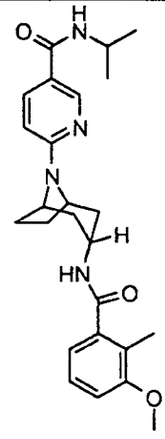
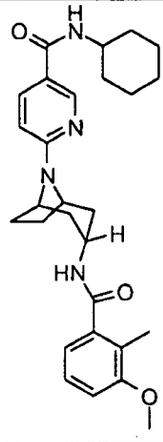
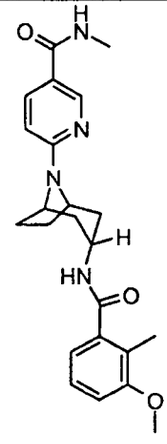
STRUCTURE	NAME & ACTIVITY
	N-[3-(1H-imidazol-1-yl)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-methylphenyl)pyridine-3-carboxamide **ACTIVITY = D**
	N-(3,5-dimethylphenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	N-1,3-benzodioxol-5-yl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**

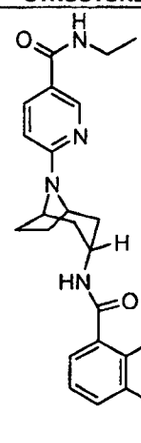
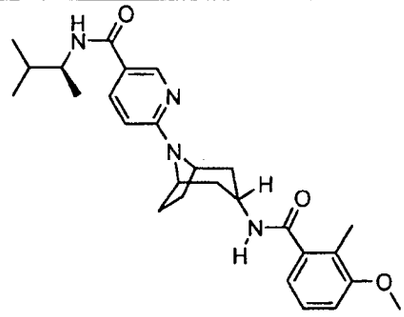
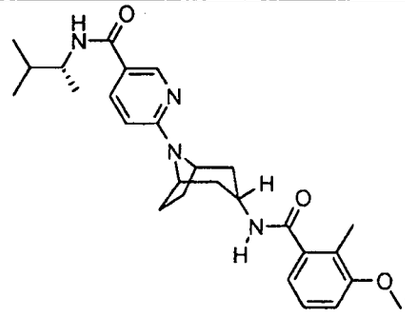
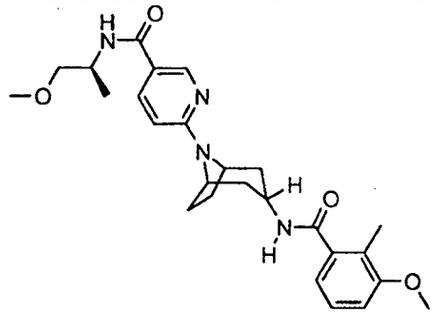
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(4-methylphenyl)pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(3-methylphenyl)pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(methyloxy)phenyl]pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(methyloxy)phenyl]pyridine-3-carboxamide **ACTIVITY = D**

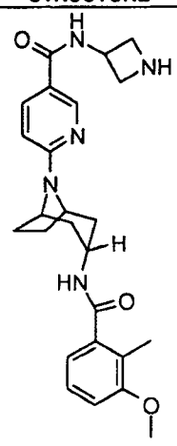
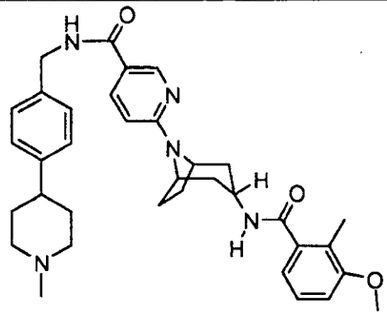
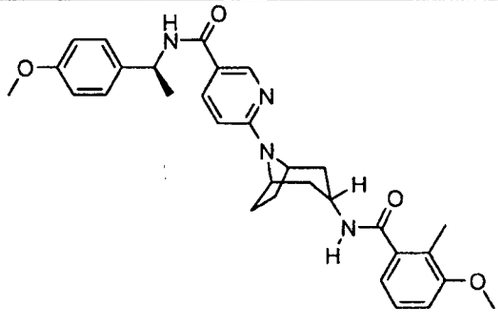
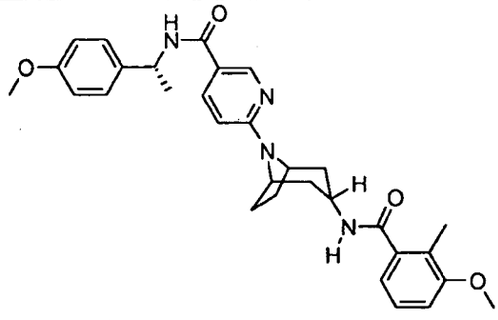
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[4-(methyloxy)phenyl]pyridine-3-carboxamide **ACTIVITY = B**
	N-(3-chlorophenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	N-(4-fluorophenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[3-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-morpholin-4-ylphenyl)methyl]pyridine-3-carboxamide **ACTIVITY = A**

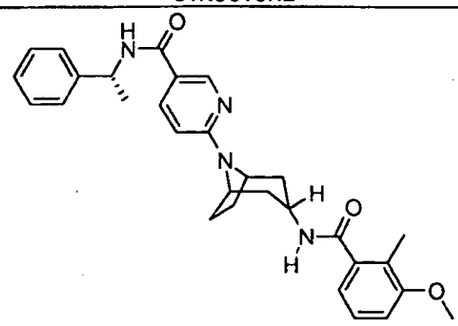
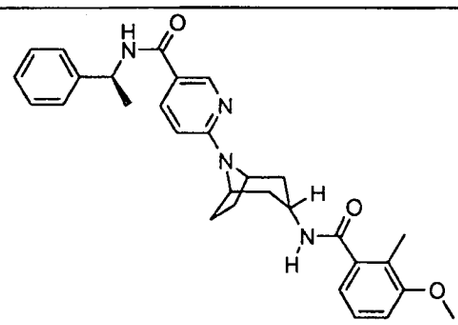
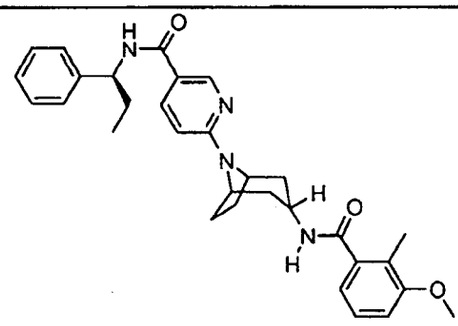
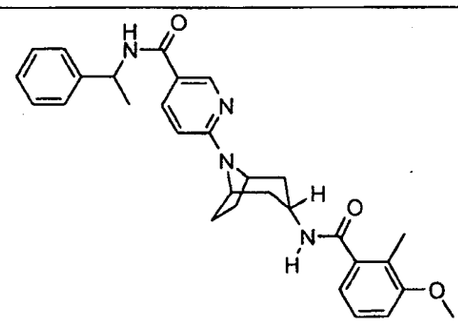
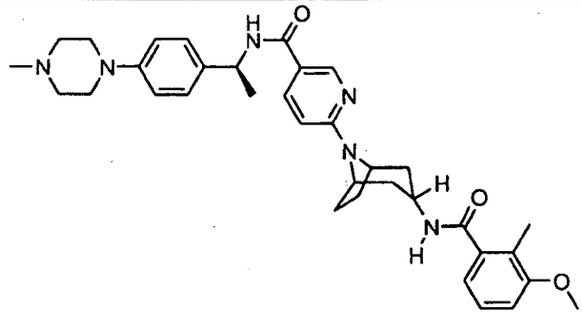
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3R)-pyrrolidin-3-yl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-piperidin-3-ylpyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-piperidin-4-ylpyridine-3-carboxamide **ACTIVITY = A**

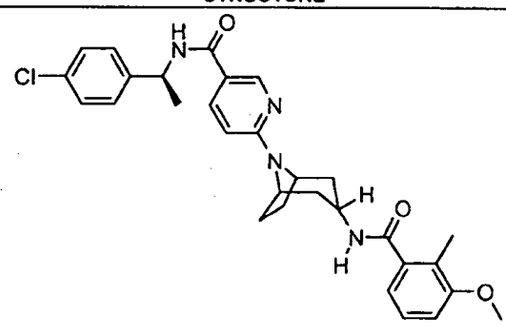
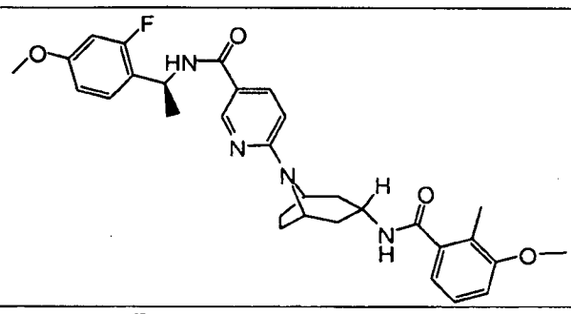
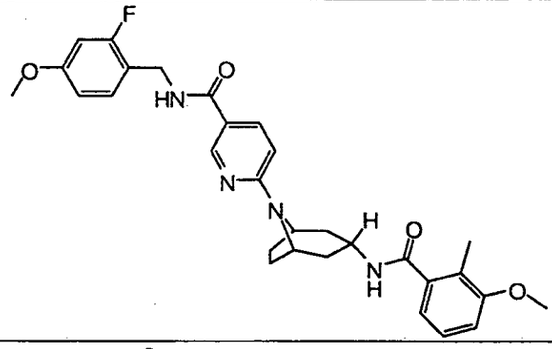
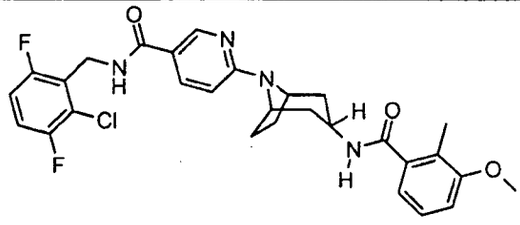
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyrrolidin-3-ylmethyl)pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(1-methylpiperidin-4-yl)pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide **ACTIVITY = A**

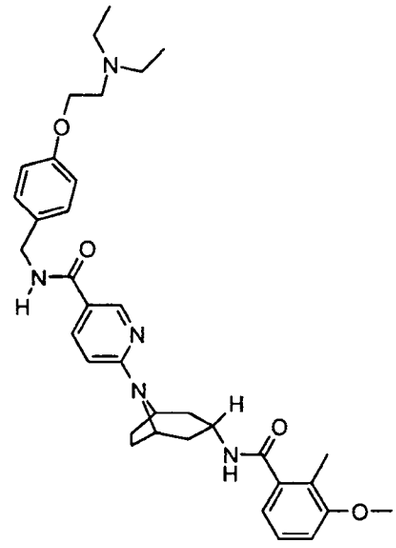
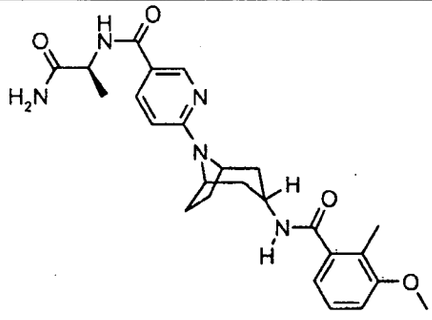
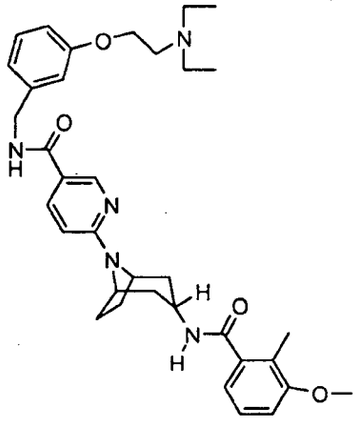
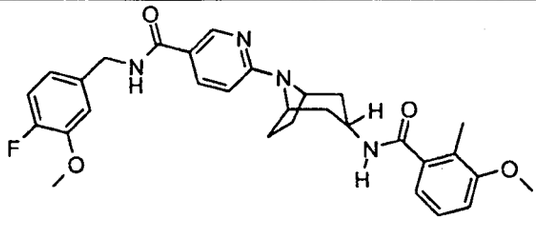
STRUCTURE	NAME & ACTIVITY
	N-(1-methylethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	N-cyclohexyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-methyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**

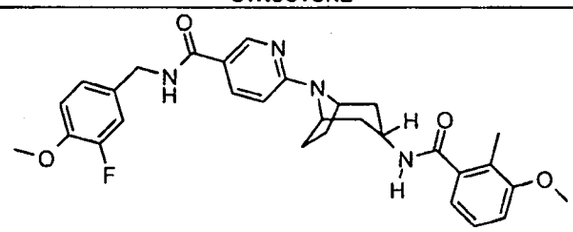
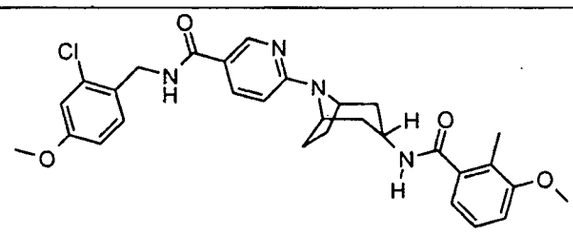
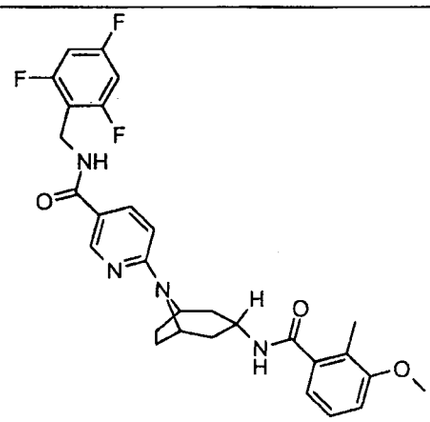
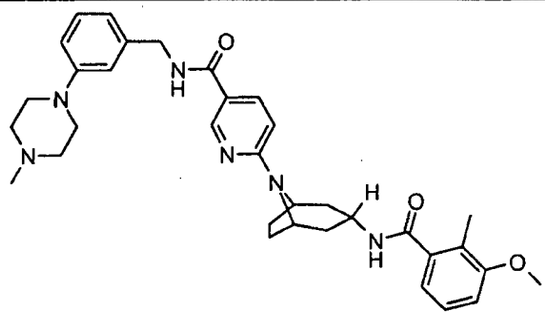
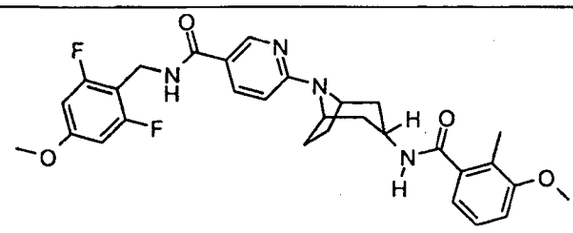
STRUCTURE	NAME & ACTIVITY
	N-ethyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-[(1S)-1,2-dimethylpropyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	N-[(1R)-1,2-dimethylpropyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	N-[(1S)-1-methyl-2-(methyloxy)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**

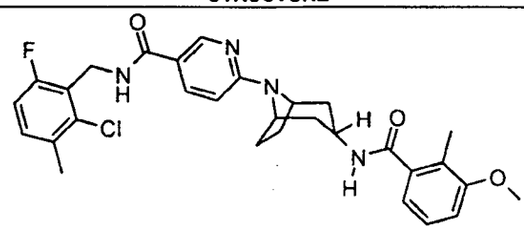
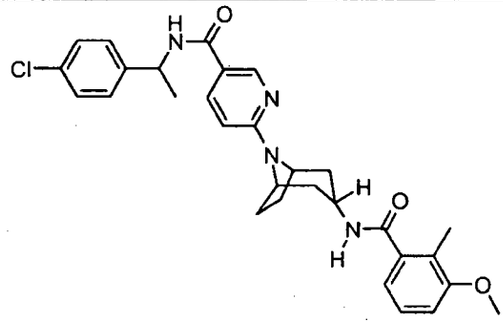
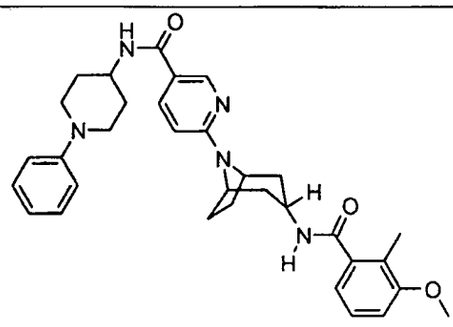
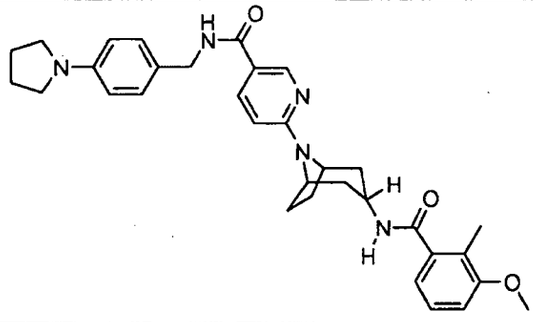
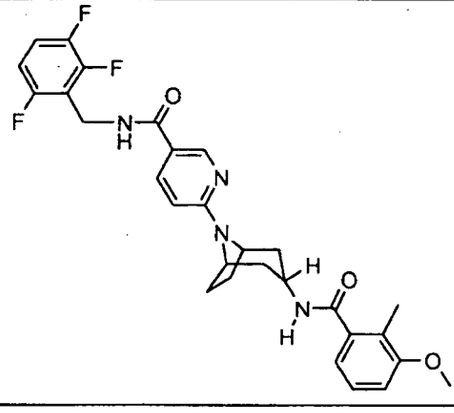
STRUCTURE	NAME & ACTIVITY
	N-azetidin-3-yl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(1-methylpiperidin-4-yl)phenyl]methyl}pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1R)-1-[4-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide **ACTIVITY = D**

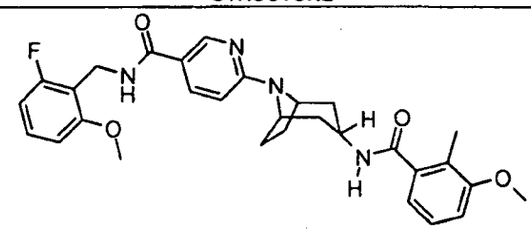
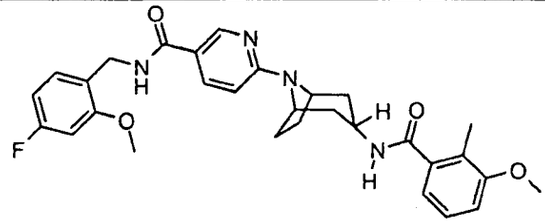
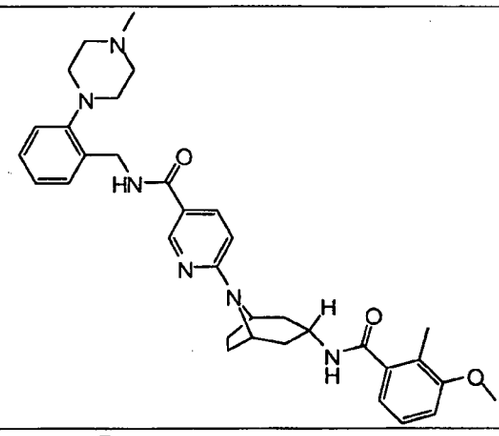
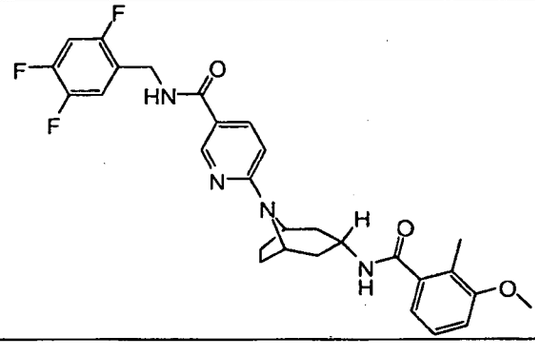
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1R)-1-phenylethyl]pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1S)-1-phenylethyl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1S)-1-phenylpropyl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-((1-phenylethyl)pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide **ACTIVITY = A**

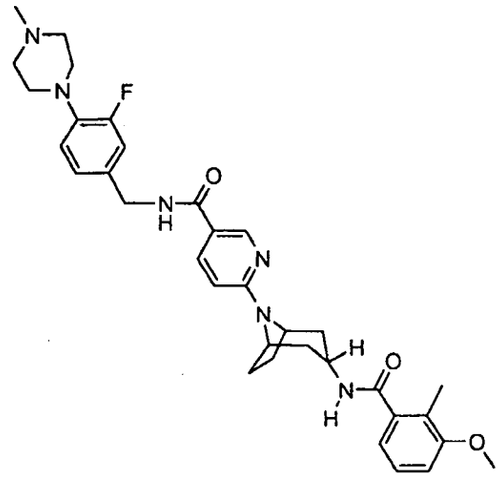
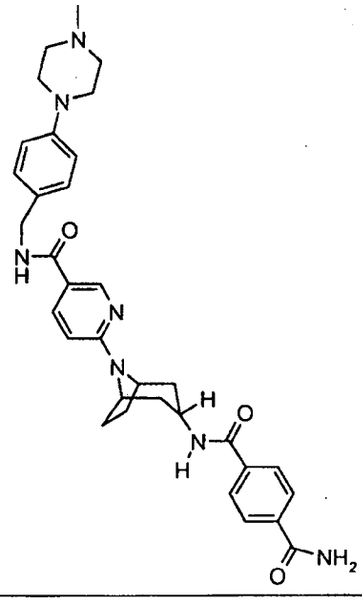
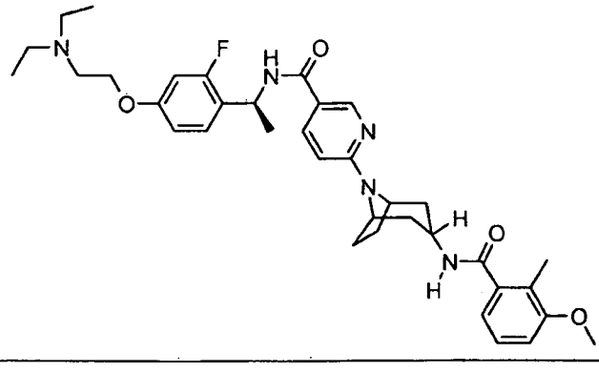
STRUCTURE	NAME & ACTIVITY
	N-[(1S)-1-(4-chlorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-{(1S)-1-[2-fluoro-4-(methyloxy)phenyl]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-{[2-fluoro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-[(2-chloro-3,6-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**

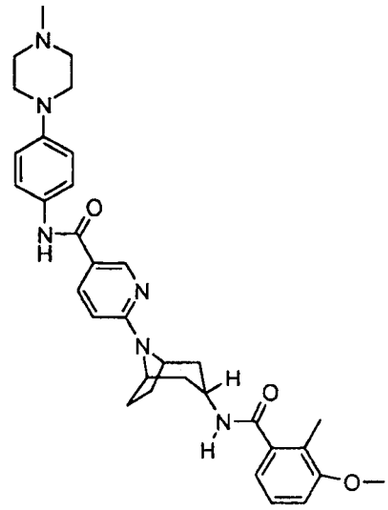
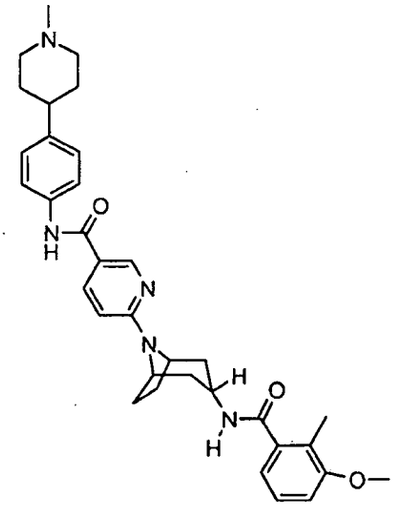
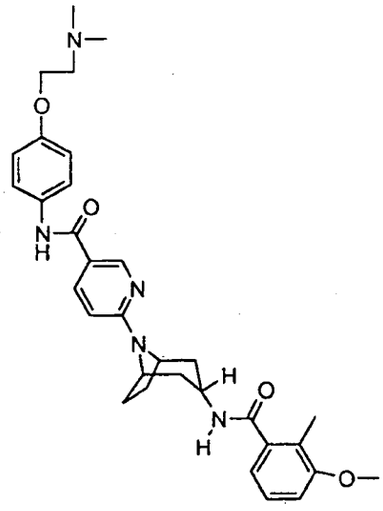
STRUCTURE	NAME & ACTIVITY
	N-[(4-{[2-(diethylamino)ethyl]oxy}phenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-[(1S)-2-amino-1-methyl-2-oxoethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-[(3-{[2-(diethylamino)ethyl]oxy}phenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-{[4-fluoro-3-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**

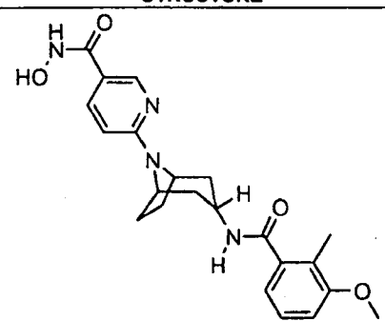
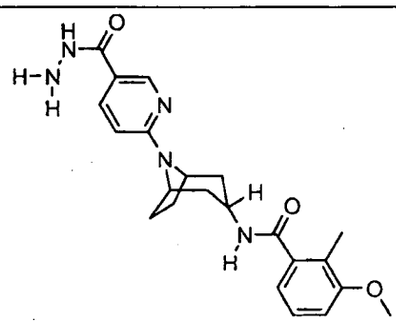
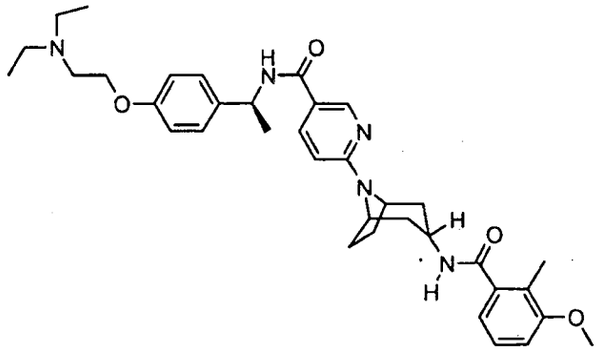
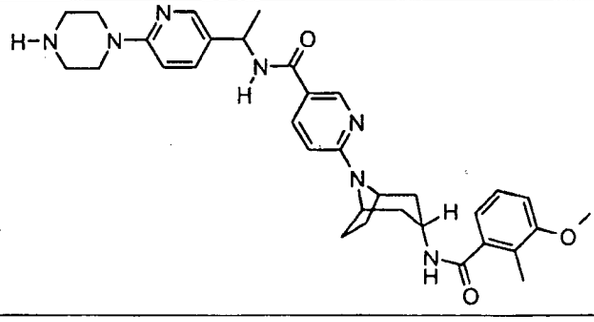
STRUCTURE	NAME & ACTIVITY
	N-{[3-fluoro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-{[2-chloro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2,4,6-trifluorophenyl)methyl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[3-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide **ACTIVITY = A**
	N-{[2,6-difluoro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**

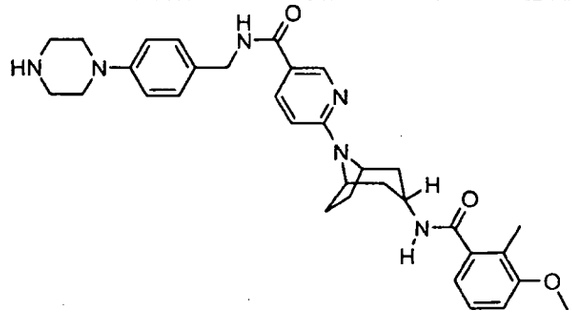
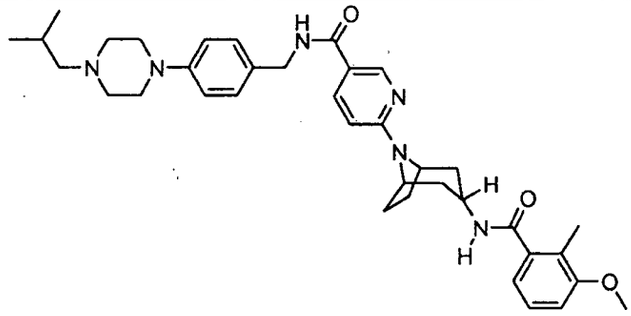
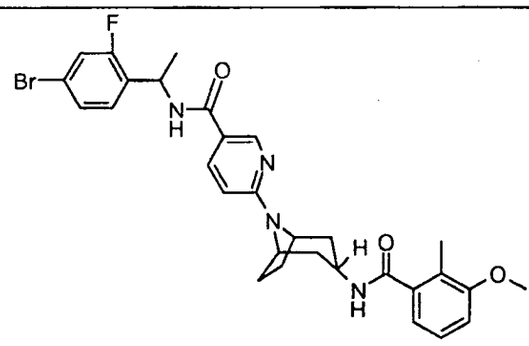
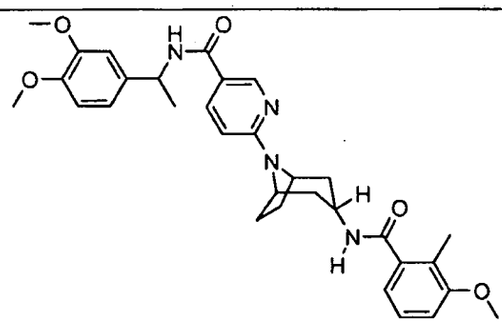
STRUCTURE	NAME & ACTIVITY
	N-[(2-chloro-6-fluoro-3-methylphenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-[1-(4-chlorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(1-phenylpiperidin-4-yl)pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-pyrrolidin-1-ylphenyl)methyl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2,3,6-trifluorophenyl)methyl]pyridine-3-carboxamide **ACTIVITY = B**

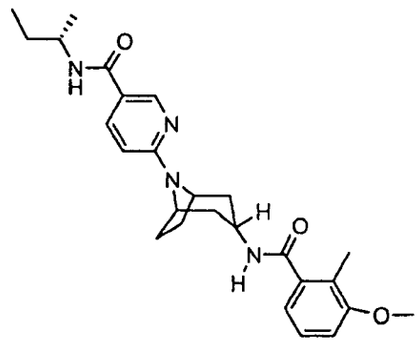
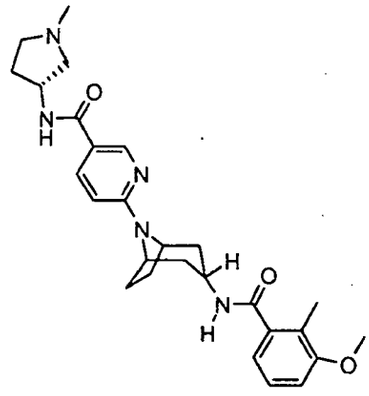
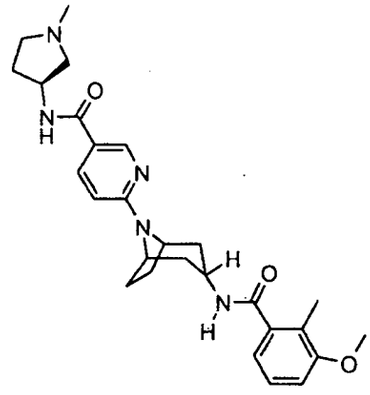
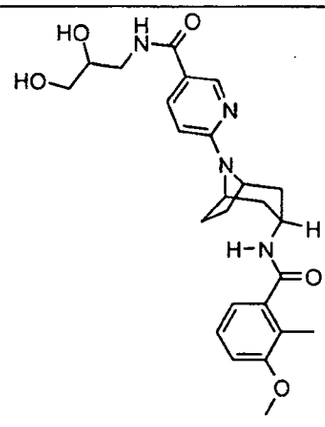
STRUCTURE	NAME & ACTIVITY
	N-{[2-fluoro-6-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	N-{[4-fluoro-2-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[2-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2,4,5-trifluorophenyl)methyl]pyridine-3-carboxamide **ACTIVITY = B**

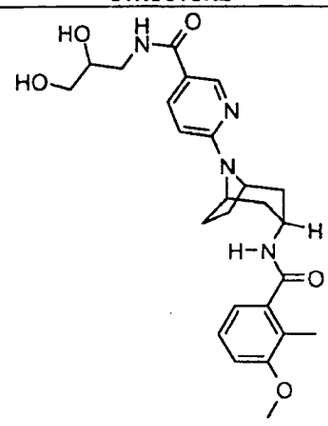
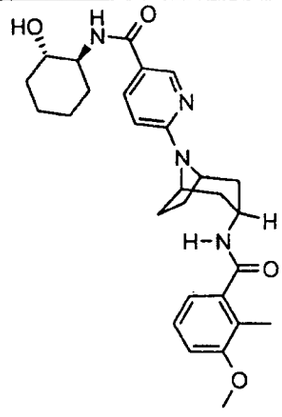
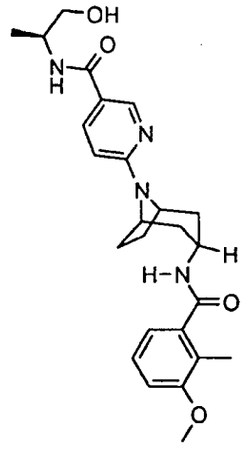
STRUCTURE	NAME & ACTIVITY
	N-{[3-fluoro-4-(4-methylpiperazin-1-yl)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-(8-{5-[({[4-(4-methylpiperazin-1-yl)phenyl]methyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-[(1S)-1-(4-{[2-(diethylamino)ethyl]oxy}-2-fluorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**

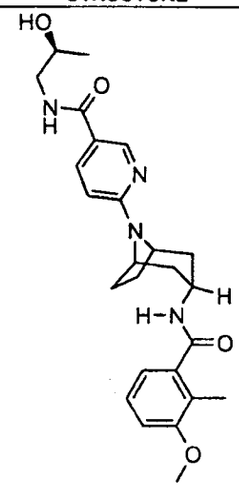
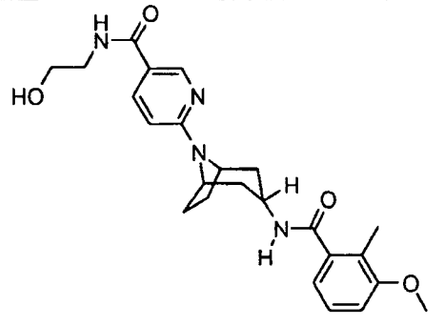
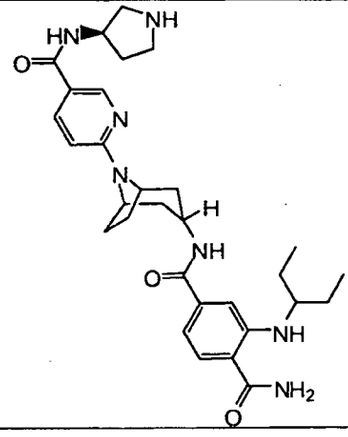
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[4-(4-methylpiperazin-1-yl)phenyl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[4-(1-methylpiperidin-4-yl)phenyl]pyridine-3-carboxamide **ACTIVITY = C**
	N-(4-{[2-(dimethylamino)ethyl]oxy}phenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**

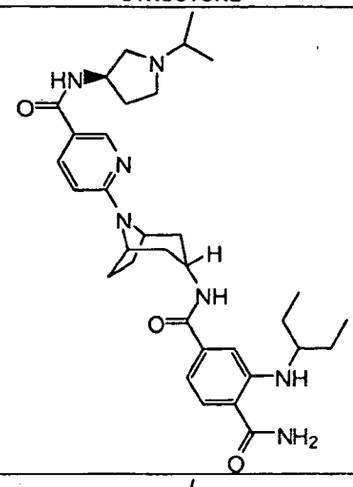
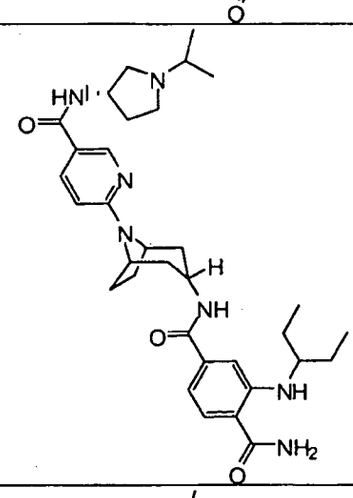
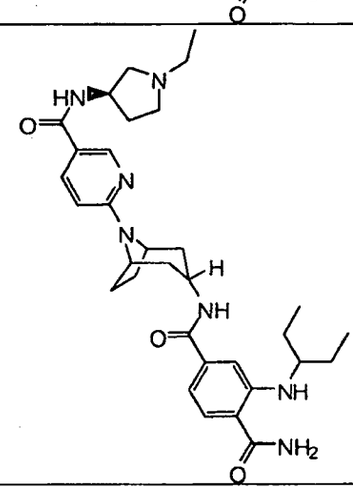
STRUCTURE	NAME & ACTIVITY
	N-hydroxy-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	N-{8-[5-(hydrazinocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-3-(methyloxy)benzamide **ACTIVITY = D**
	N-[(1S)-1-(4-{[2-(diethylamino)ethyl]oxy}phenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[1-(6-piperazin-1-ylpyridin-3-yl)ethyl]pyridine-3-carboxamide **ACTIVITY = A**

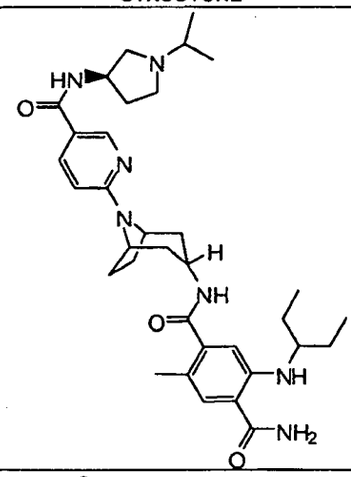
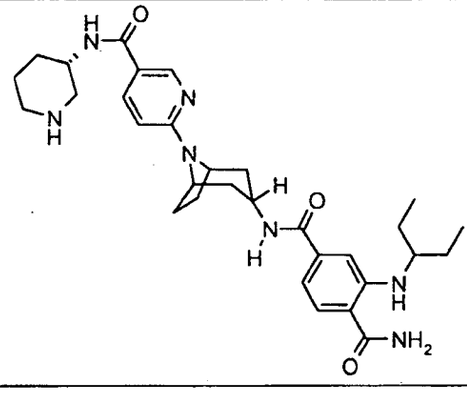
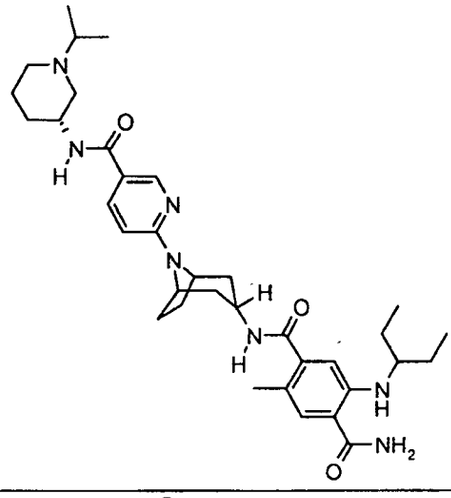
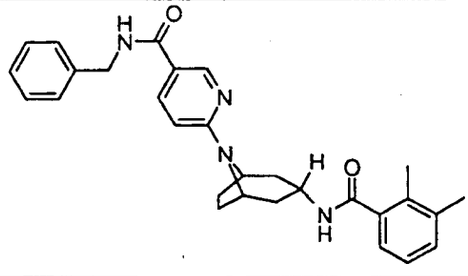
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-piperazin-1-ylphenyl)methyl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-({4-[4-(2-methylpropyl)piperazin-1-yl]phenyl}methyl)pyridine-3-carboxamide **ACTIVITY = A**
	N-[1-(4-bromo-2-fluorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	N-{1-[3,4-bis(methyloxy)phenyl]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**

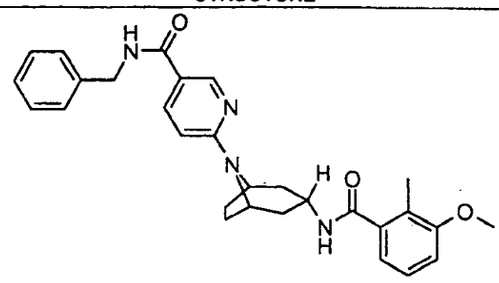
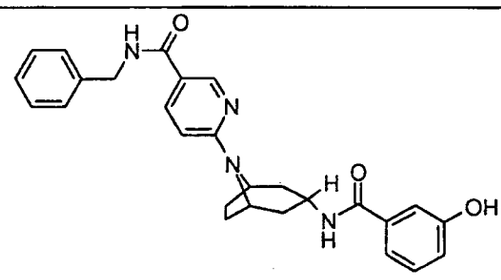
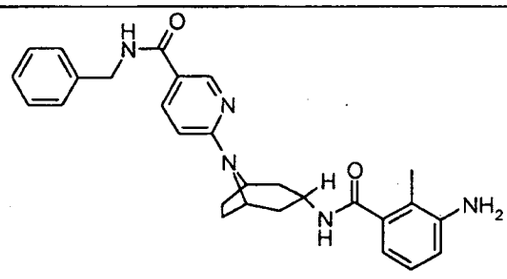
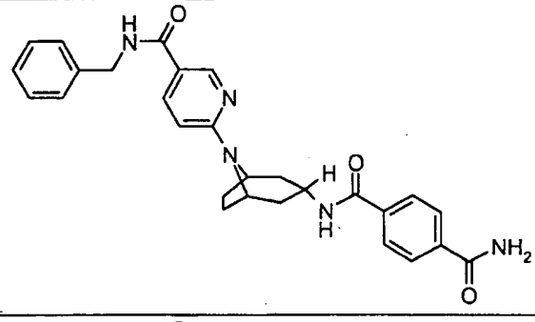
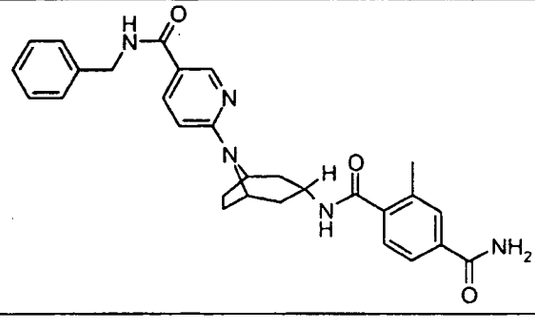
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1S)-1-methylpropyl]pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3R)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3S)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide **ACTIVITY = C**
	N-(2,3-dihydroxypropyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**

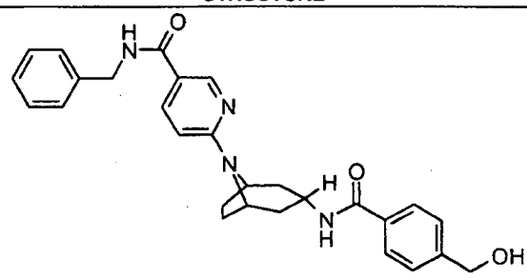
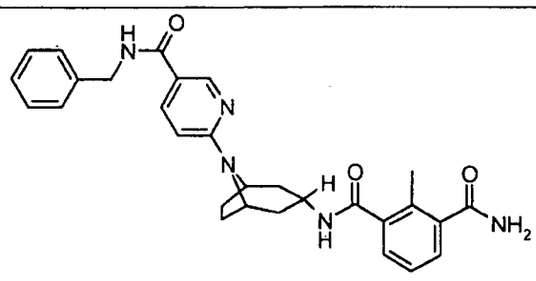
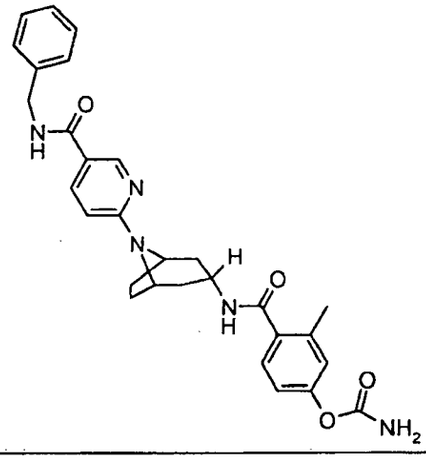
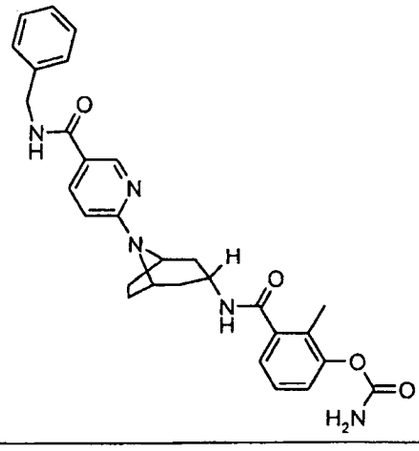
STRUCTURE	NAME & ACTIVITY
	N-[(1S,2S)-2-hydroxycyclopentyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-[(1S,2S)-2-hydroxycyclohexyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	N-[(1S)-2-hydroxy-1-methylethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**

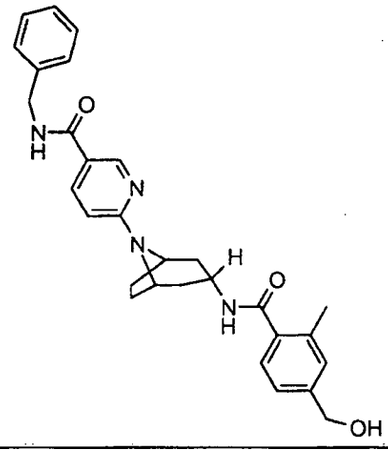
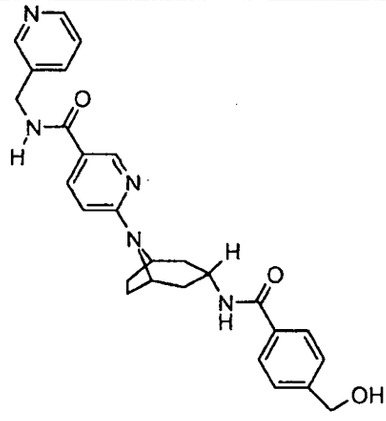
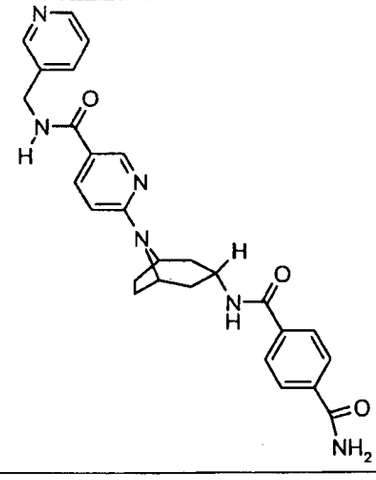
STRUCTURE	NAME & ACTIVITY
	N-[(2S)-2-hydroxypropyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	N-(2-hydroxyethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	2-[(1-ethylpropyl)amino]-N4-[8-(5-{[(3R)-pyrrolidin-3-ylamino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = A**

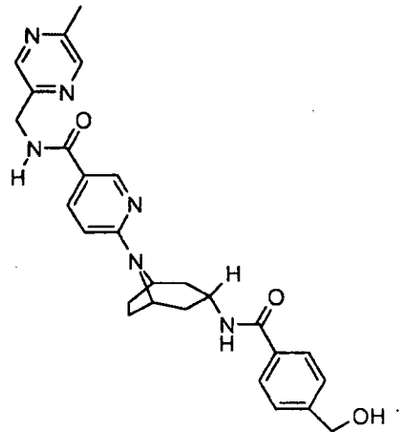
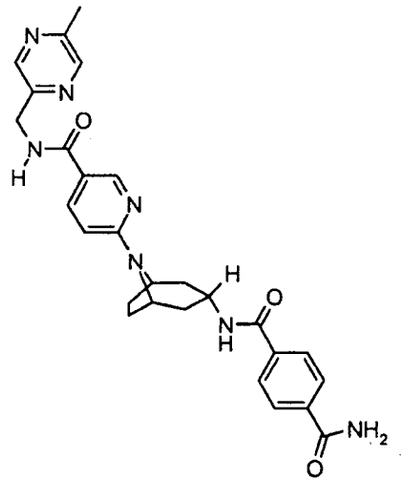
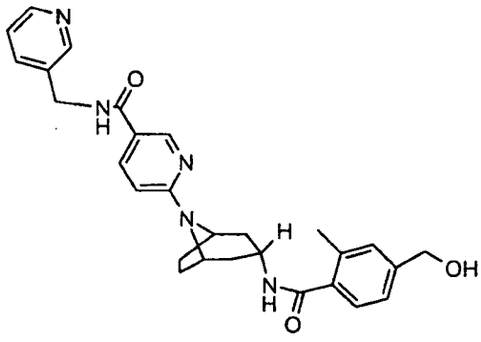
STRUCTURE	NAME & ACTIVITY
	2-[(1-ethylpropyl)amino]-N4-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(1-ethylpropyl)amino]-N4-{8-[5-({[(3S)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(1-ethylpropyl)amino]-N4-{8-[5-({[(3R)-1-ethylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**

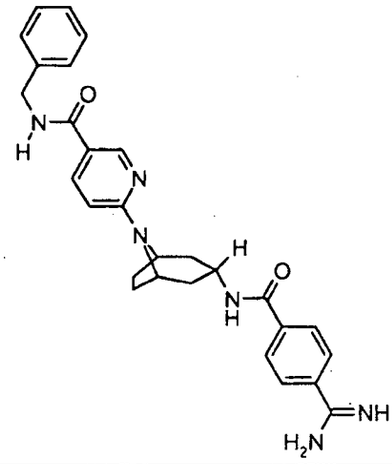
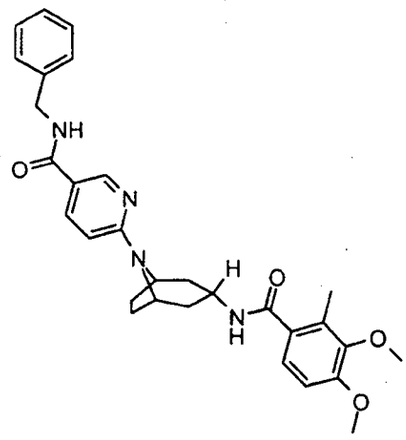
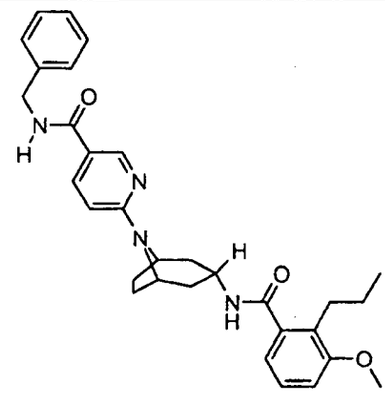
STRUCTURE	NAME & ACTIVITY
	5-[(1-ethylpropyl)amino]-2-methyl-N-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(1-ethylpropyl)amino]-N4-[8-(5-{[(3S)-piperidin-3-ylamino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = A**
	5-[(1-ethylpropyl)amino]-2-methyl-N-{8-[5-({[(3R)-1-(1-methylethyl)piperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	6-(3-endo-{[(2,3-dimethylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = D**

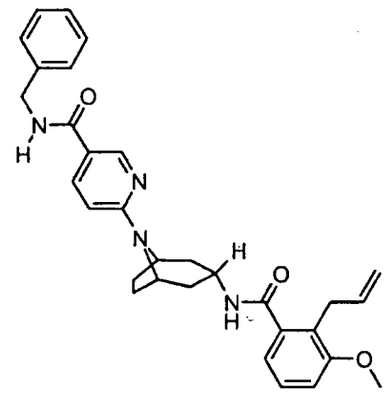
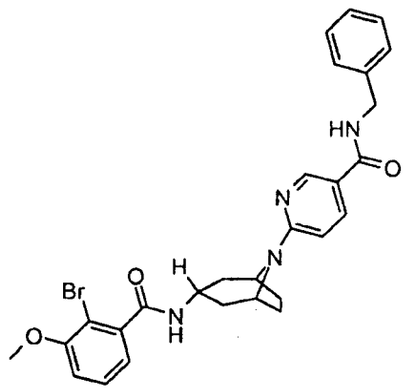
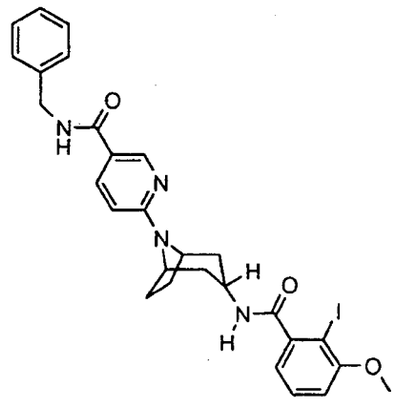
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = A**
	6-(3-endo-{[(3-hydroxy-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = C**
	6-(3-endo-{[(3-amino-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = D**
	N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-methyl-N1-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = B**

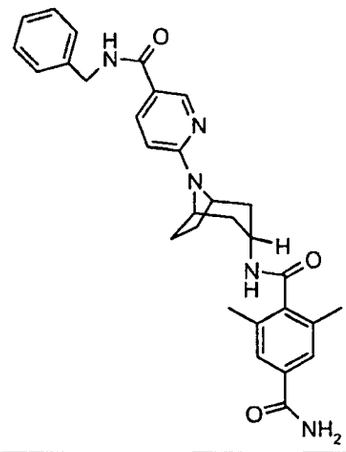
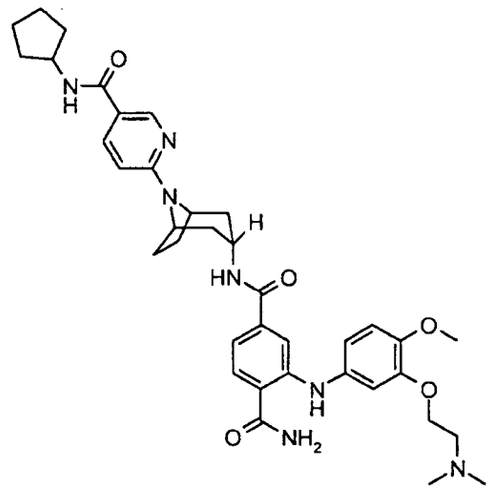
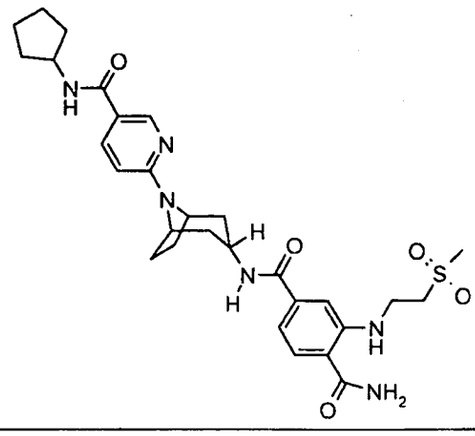
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = A**
	2-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,3-dicarboxamide **ACTIVITY = D**
	3-methyl-4-({[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]amino}carbonyl)phenyl carbamate **ACTIVITY = D**
	2-methyl-3-({[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]amino}carbonyl)phenyl carbamate **ACTIVITY = D**

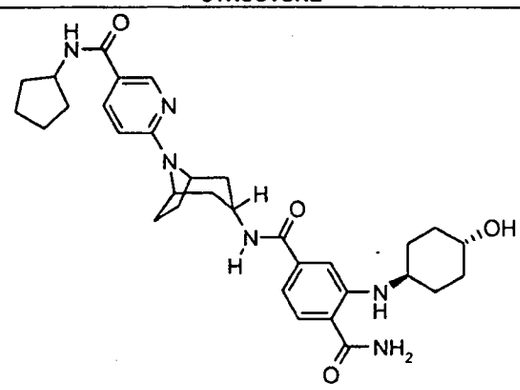
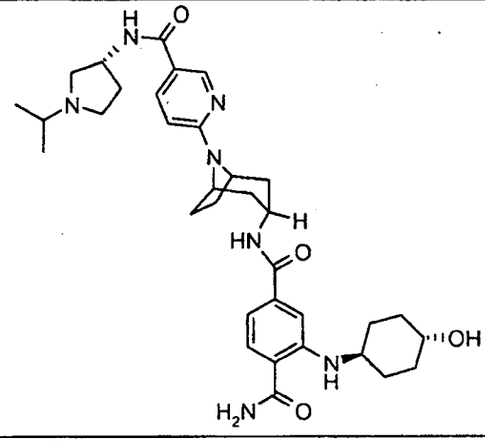
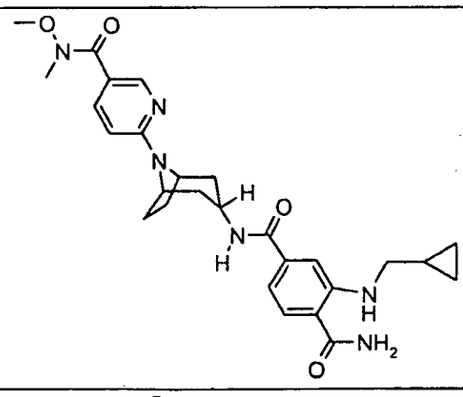
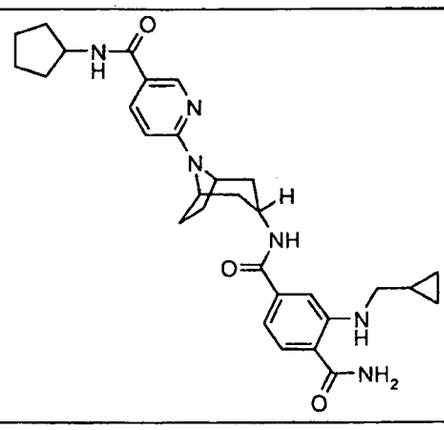
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[4-(hydroxymethyl)-2-methylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyridin-3-ylmethyl)pyridine-3-carboxamide **ACTIVITY = A**
	N-[8-(5-{[(pyridin-3-ylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = A**

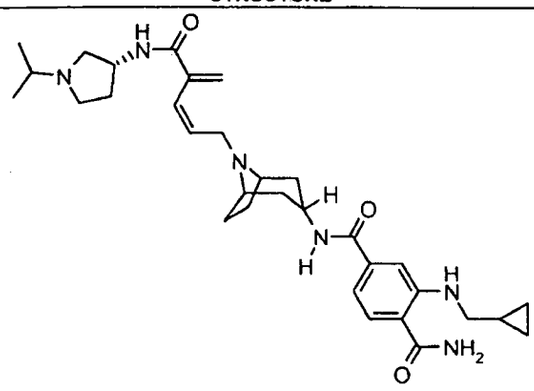
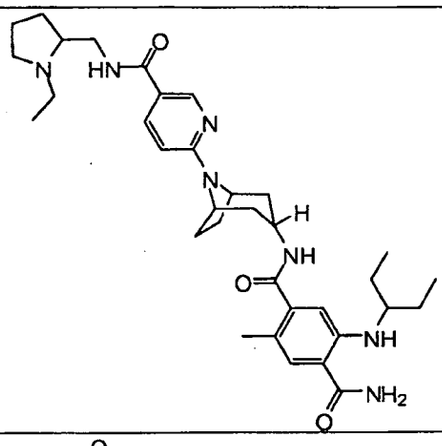
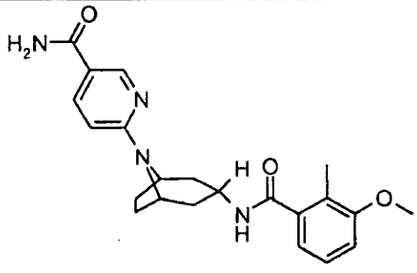
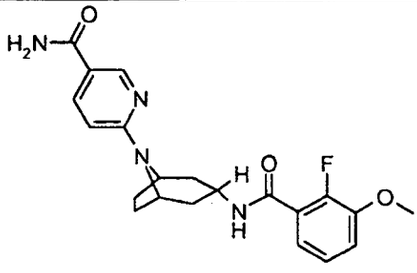
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(5-methylpyrazin-2-yl)methyl]pyridine-3-carboxamide **ACTIVITY = A**
	N-{8-[5-({[(5-methylpyrazin-2-yl)methyl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = C**
	6-[3-endo-({[4-(hydroxymethyl)-2-methylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyridin-3-ylmethyl)pyridine-3-carboxamide **ACTIVITY = A**

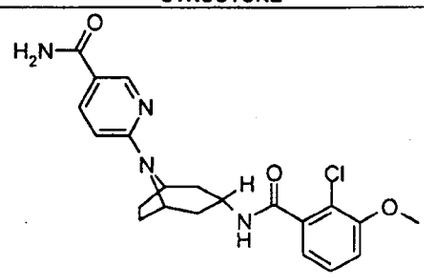
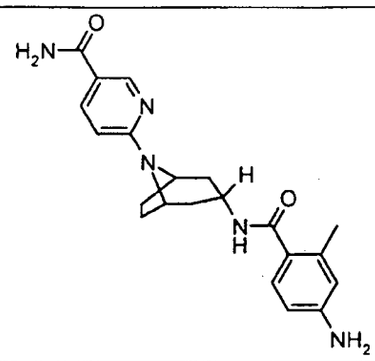
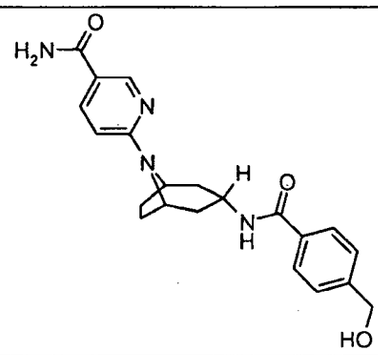
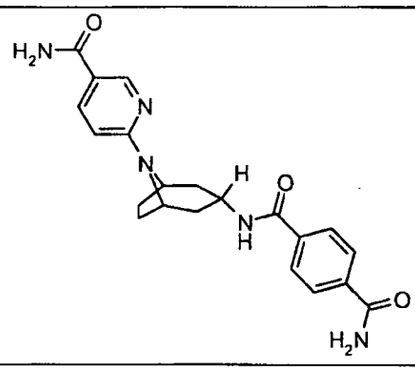
STRUCTURE	NAME & ACTIVITY
	6-{3-endo-[({4-[amino(imino)methyl]phenyl}carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[2-methyl-3,4-bis(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[3-(methyloxy)-2-propylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = D**

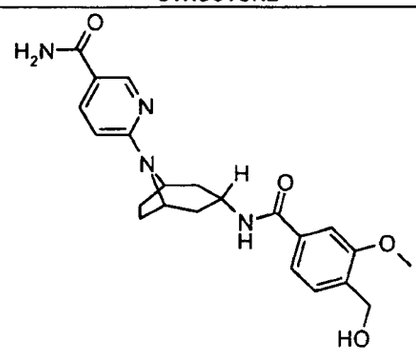
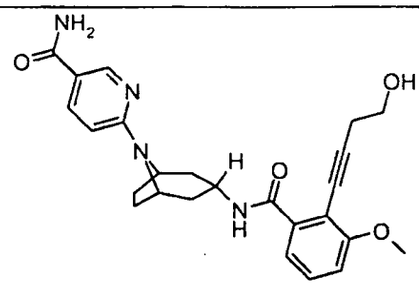
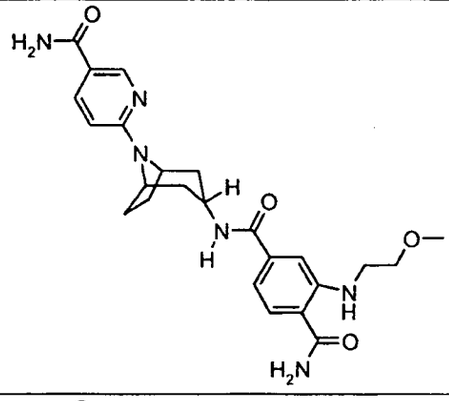
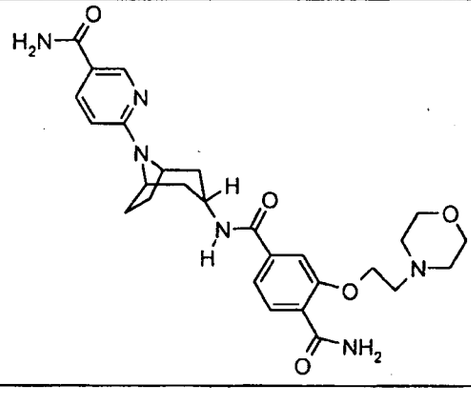
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[3-(methyloxy)-2-prop-2-en-1-ylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-bromo-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-iodo-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = D**

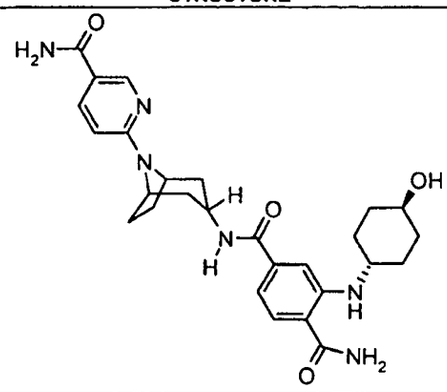
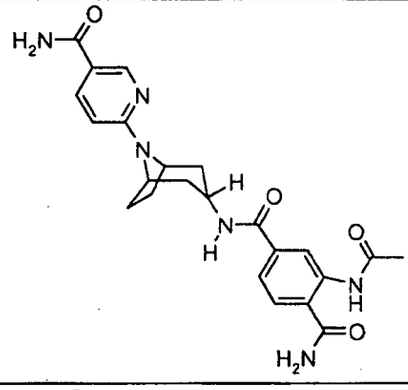
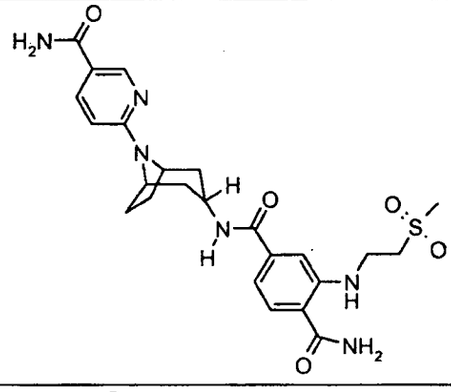
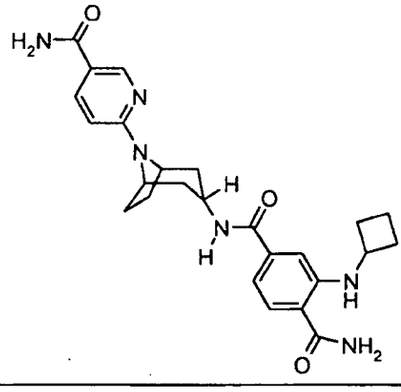
STRUCTURE	NAME & ACTIVITY
	2,6-dimethyl-N1-{8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = B**
	N4-(8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-(8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[2-(methylsulfonyl)ethyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**

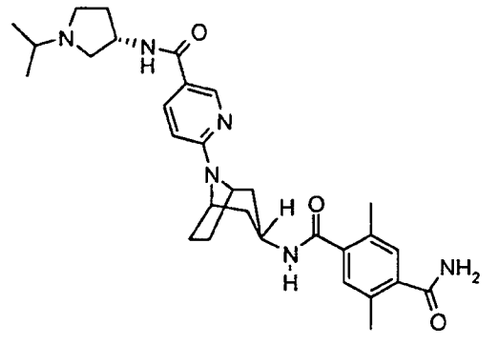
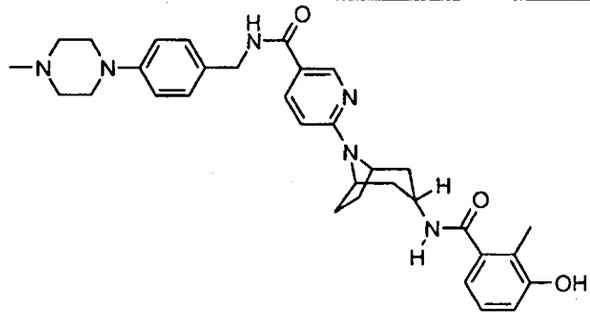
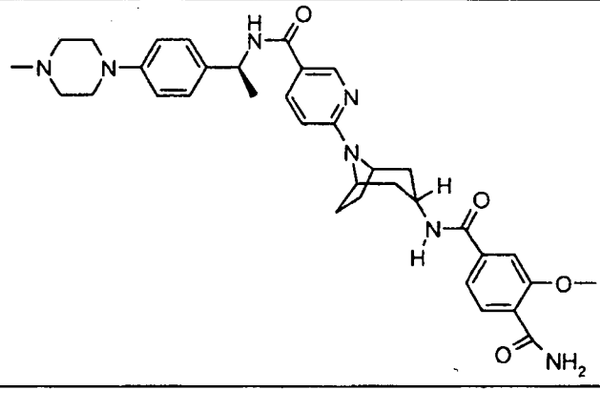
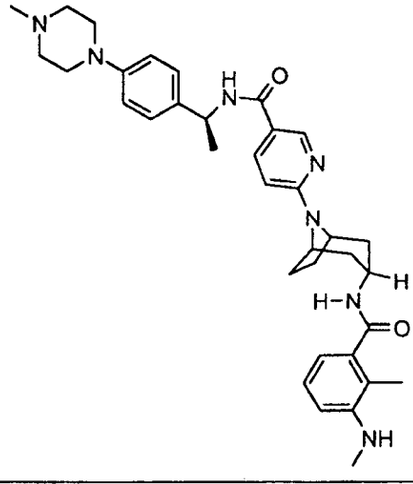
STRUCTURE	NAME & ACTIVITY
	N4-(8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-[(4-trans-hydroxycyclohexyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(4-trans-hydroxycyclohexyl)amino]-N4-{8-[5-({[1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-[8-(5-{[methyl(methyloxy)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = C**
	N4-(8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**

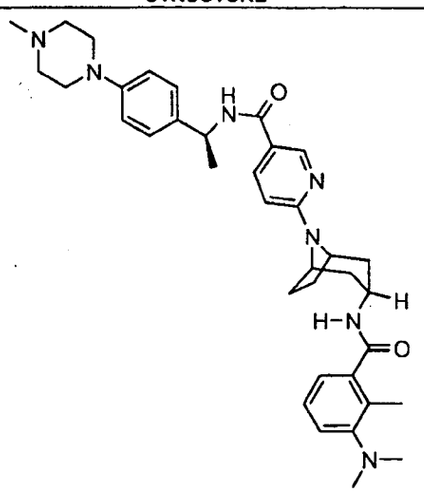
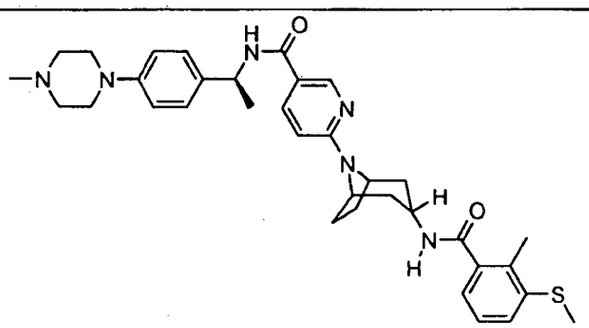
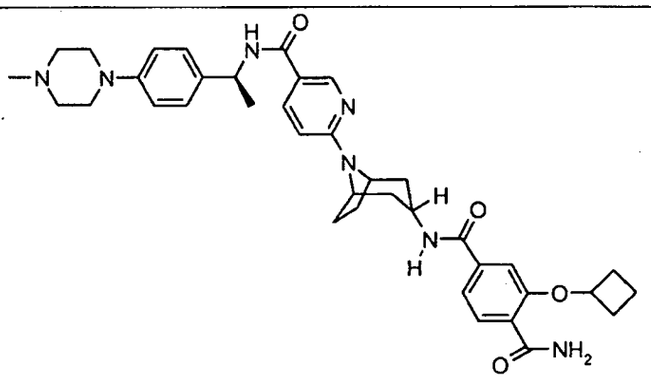
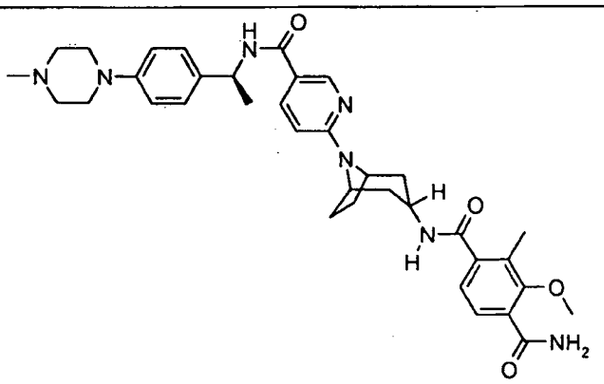
STRUCTURE	NAME & ACTIVITY
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	5-[(1-ethylpropyl)amino]-N-{8-[5-({[(1-ethylpyrrolidin-2-yl)methyl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-fluoro-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**

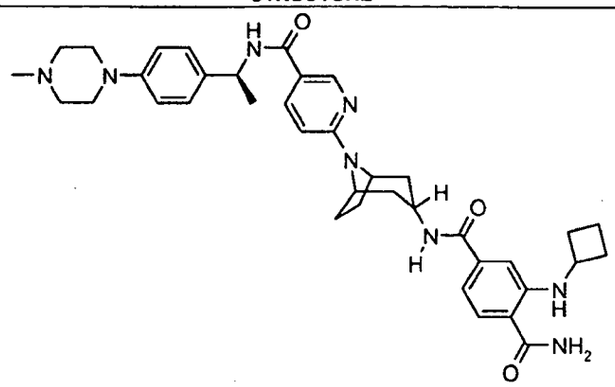
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[2-chloro-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	6-(3-endo-{[(4-amino-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**
	N-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = C**

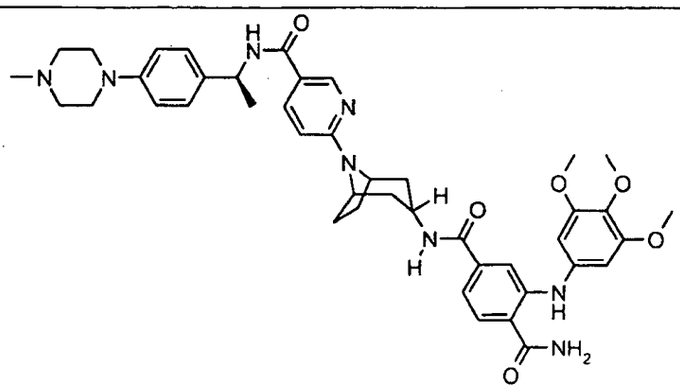
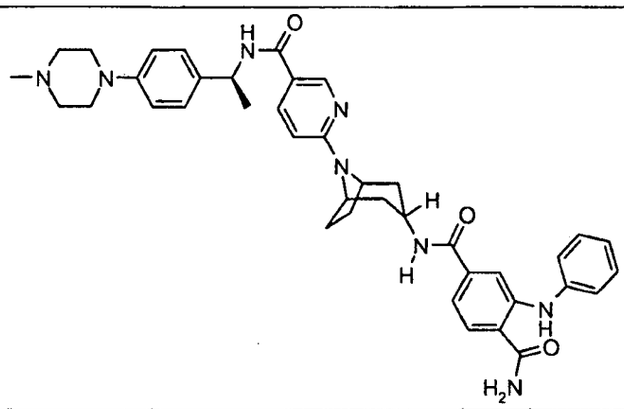
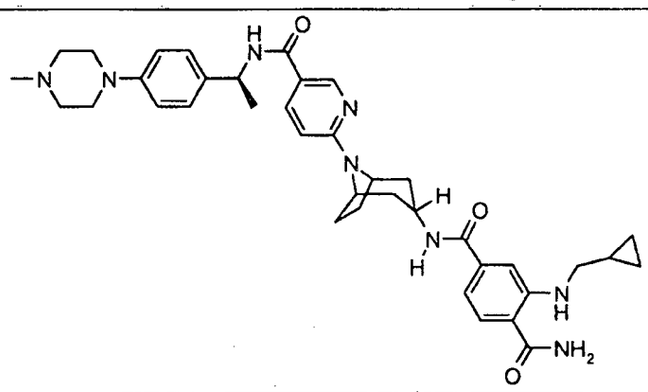
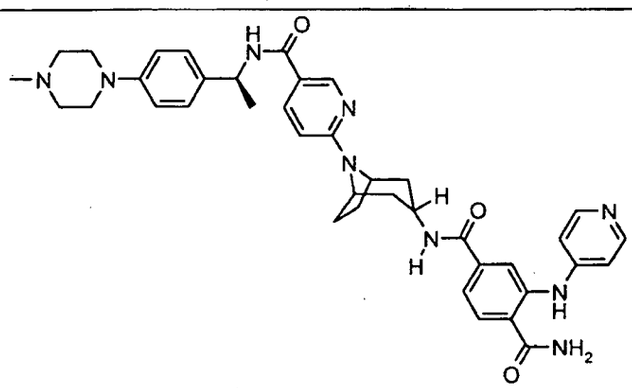
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[4-(hydroxymethyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	6-[3-endo-({[2-(4-hydroxybut-1-yn-1-yl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[2-(methyloxy)ethyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(2-morpholin-4-ylethyl)oxybenzene-1,4-dicarboxylate **ACTIVITY = C**

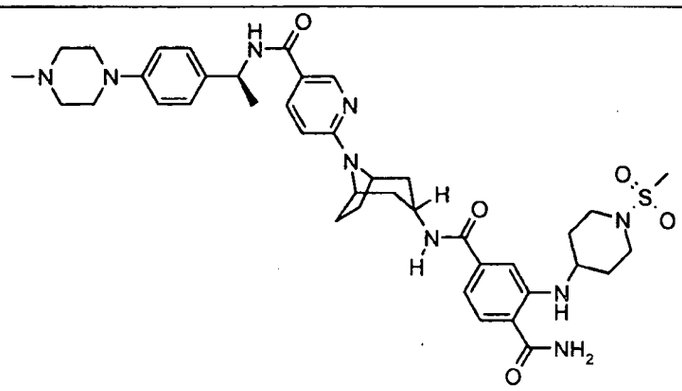
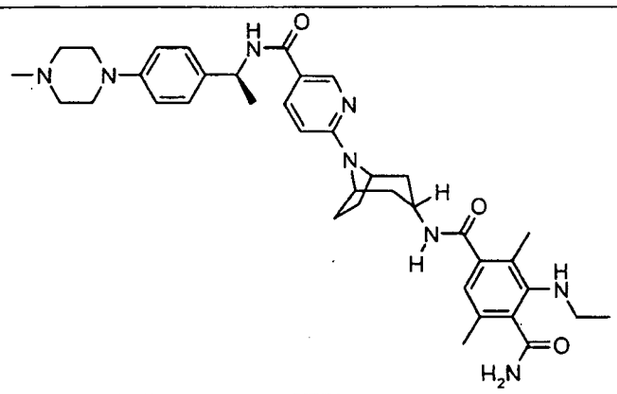
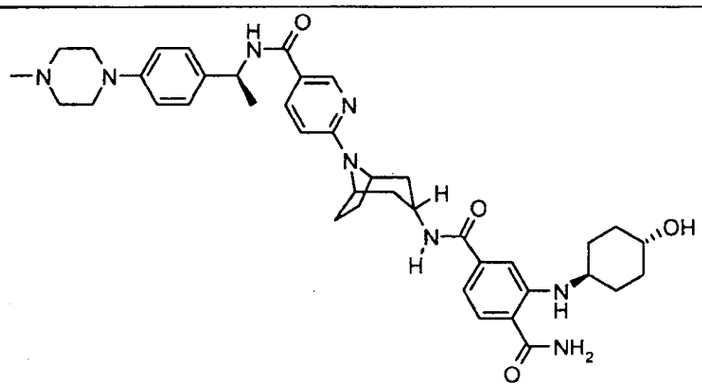
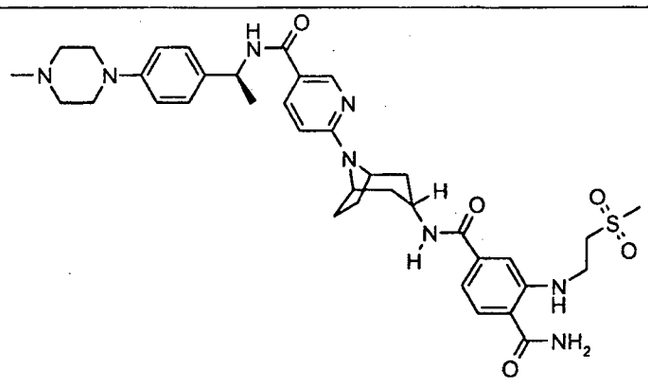
STRUCTURE	NAME & ACTIVITY
	N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(4-hydroxycyclohexyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-(acetylamino)-N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = C**
	N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[2-(methylsulfonyl)ethyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(cyclobutylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**

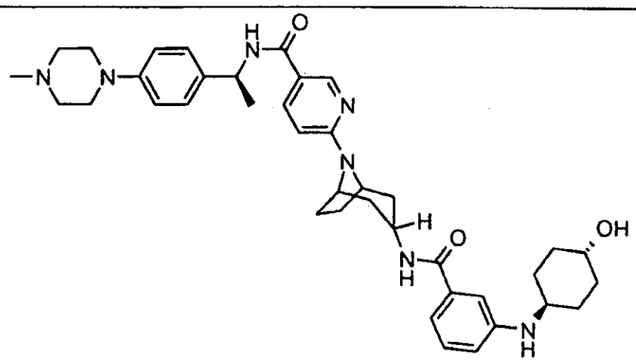
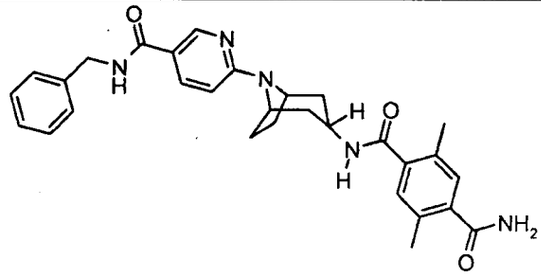
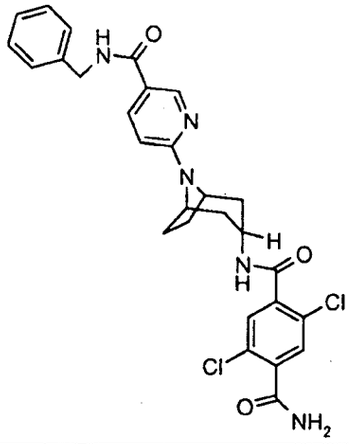
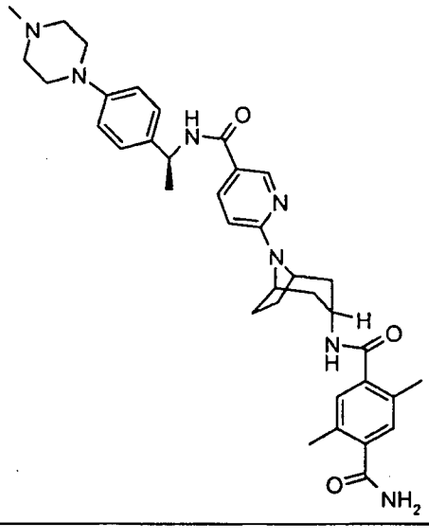
STRUCTURE	NAME & ACTIVITY
	2,5-dimethyl-N-{8-[5-({[(3S)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	6-(3-endo-{[(3-hydroxy-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide **ACTIVITY = A**
	2-(methyloxy)-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = A**
	6-[3-endo-({[2-methyl-3-(methylamino)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide **ACTIVITY = A**

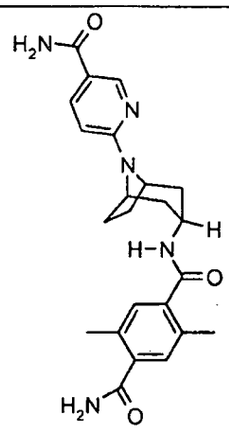
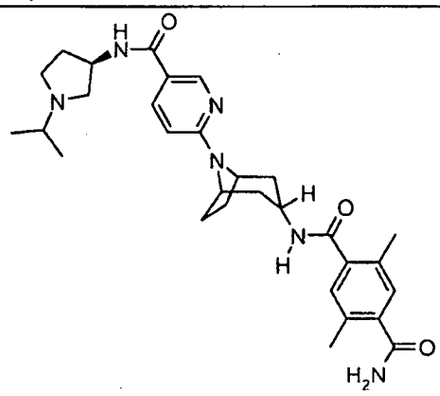
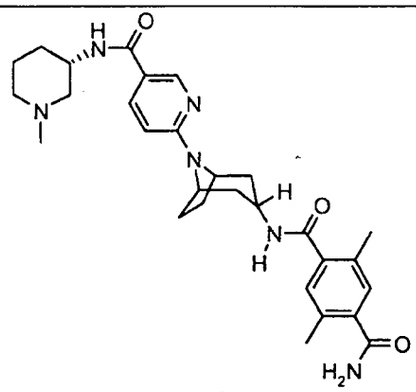
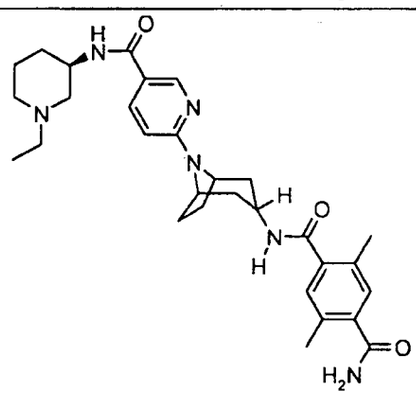
STRUCTURE	NAME & ACTIVITY
	6-[3-endo-({[3-(dimethylamino)-2-methylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[2-methyl-3-(methylthio)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide **ACTIVITY = B**
	2-(cyclobutyloxy)-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = B**
	2-methyl-3-(methyloxy)-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = A**

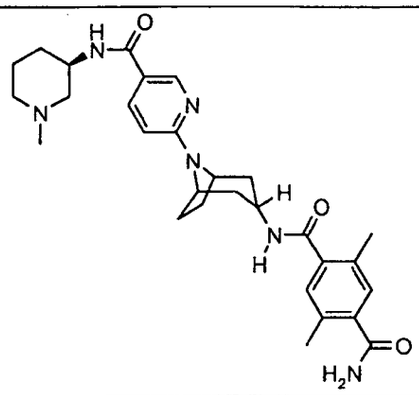
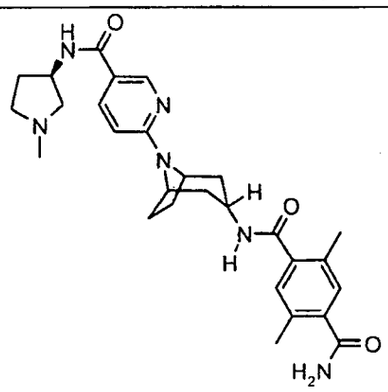
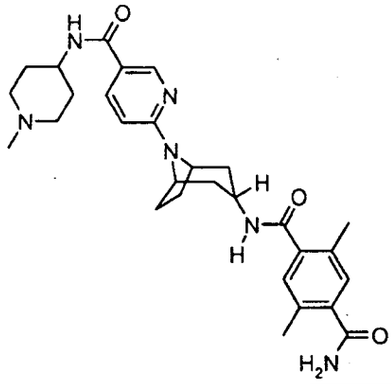
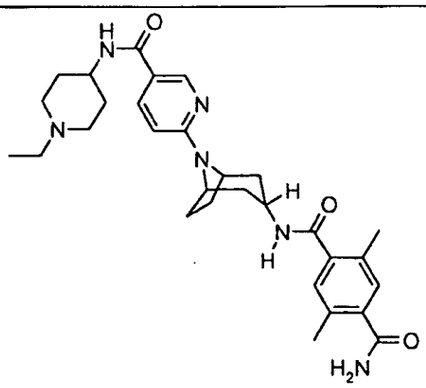
STRUCTURE	NAME & ACTIVITY
	2-(cyclobutylamino)-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide ACTIVITY = A

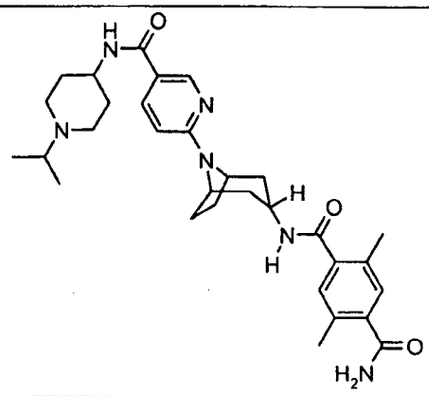
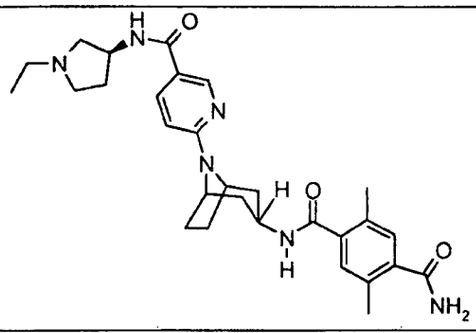
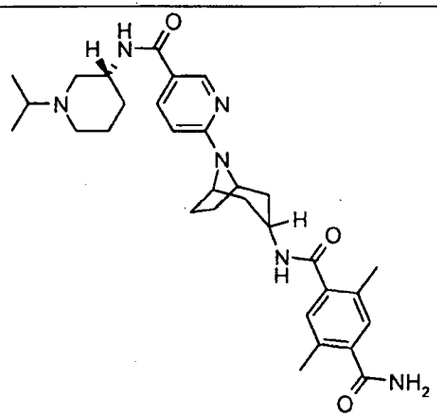
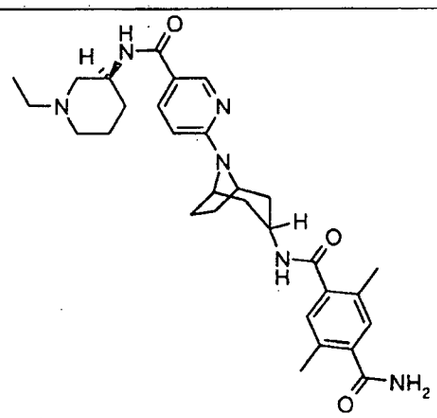
	N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[3,4,5-tris(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-(phenylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-(pyridin-4-ylamino)benzene-1,4-dicarboxylate **ACTIVITY = A**

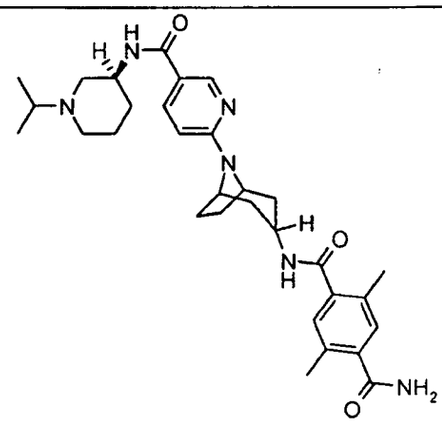
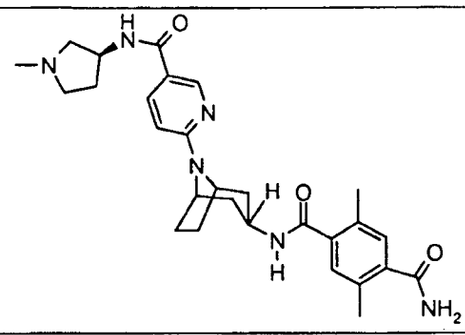
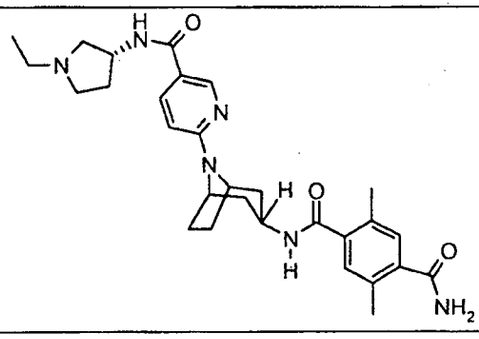
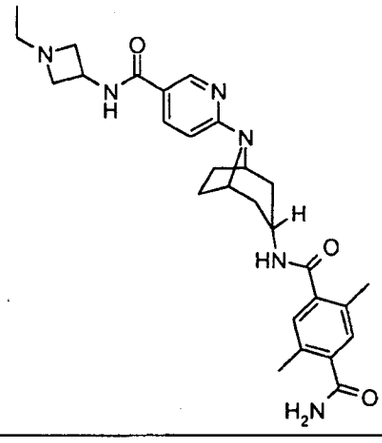
	N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[1-(methylsulfonyl)piperidin-4-yl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	3-(ethylamino)-2,5-dimethyl-N1-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = D**
	2-[(4-hydroxycyclohexyl)amino]-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[2-(methylsulfonyl)ethyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**

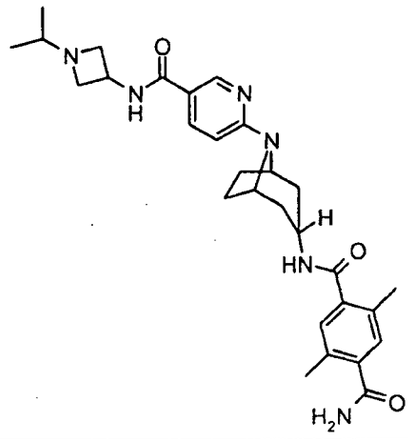
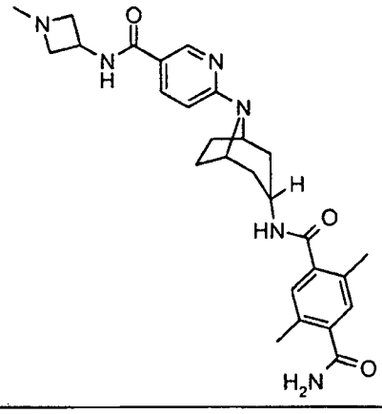
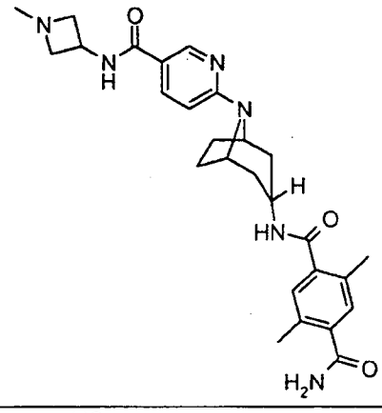
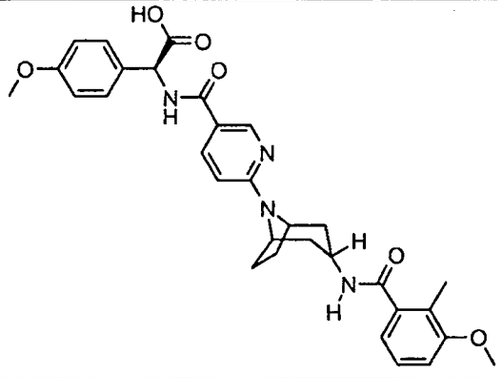
	6-{3-endo-[({3-[(4-hydroxycyclohexyl)amino]phenyl}carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide **ACTIVITY = D**
	2,5-dimethyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = A**
	2,5-dichloro-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = A**
	2,5-dimethyl-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = A**

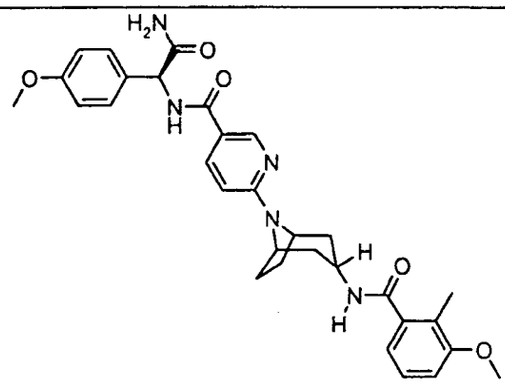
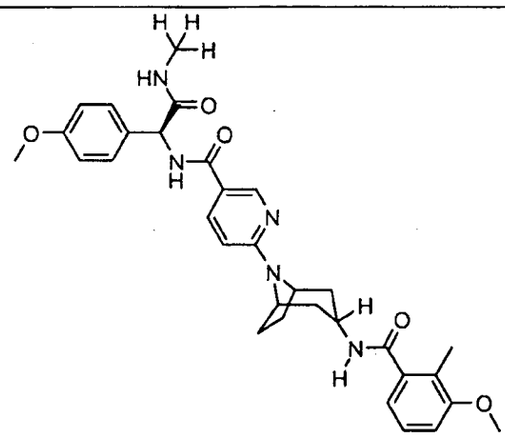
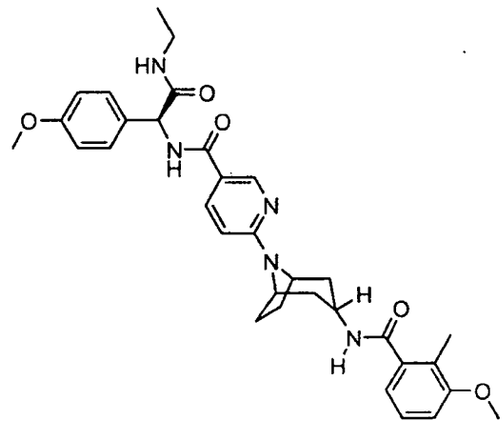
	N-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	2,5-dimethyl-N-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2,5-dimethyl-N-{8-[5-({[(3S)-1-methylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-({[(3R)-1-ethylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide **ACTIVITY = A**

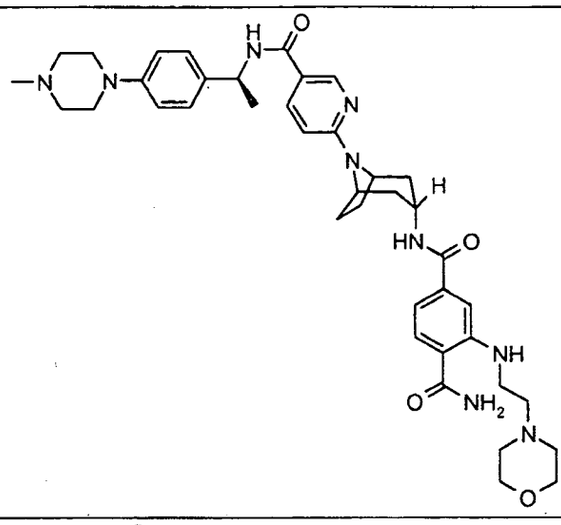
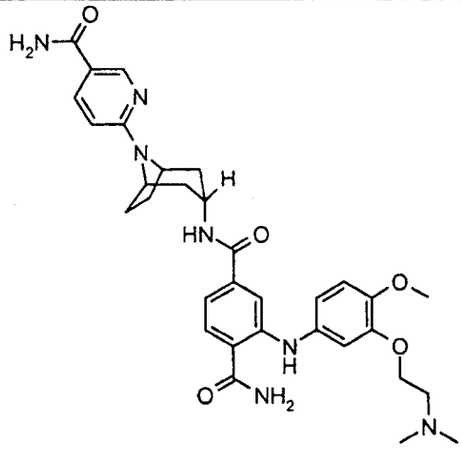
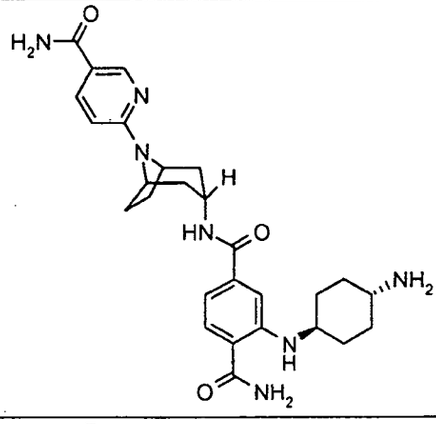
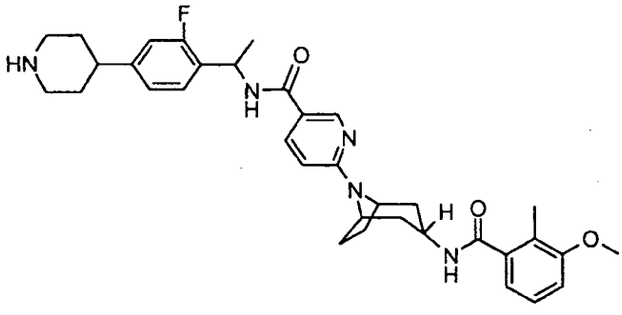
	2,5-dimethyl-N-{8-[5-({[(3R)-1-methylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2,5-dimethyl-N-{8-[5-({[(3R)-1-methylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = B**
	2,5-dimethyl-N-[8-(5-{[(1-methylpiperidin-4-yl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = B**
	N-[8-(5-{[(1-ethylpiperidin-4-yl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2,5-dimethylbenzene-1,4-dicarboxamide **ACTIVITY = B**

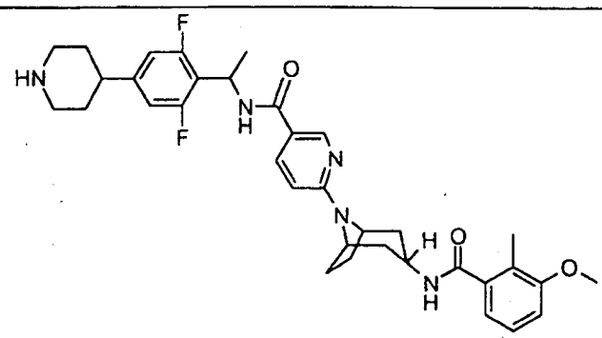
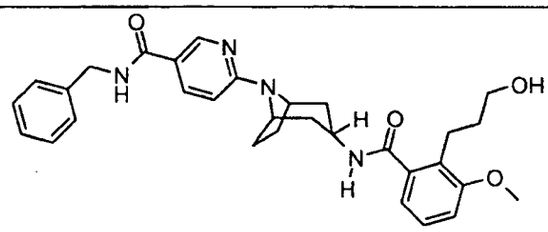
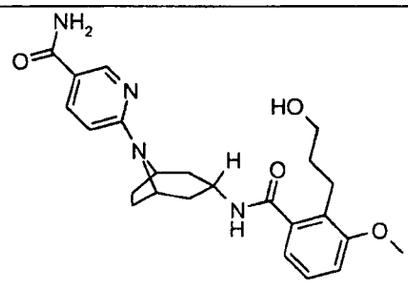
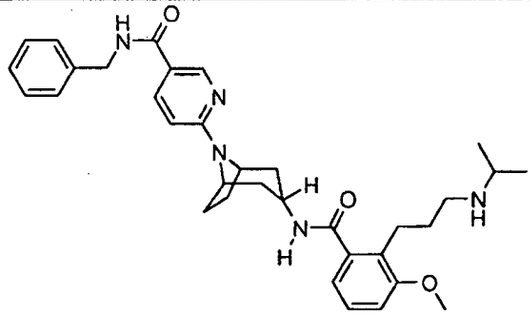
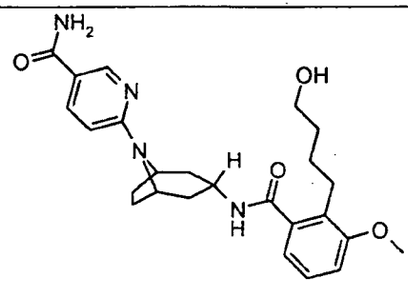
	2,5-dimethyl-N-{8-[5-({[1-(1-methylethyl)piperidin-4-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = B**
	N-{8-[5-({[(3S)-1-ethylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	2,5-dimethyl-N-{8-[5-({[(3R)-1-(1-methylethyl)piperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-({[(3S)-1-ethylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide **ACTIVITY = B**

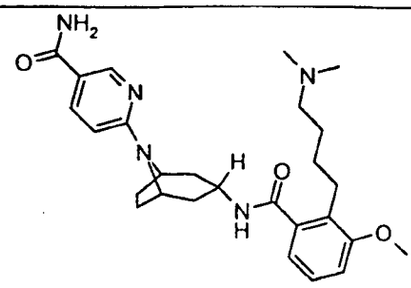
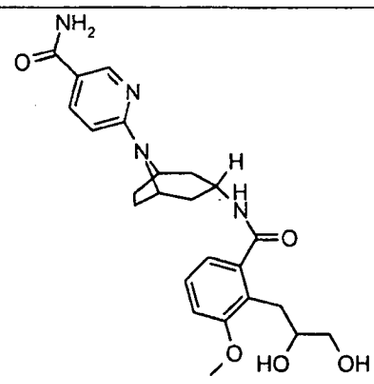
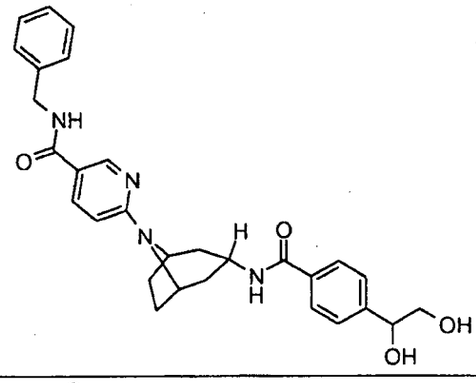
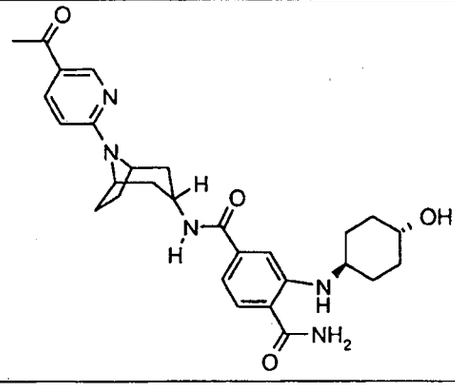
	2,5-dimethyl-N-{8-[5-({[(3S)-1-(1-methylethyl)piperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = B**
	2,5-dimethyl-N-{8-[5-({[(3S)-1-methylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-({[(3R)-1-ethylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	N-[8-(5-{[(1-ethylazetidin-3-yl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2,5-dimethylbenzene-1,4-dicarboxamide **ACTIVITY = A**

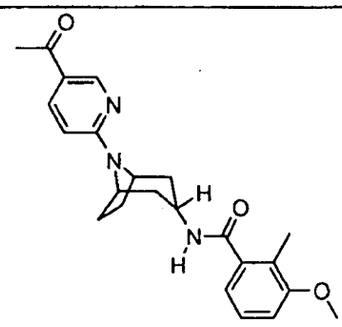
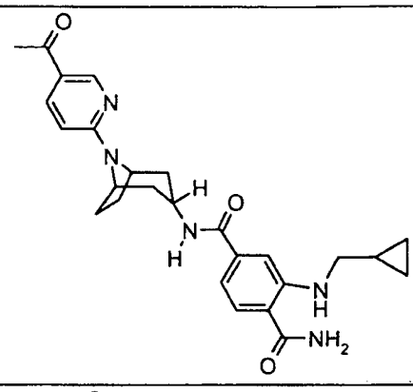
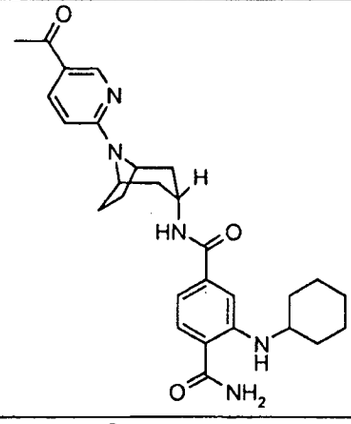
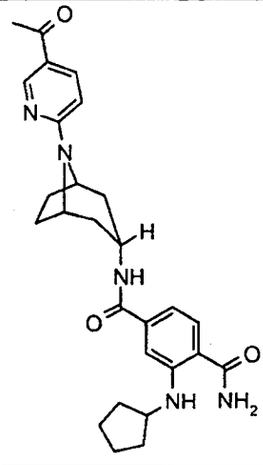
	2,5-dimethyl-N-{8-[5-({[1-(1-methylethyl)azetidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2,5-dimethyl-N-[8-(5-{[(1-methylazetidin-3-yl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = A**
	methyl (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoate **ACTIVITY = C**
	(2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoic acid **ACTIVITY = C**

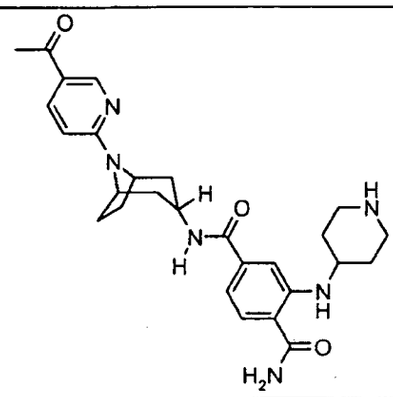
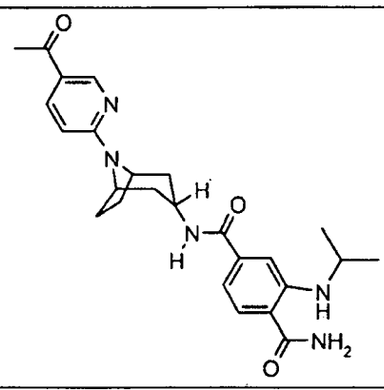
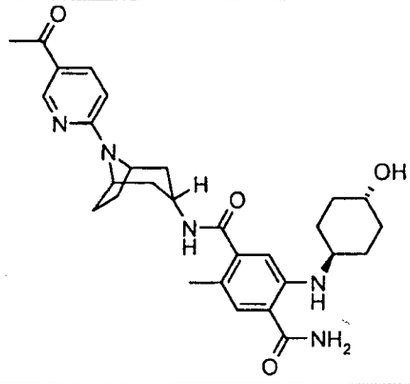
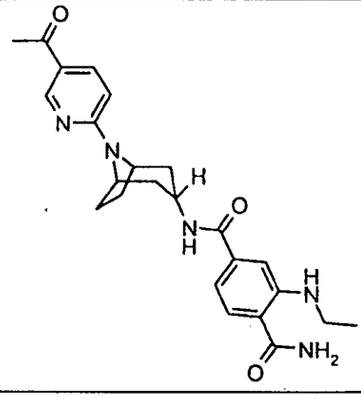
	N-{(1S)-2-amino-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-{(1S)-2-(methylamino)-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**
	N-{(1S)-2-(ethylamino)-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**

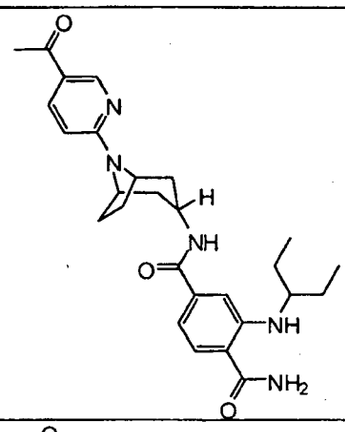
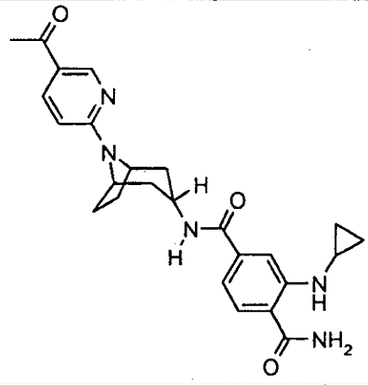
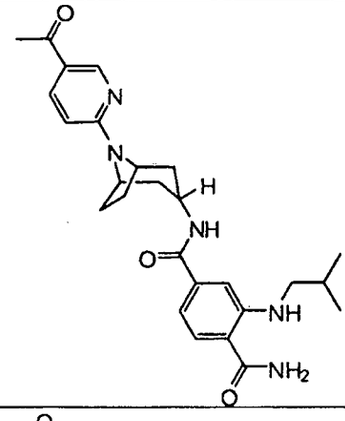
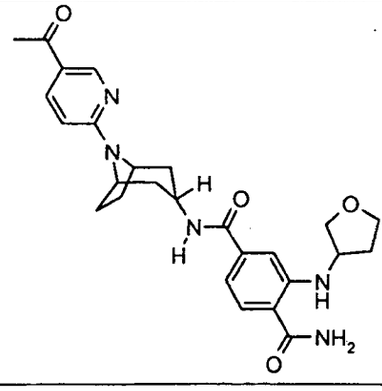
	N4-{8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(2-morpholin-4-ylethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(trans-4-aminocyclohexyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-[1-(2-fluoro-4-piperidin-4-ylphenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = A**

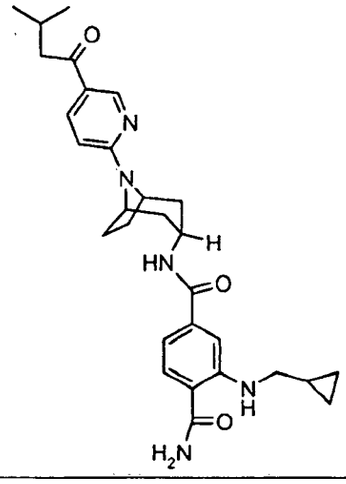
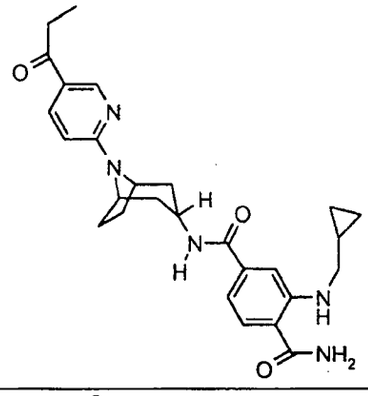
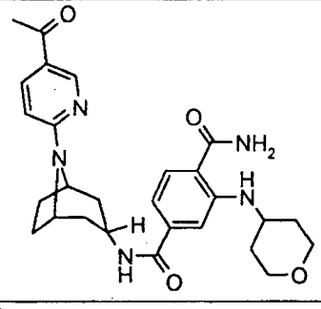
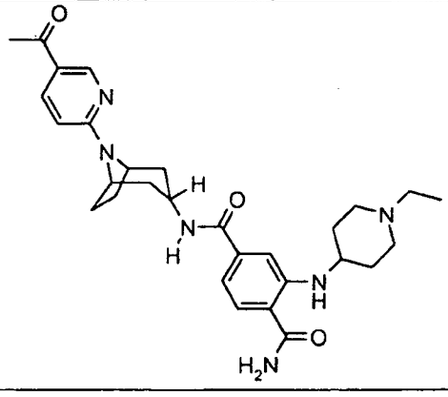
	N-[1-(2,6-difluoro-4-piperidin-4-ylphenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[2-(3-hydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = A**
	6-[3-endo-({[2-(3-hydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-{3-[(1-methylethyl)amino]propyl}-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-(4-hydroxybutyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = B**

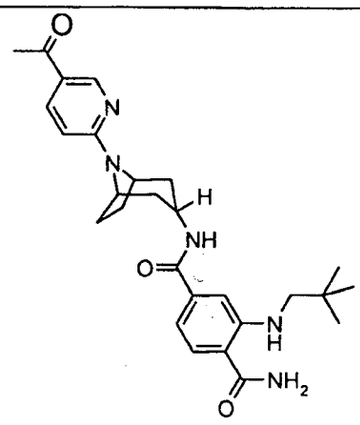
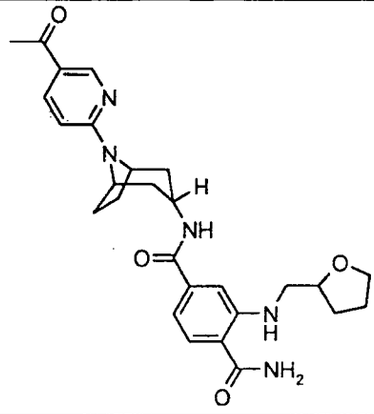
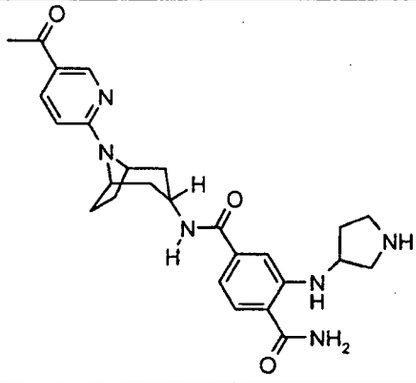
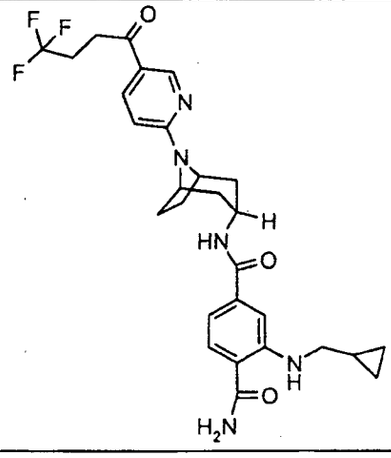
	6-{3-endo-[({2-[4-(dimethylamino)butyl]-3-(methyloxy)phenyl}carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}pyridine-3-carboxamide **ACTIVITY = C**
	6-[3-endo-({[2-(2,3-dihydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide **ACTIVITY = D**
	6-[3-endo-({[4-(1,2-dihydroxyethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide **ACTIVITY = C**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(trans-4-hydroxycyclohexyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**

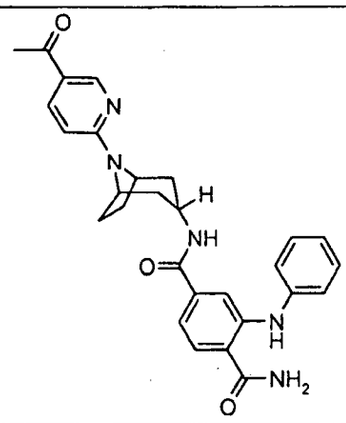
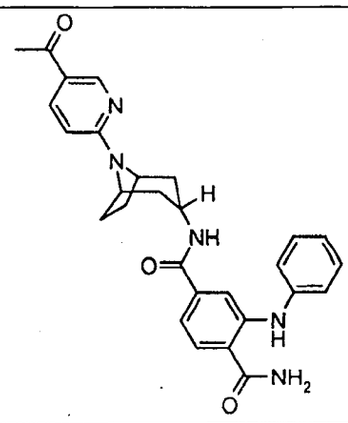
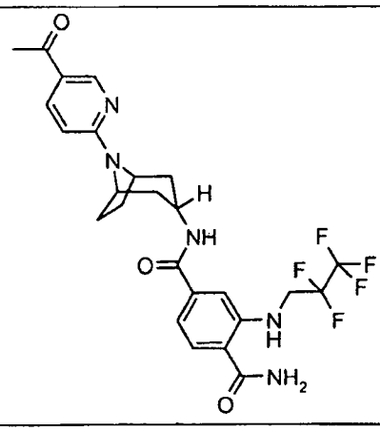
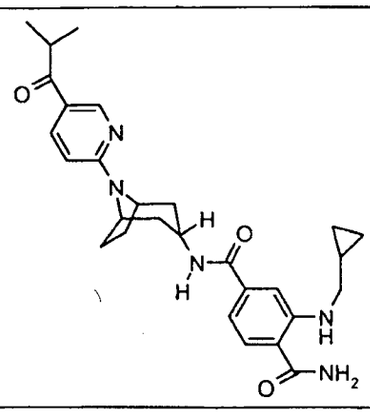
	N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-methyl-3-(methyloxy)benzamide **ACTIVITY = B**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(cyclohexylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(cyclopentylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**

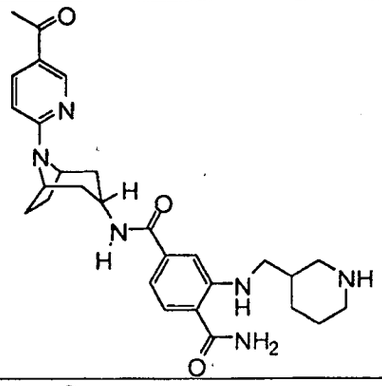
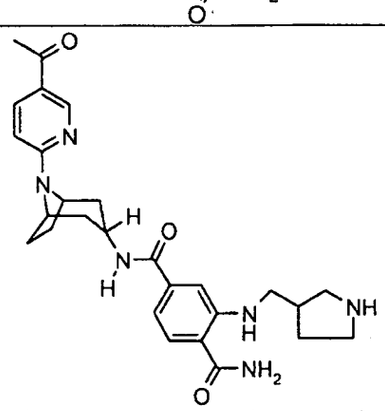
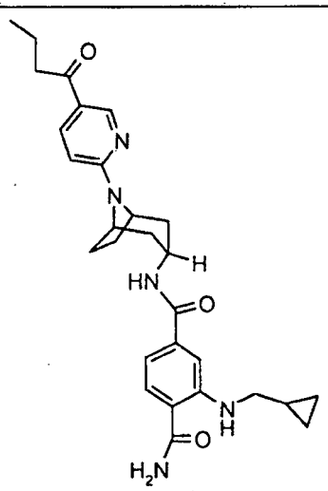
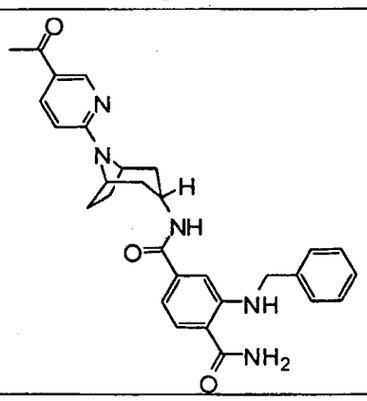
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(piperidin-4-ylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-methylethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-5-[(trans-4-hydroxycyclohexyl)amino]-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(ethylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**

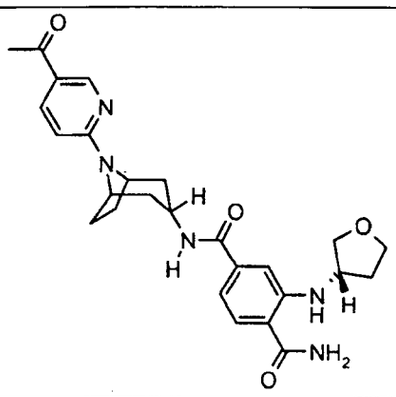
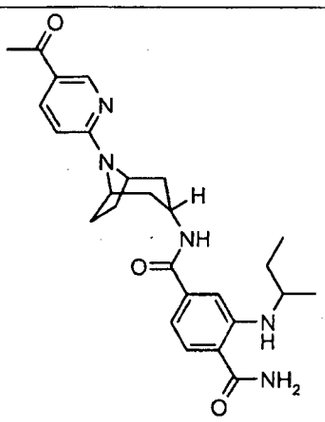
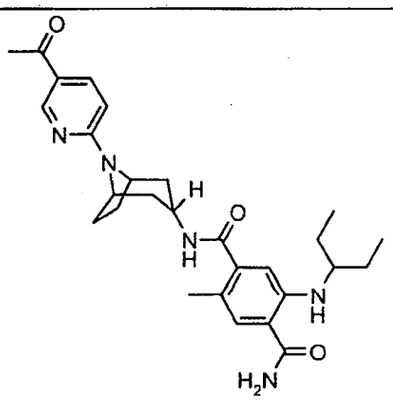
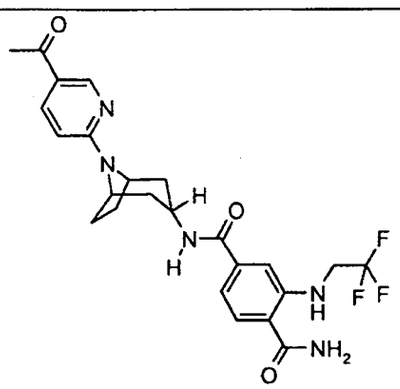
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(cyclopropylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2-methylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(tetrahydrofuran-3-ylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**

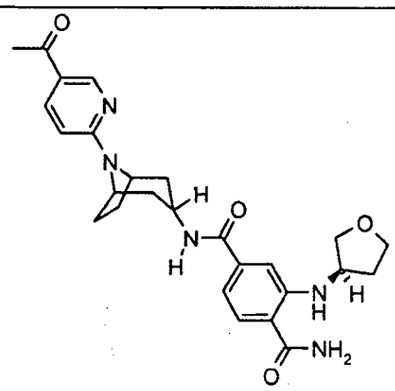
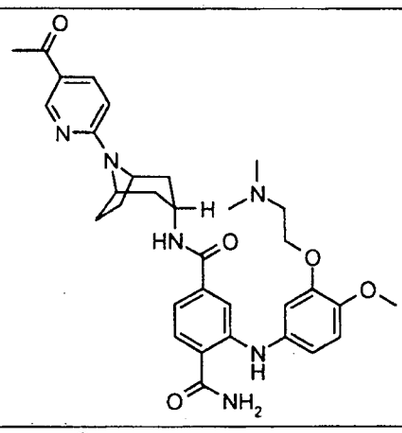
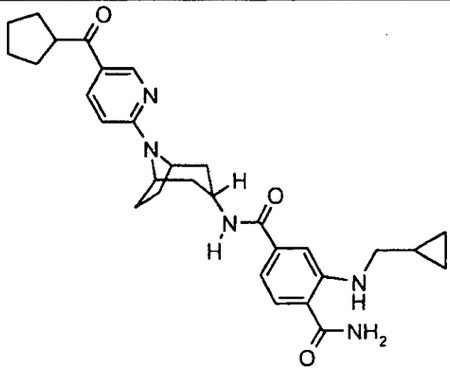
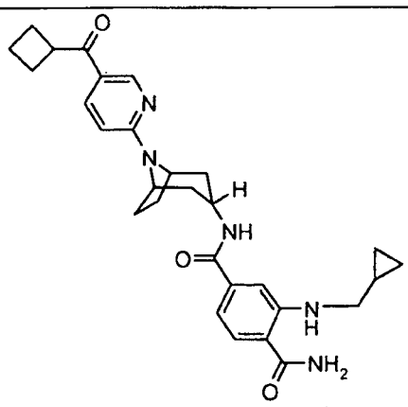
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-methylbutanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = C**
	2-[(cyclopropylmethyl)amino]-N4-[8-(5-propanoylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(tetrahydro-2H-pyran-4-ylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-ethylpiperidin-4-yl)amino]benzene-1,4-dicarboxamide **ACTIVITY = B**

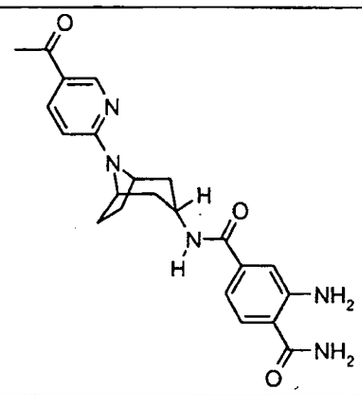
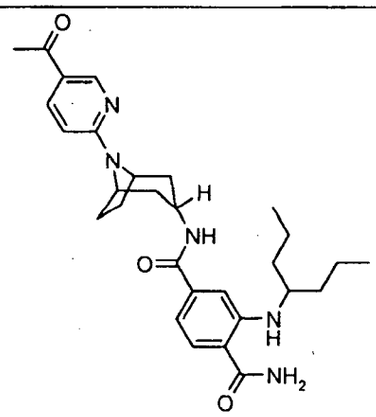
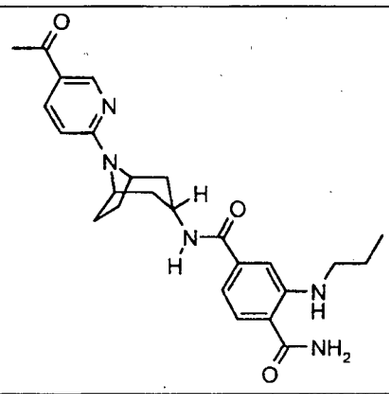
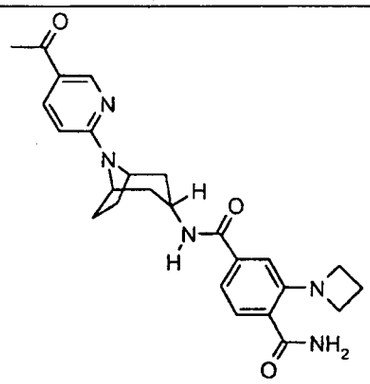
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2-dimethylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(tetrahydrofuran-2-ylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(pyrrolidin-3-ylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(4,4,4-trifluorobutanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = D**

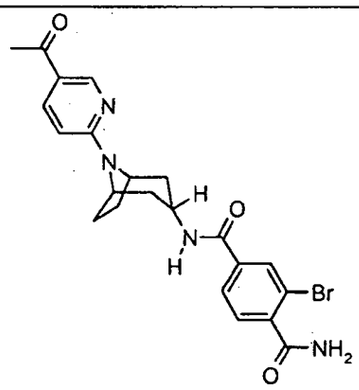
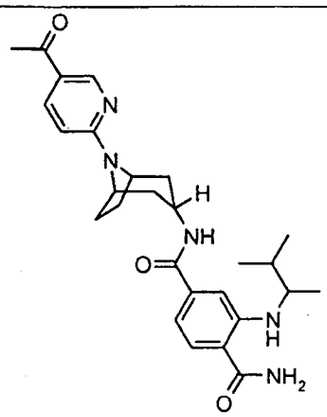
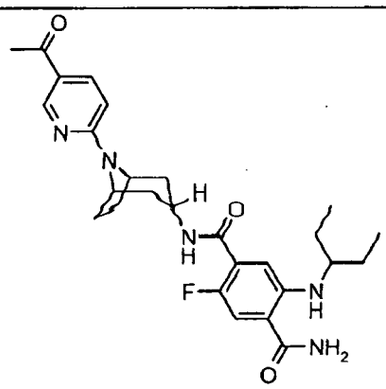
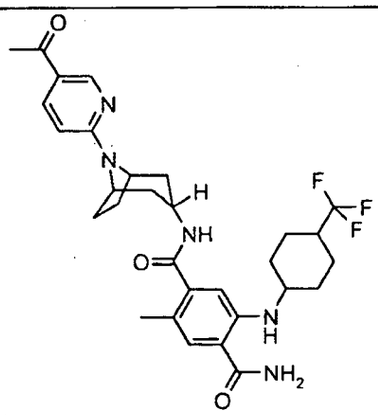
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(phenylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2-aminoethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2,3,3,3-pentafluoropropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(2-methylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = C**

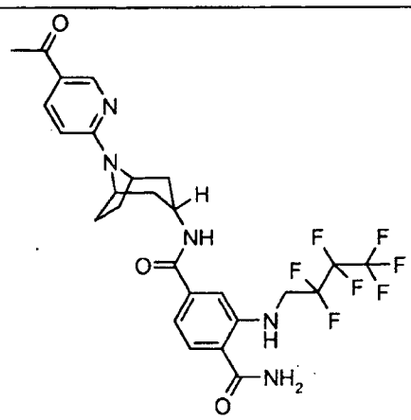
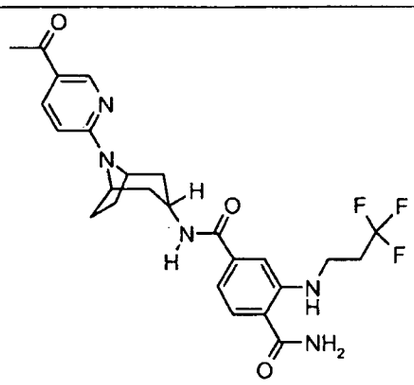
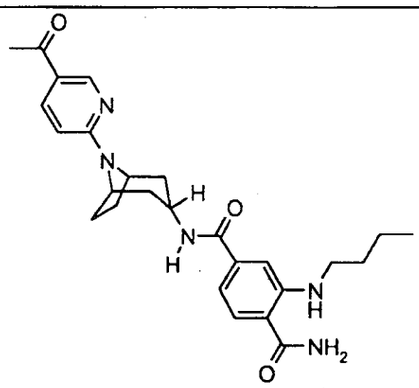
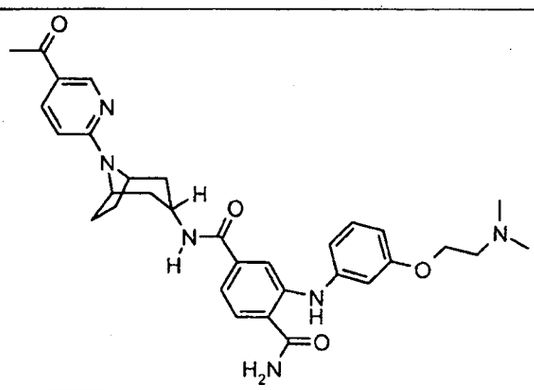
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(piperidin-3-ylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(pyrrolidin-3-ylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-butanoylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = B**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(phenylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = B**

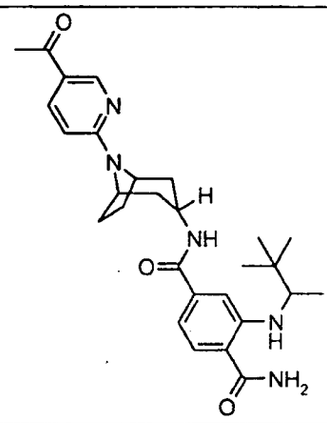
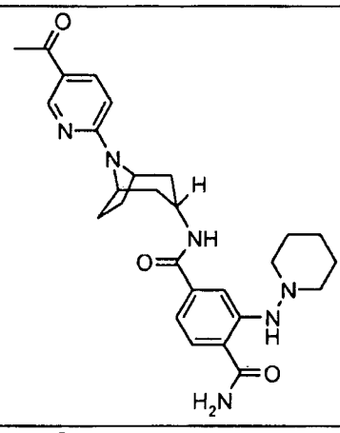
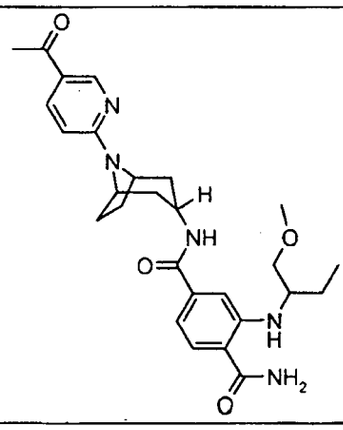
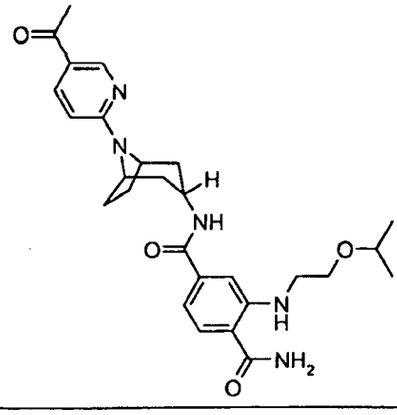
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(3S)-tetrahydrofuran-3-ylamino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-methylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-5-[(1-ethylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2,2-trifluoroethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**

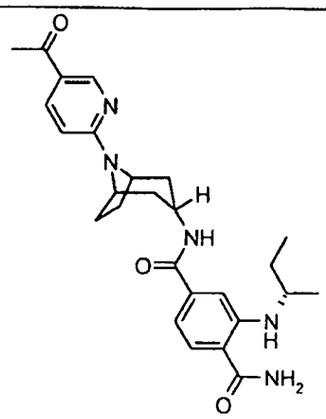
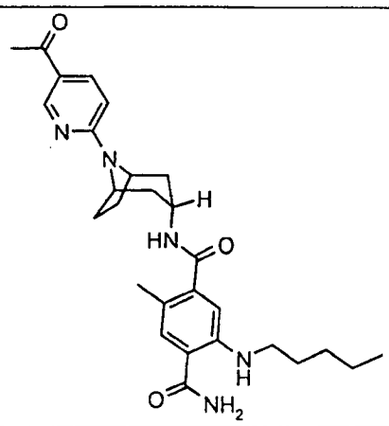
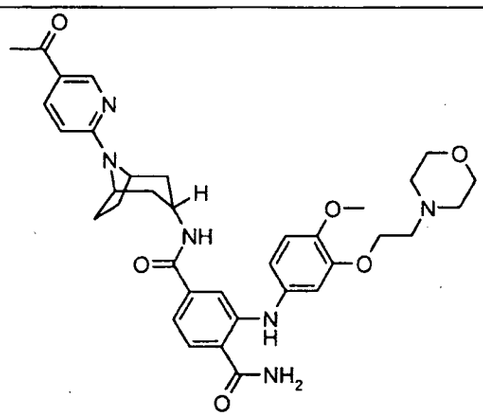
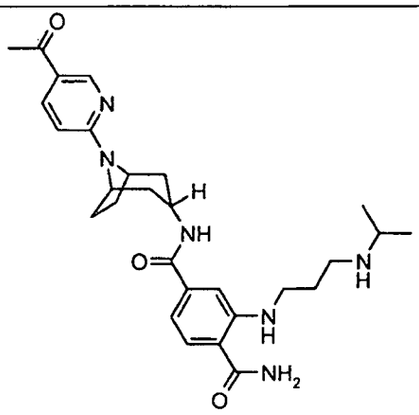
	N4-{8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(3R)-tetrahydrofuran-3-ylamino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(cyclopentylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = D**
	N4-{8-[5-(cyclobutylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = C**

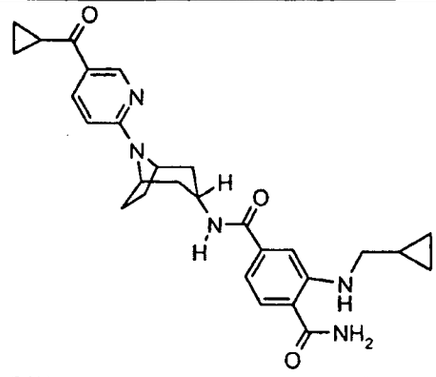
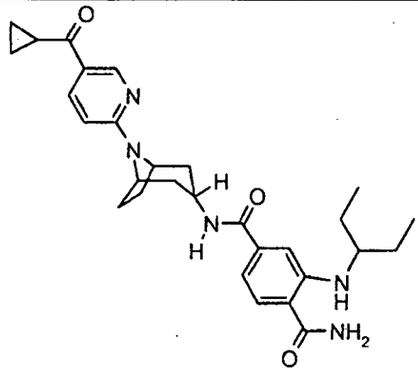
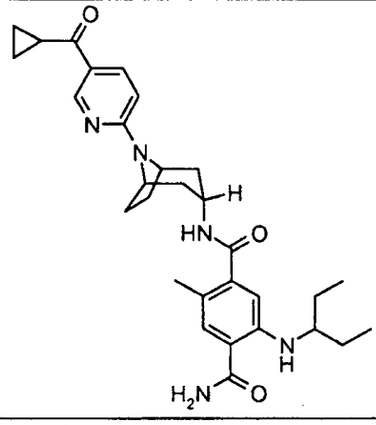
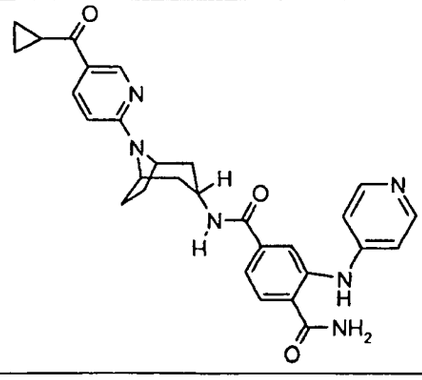
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-aminobenzene-1,4-dicarboxamide **ACTIVITY = B**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-propylbutyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(propylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-azetidin-1-ylbenzene-1,4-dicarboxamide **ACTIVITY = D**

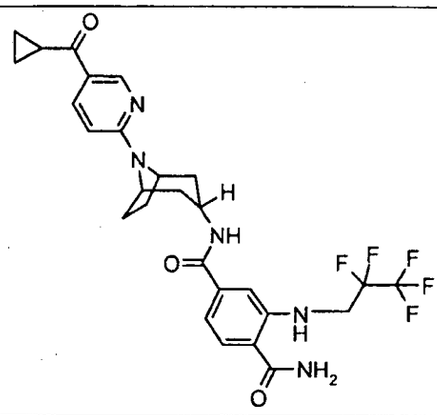
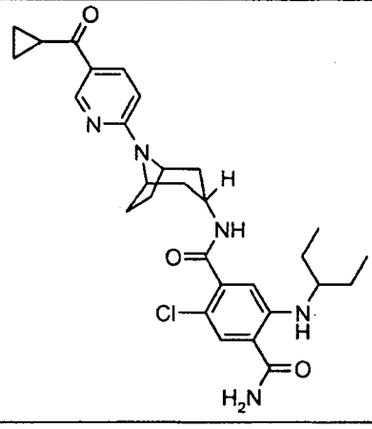
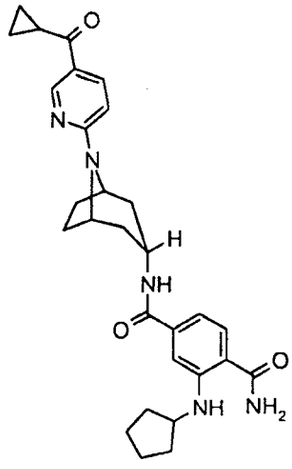
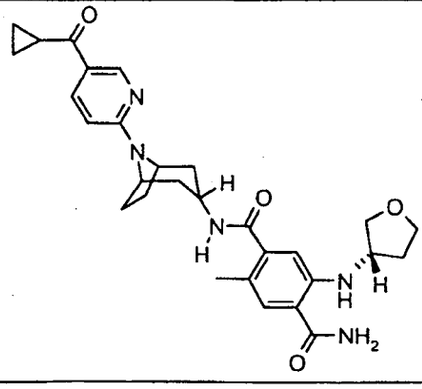
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-bromobenzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1,2-dimethylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-5-[(1-ethylpropyl)amino]-2-fluorobenzene-1,4-dicarboxamide **ACTIVITY = A**
	N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-methyl-5-{[4-(trifluoromethyl)cyclohexyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**

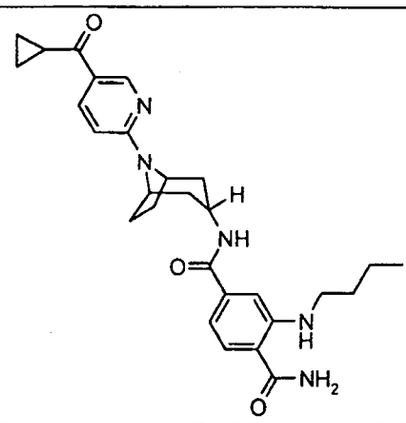
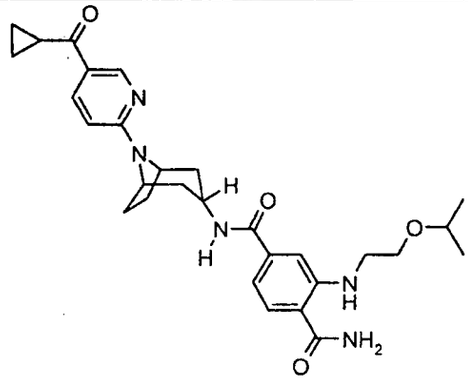
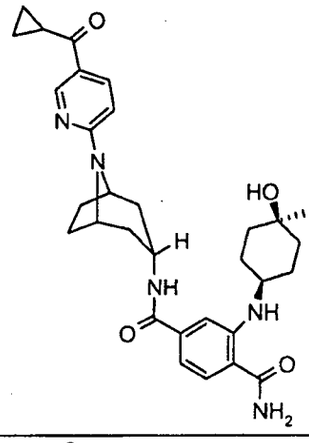
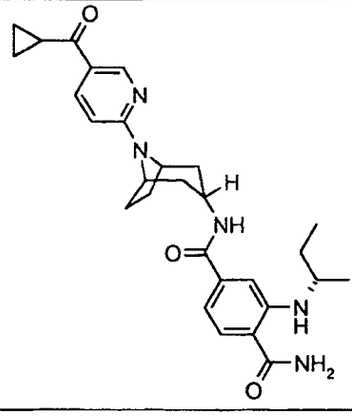
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2,3,3,4,4,4-heptafluorobutyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = B**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(3,3,3-trifluoropropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(butylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(3-{[2-(dimethylamino)ethyl]oxy}phenyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**

	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1,2,2-trimethylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(piperidin-1-ylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({1-[(methyloxy)methyl]propyl}amino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({2-[(1-methylethyl)oxy]ethyl}amino)benzene-1,4-dicarboxamide **ACTIVITY = A**

	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-{[(1S)-1-methylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-methyl-5-(pentylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({4-(methyloxy)-3-[(2-morpholin-4-ylethyl)oxy]phenyl}amino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({3-[(1-methylethyl)amino]propyl}amino)benzene-1,4-dicarboxamide **ACTIVITY = B**

	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(pyridin-4-ylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**

	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(2,2,3,3,3-pentafluoropropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-chloro-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-(cyclopentylamino)-N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(3S)-tetrahydrofuran-3-ylamino]benzene-1,4-dicarboxamide **ACTIVITY = A**

	2-(butylamino)-N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-({2-[(1-methylethyl)oxy]ethyl}amino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cis-4-hydroxy-4-methylcyclohexyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1S)-1-methylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**

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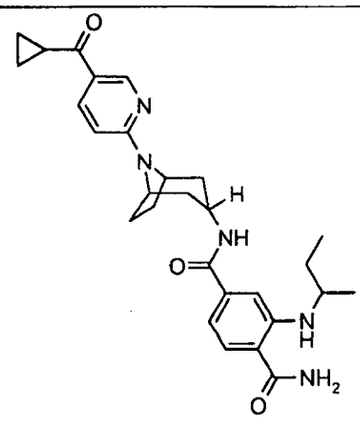
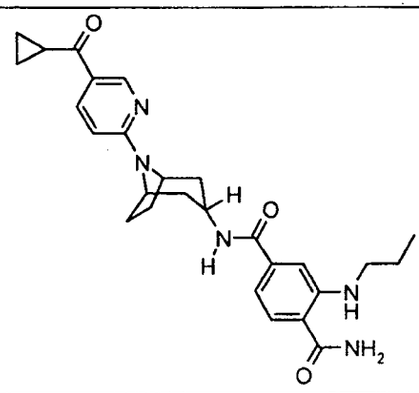
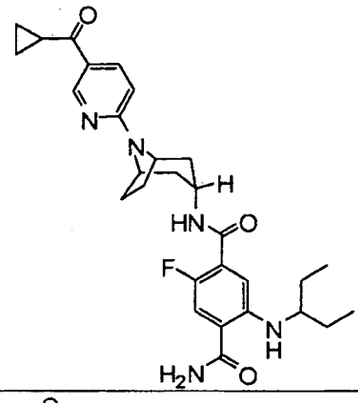
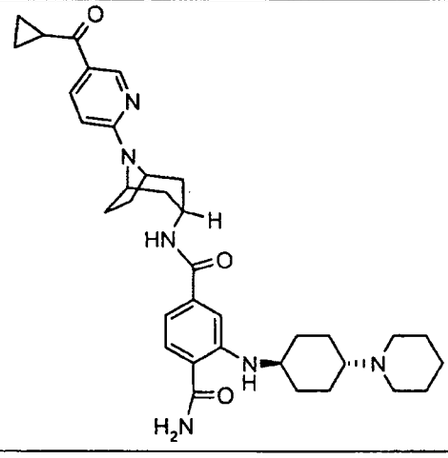
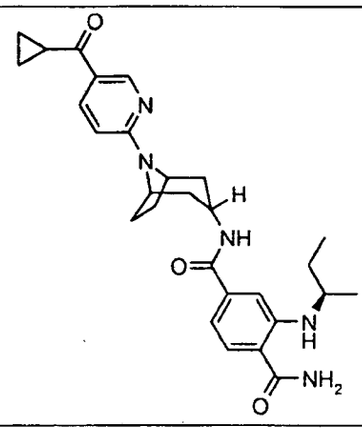
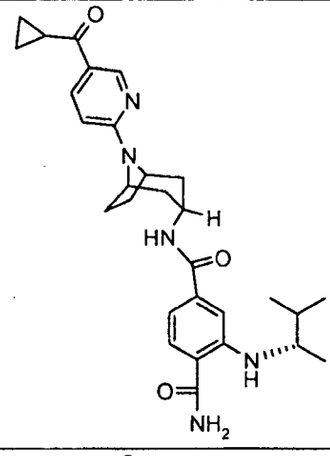
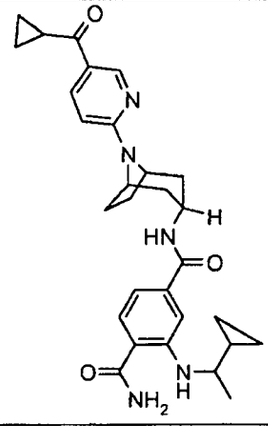
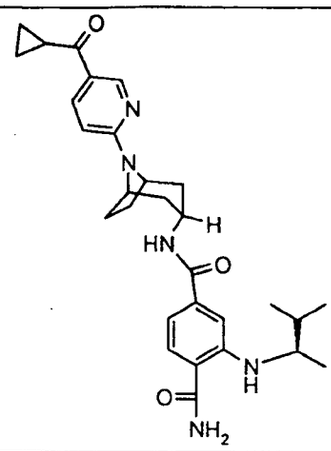
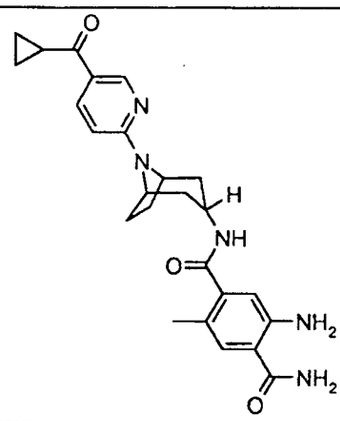
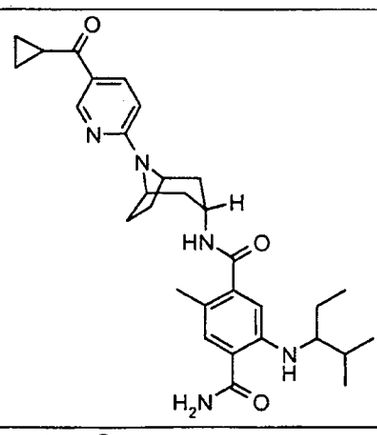
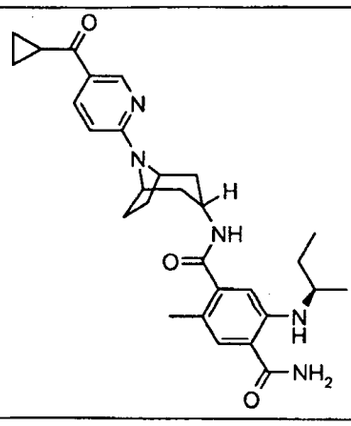
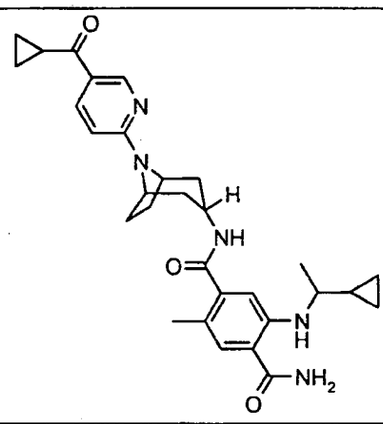
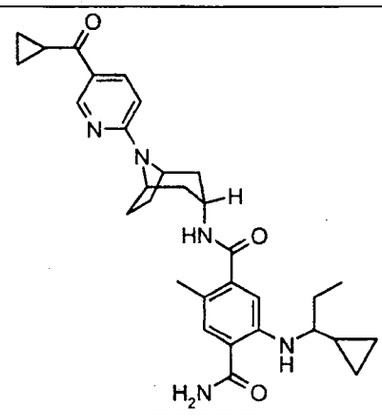
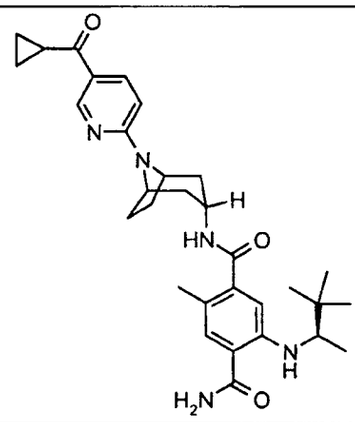
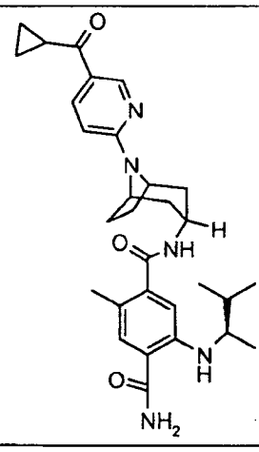
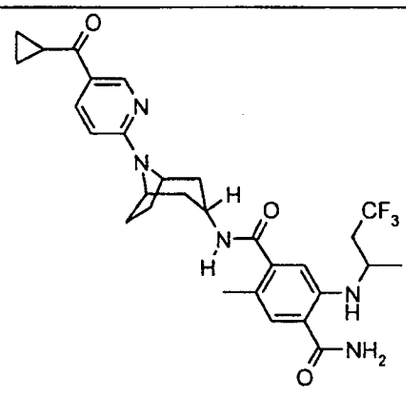
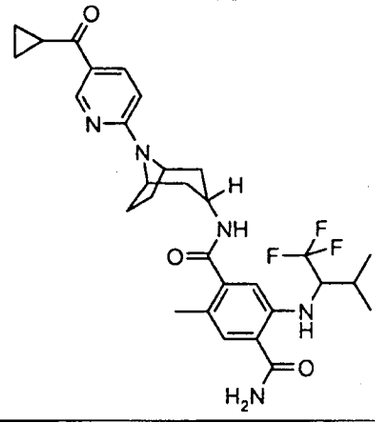
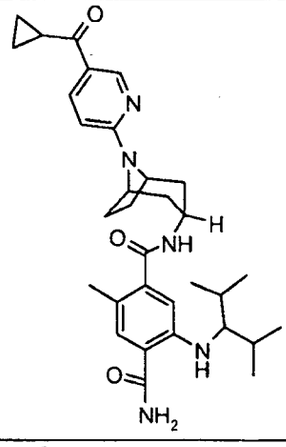
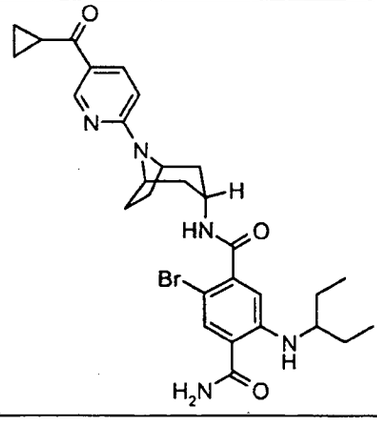
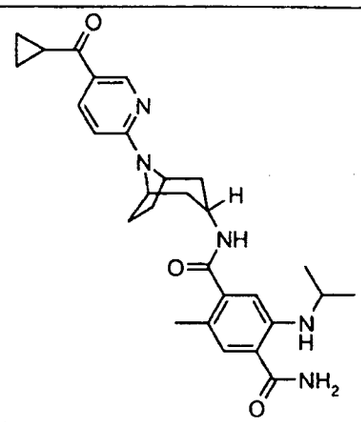
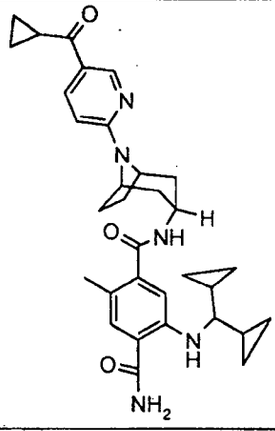
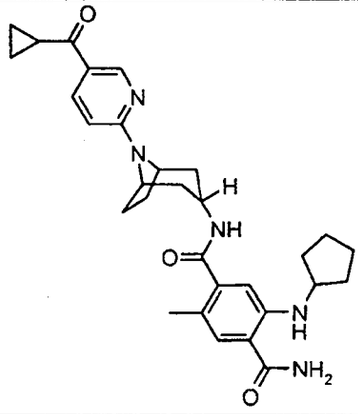
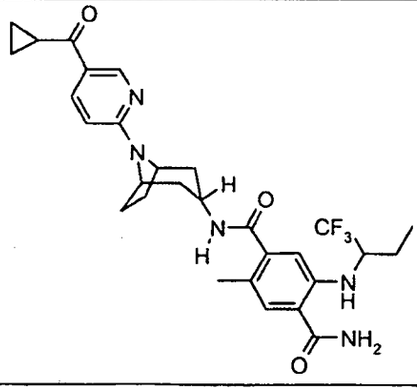
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(1-methylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(propylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]-2-fluorobenzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(trans-4-piperidin-1-ylcyclohexyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**

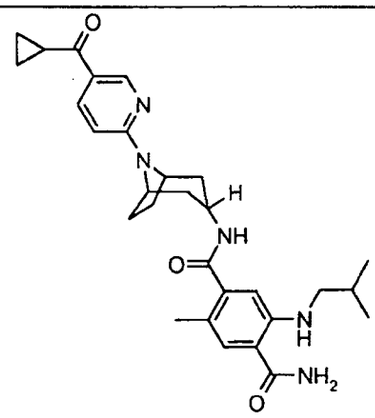
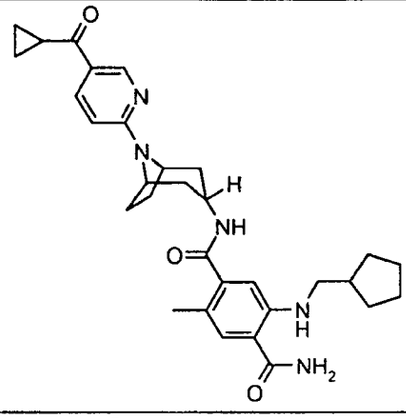
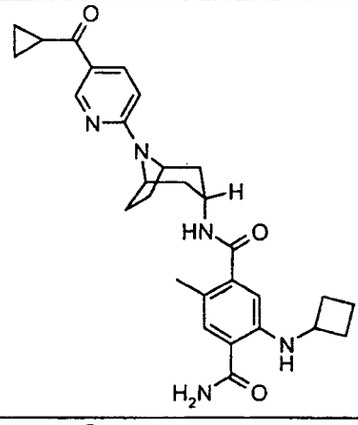
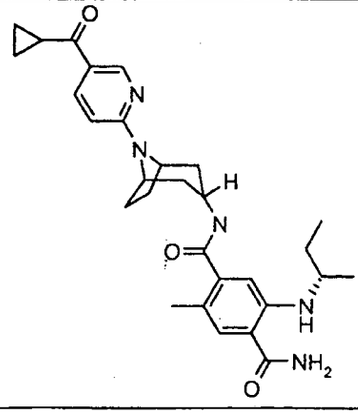
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1S)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(1-cyclopropylethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**

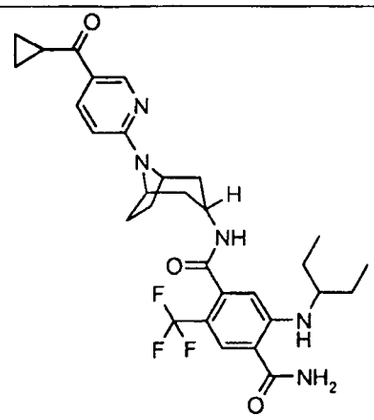
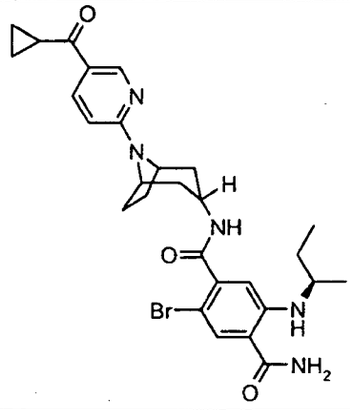
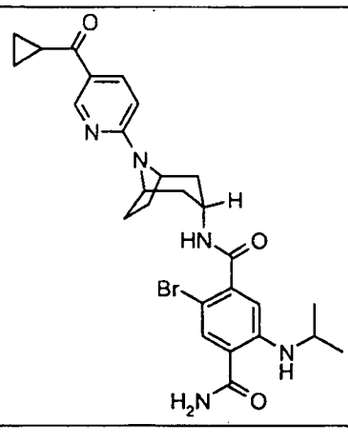
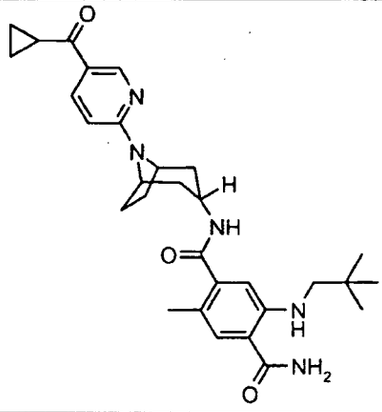
	N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1R)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	5-amino-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethyl-2-methylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**

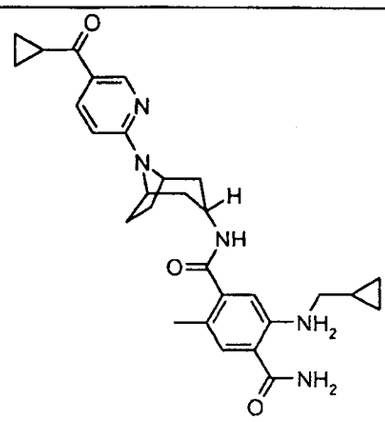
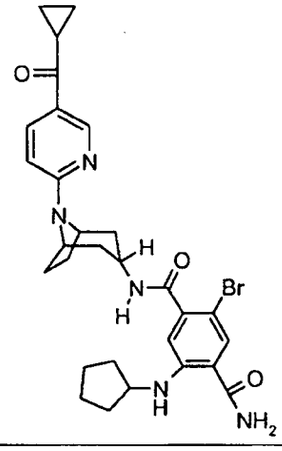
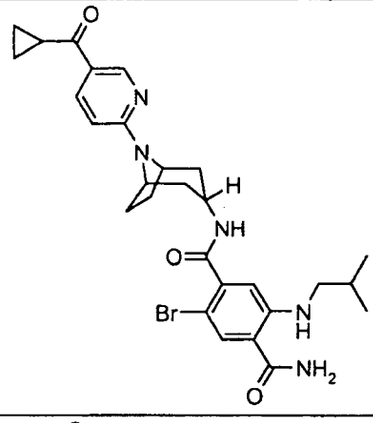
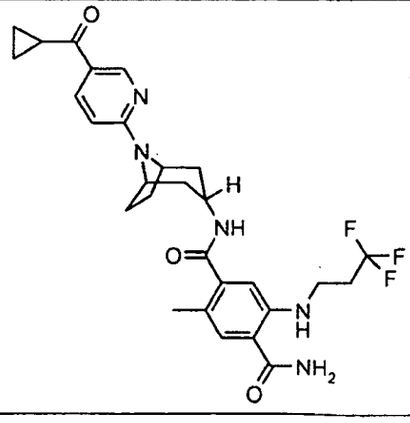
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-cyclopropylethyl)amino]-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-cyclopropylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[(1R)-1,2,2-trimethylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1R)-1,2-dimethylpropyl]amino}-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**

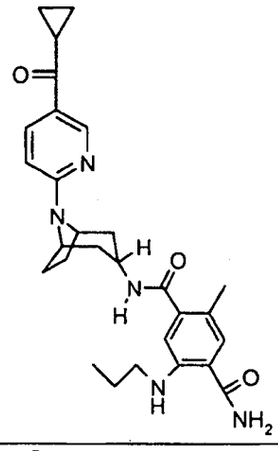
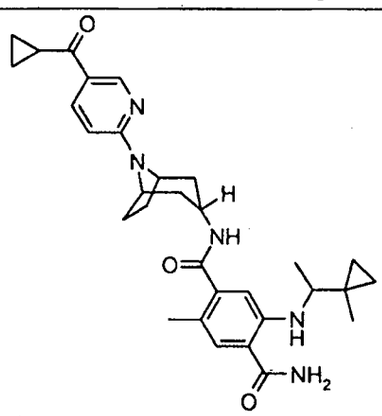
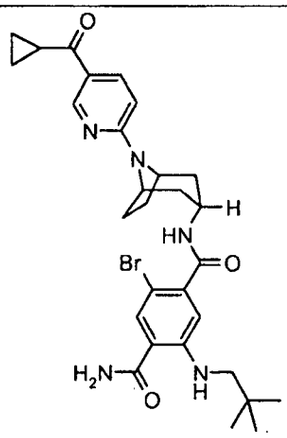
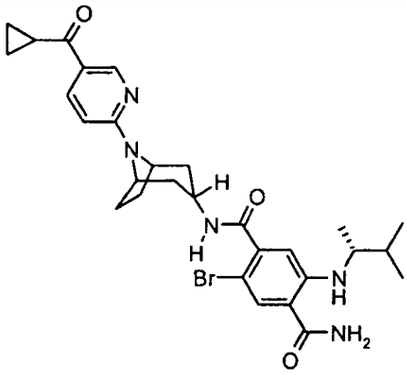
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(3,3,3-trifluoro-1-methylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[2-methyl-1-(trifluoromethyl)propyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[2-methyl-1-(1-methylethyl)propyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**

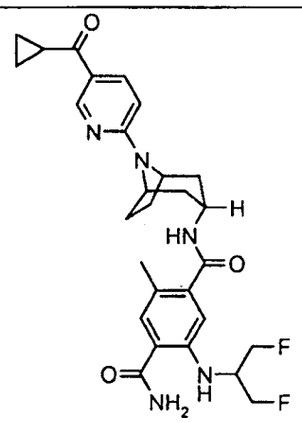
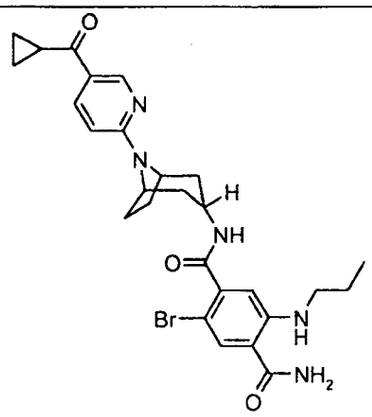
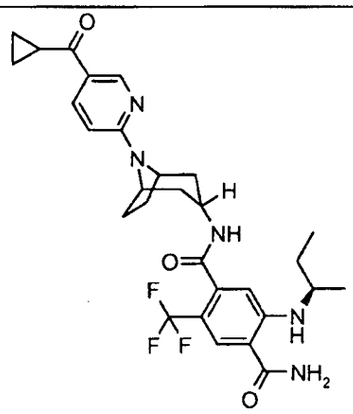
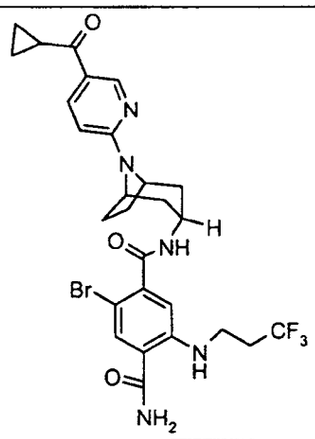
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(1-methylethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(dicyclopropylmethyl)amino]-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	5-(cyclopentylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridine-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[1-(trifluoromethyl)propyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**

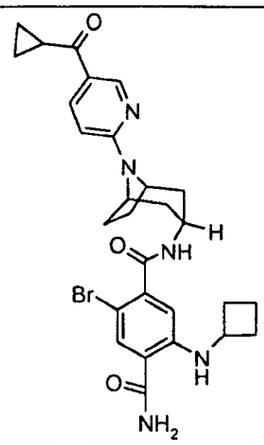
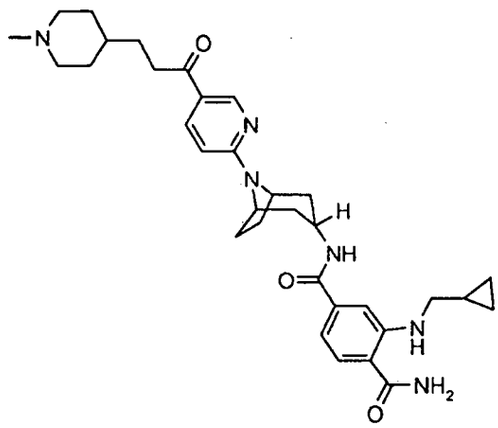
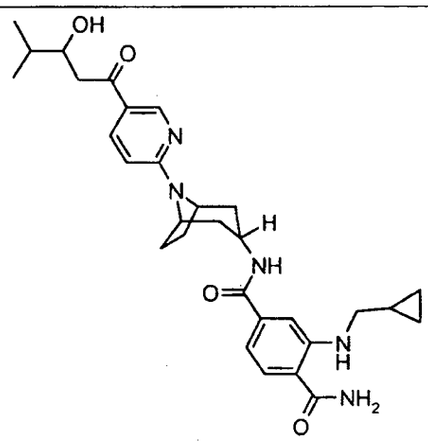
	N-{8-[5-(cyclopropylcarbonyl)pyridine-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(2-methylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	5-[(cyclopentylmethyl)amino]-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	5-(cyclobutylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridine-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[(1S)-1-methylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**

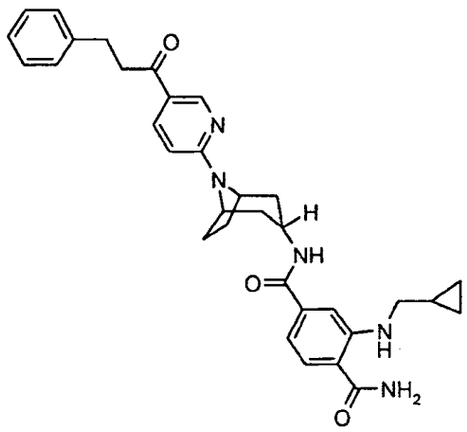
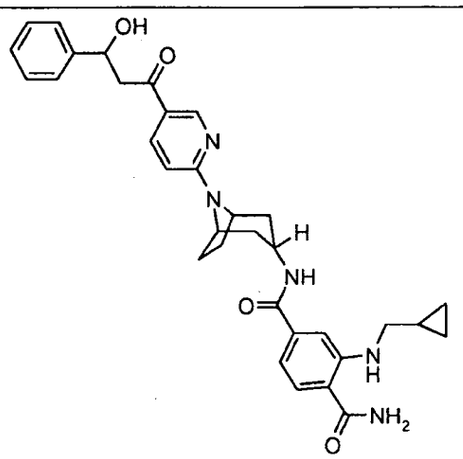
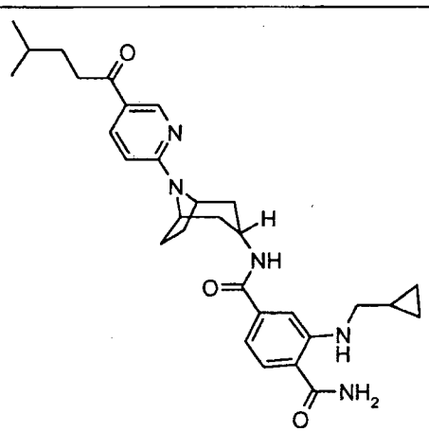
	N-{8-[5-(cyclopropylcarbonyl)pyridine-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]-2-(trifluoromethyl)benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-methylethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(2,2-dimethylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**

	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(cyclopropylmethyl)amino]-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-5-(cyclopentylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(2-methylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(3,3,3-trifluoropropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**

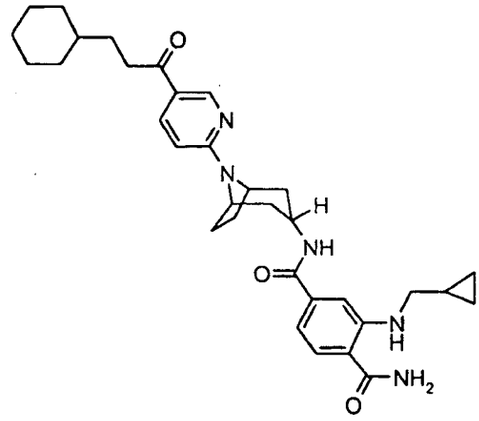
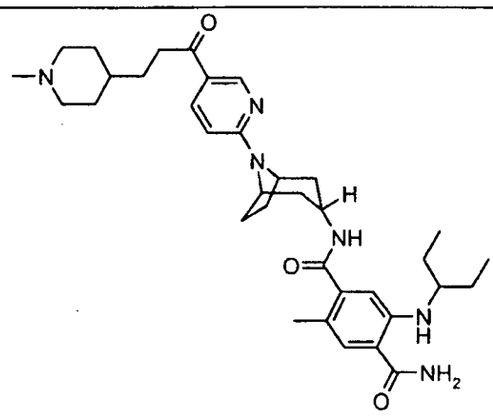
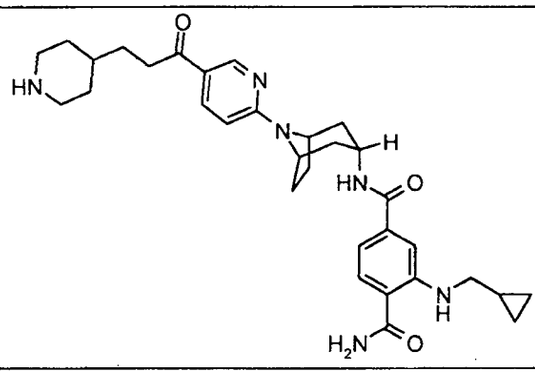
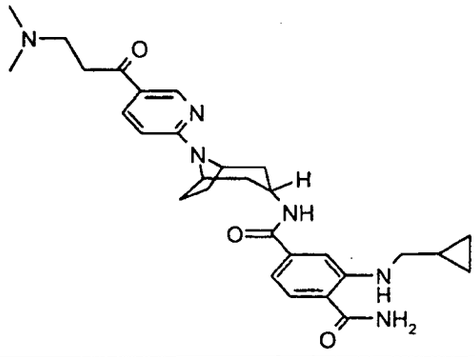
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-(propylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[1-(1-methylcyclopropyl)ethyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(2,2-dimethylpropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1R)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**

	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[2-fluoro-1-(fluoromethyl)ethyl]amino}-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-(propylamino)benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1R)-1-methylpropyl]amino}-2-(trifluoromethyl)benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(3,3,3-trifluoropropyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**

	2-bromo-5-(cyclobutylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(1-methylpiperidin-4-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-hydroxy-4-methylpentanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**

	2-[(cyclopropylmethyl)amino]-N4-{8-{5-(3-phenylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = D**
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-hydroxy-3-phenylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = B**
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(4-methylpentanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**

150.

	N4-{8-[5-(3-cyclohexylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = C**
	5-[(1-ethylpropyl)amino]-2-methyl-N-(8-{5-[3-(1-methylpiperidin-4-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-piperidin-4-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(N,N-dimethyl-beta-alanyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**

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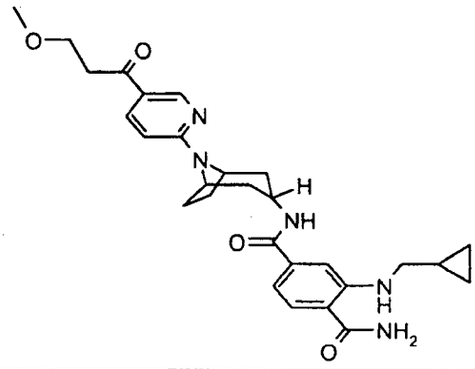
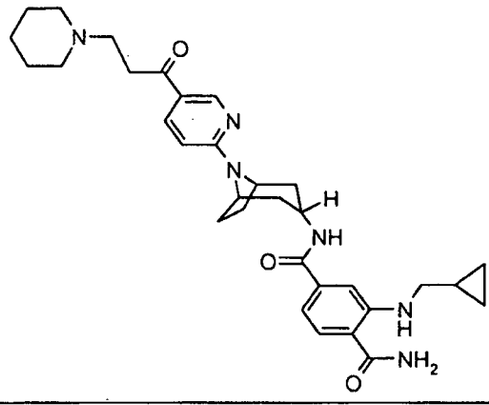
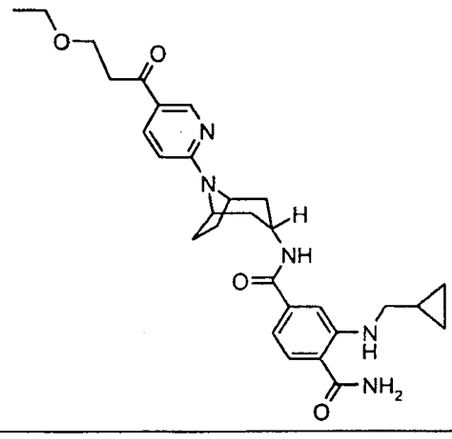
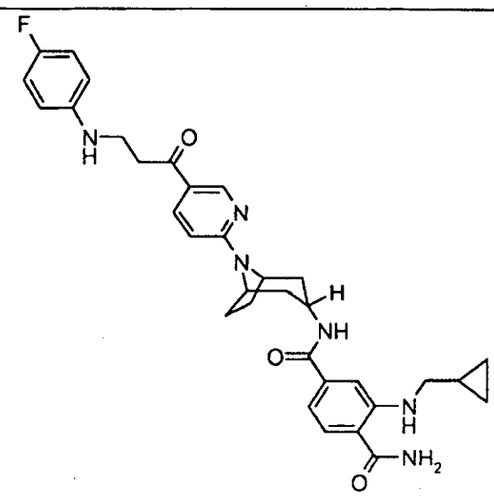
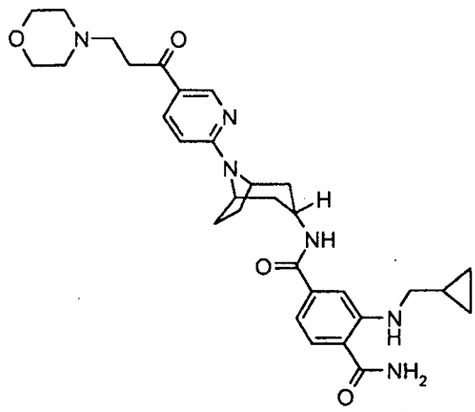
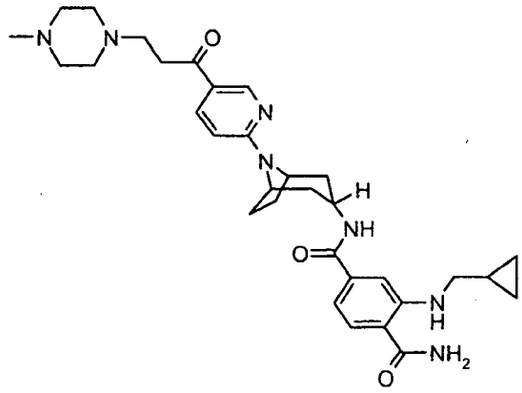
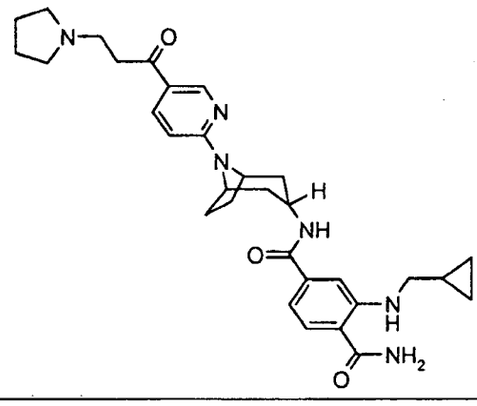
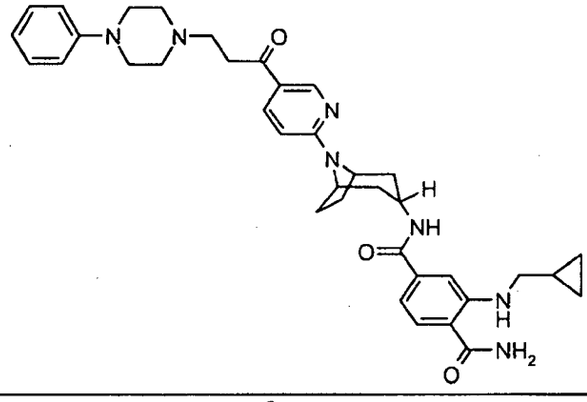
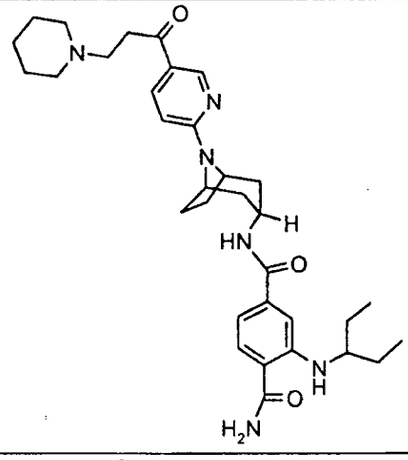
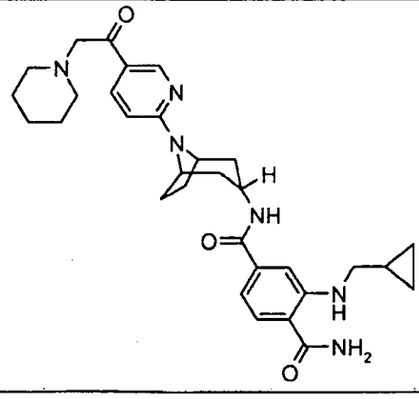
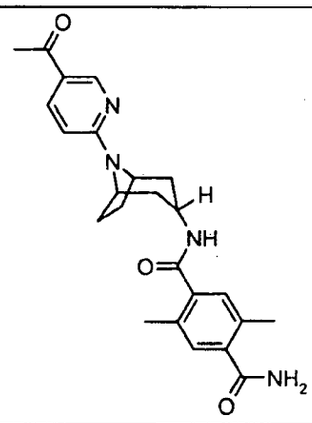
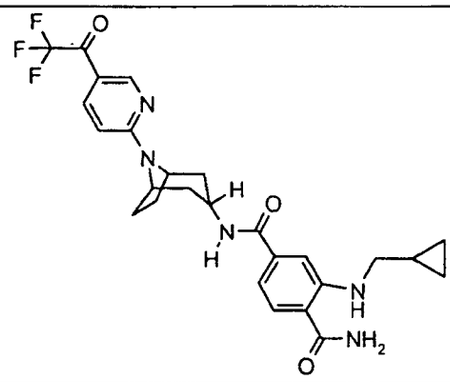
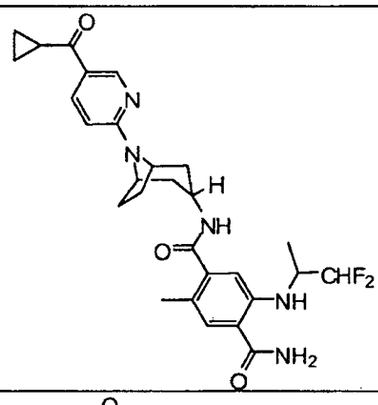
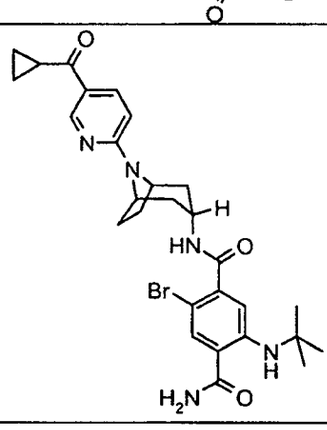
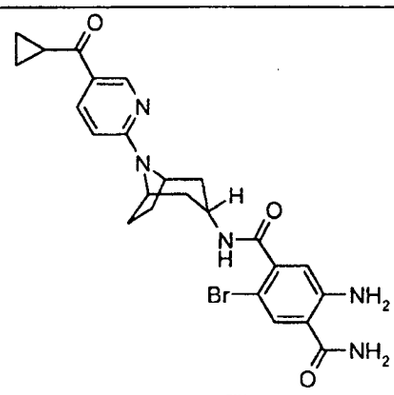
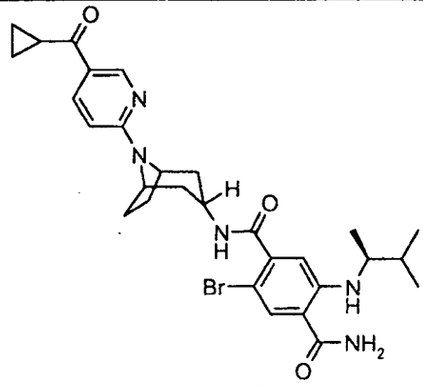
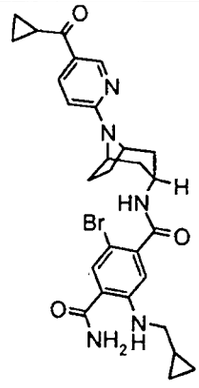
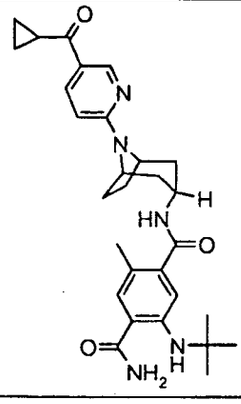
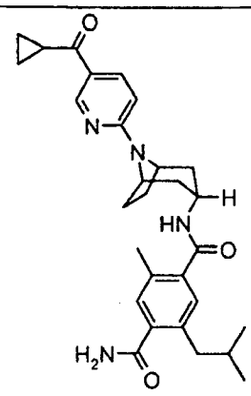
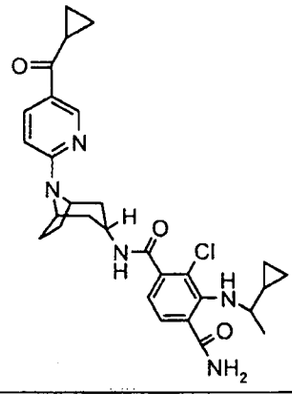
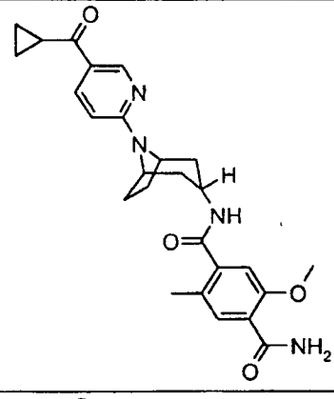
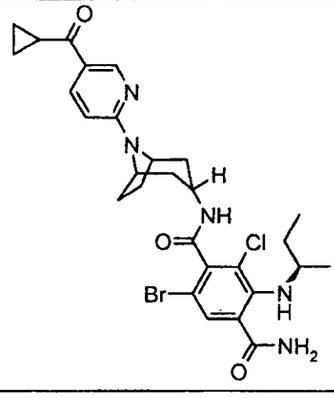
	2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(methyloxy)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-piperidin-1-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(ethyloxy)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = A**

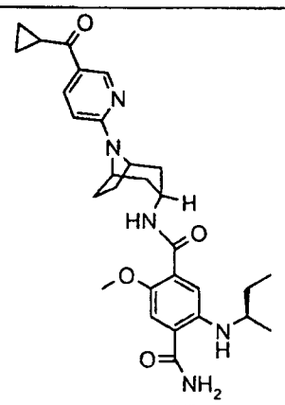
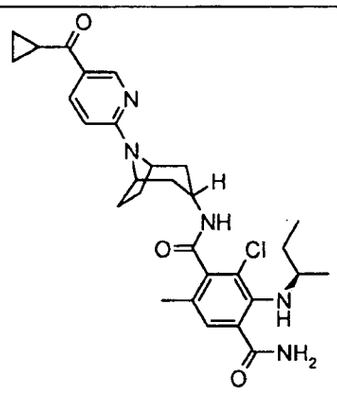
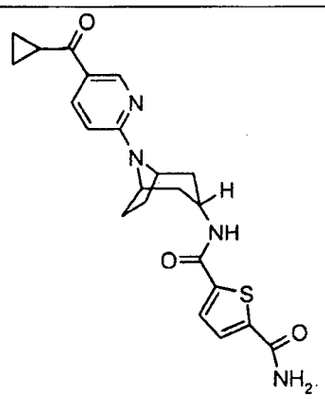
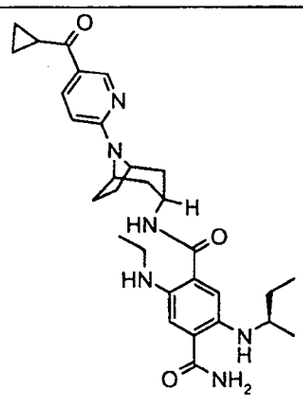
	2-[(cyclopropylmethyl)amino]-N4-(8-{5-[N-(4-fluorophenyl)-beta-alanyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = D**
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-morpholin-4-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(4-methylpiperazin-1-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = A**

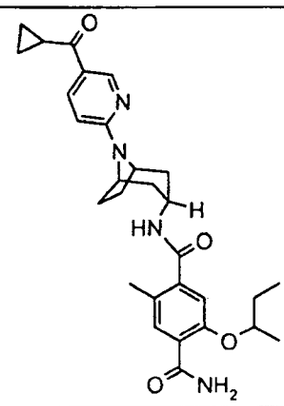
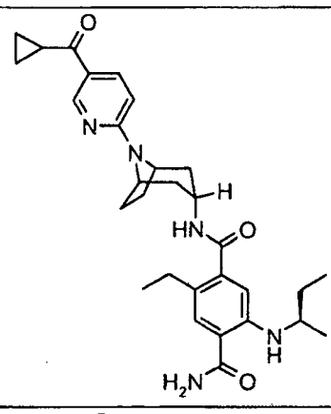
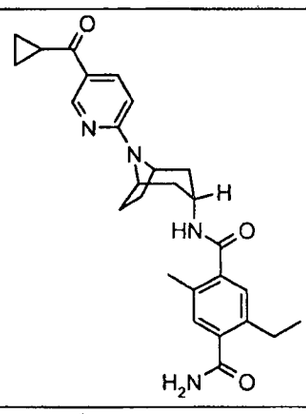
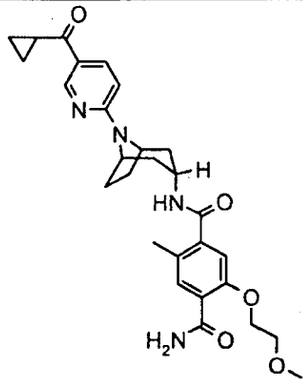
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-pyrrolidin-1-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-{8-{5-[3-(4-phenylpiperazin-1-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide **ACTIVITY = B**
	2-[(1-ethylpropyl)amino]-N4-{8-[5-(3-piperidin-1-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(piperidin-1-ylacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = D**

	N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2,5-dimethylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	2-[(cyclopropylmethyl)amino]-N4-{8-[5-(trifluoroacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = D**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(2,2-difluoro-1-methylethyl)amino]-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1,1-dimethylethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**

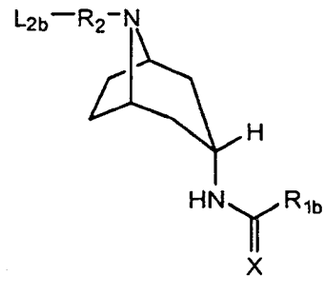
	5-amino-2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1S)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1,1-dimethylethyl)amino]-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**

	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-(2-methylpropyl)benzene-1,4-dicarboxamide **ACTIVITY = A**
	2-chloro-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-3-[(1-cyclopropylethyl)amino]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-(methyloxy)benzene-1,4-dicarboxamide **ACTIVITY = A**
	5-bromo-3-chloro-N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**

	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(methyloxy)-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	3-chloro-N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-methyl-2-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}thiophene-2,5-dicarboxamide **ACTIVITY = C**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(ethylamino)-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = D**

	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(1-methylpropyl)oxy]benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-ethyl-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-ethyl-2-methylbenzene-1,4-dicarboxamide **ACTIVITY = A**
	N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[2-(methyloxy)ethyl]oxy}benzene-1,4-dicarboxamide **ACTIVITY = B**

[0082] Another aspect of the disclosure relates to a compound according to Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

R_{1b} is selected from heteroaryl optionally substituted with 1, 2 or 3 groups selected from $-NH_2$, halogen, phenyl and alkyl;

R_2 is a phenyl or a heteroaryl that can contain 1, 2 or 3 heteroatoms, wherein the aryl or heteroaryl can be substituted with 1, 2 or 3 groups selected from alkyl, -OH, alkoxy, and halogen;

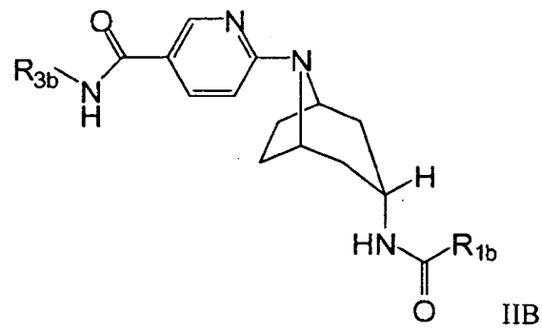
R_{3b} is selected from hydrogen, $-CF_3$, $-NH_2$, -OH, alkyl optionally substituted with 1, 2 or 3 R_{5b}, alkoxy, dialkylaminoalkyl, cycloalkyl optionally substituted with arylalkoxy, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy and heterocycloalkyl optionally substituted with alkyl or aryl, alkenyl, alkynyl, heterocycloalkyl optionally substituted with a group selected from alkyl, -C(O)O-alkyl and arylalkyl, arylalkyl optionally substituted with alkylheterocycloalkyl at any ring position of the aryl group, and heteroaryl;

R_{5b} is selected from halogen, cycloalkyl, heteroaryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl and alkoxy, alkylthio, heterocycloalkyl optionally substituted with 1, 2, or 3 groups selected from alkyl, halogen, phenyl and oxo, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy and heterocycloalkyl optionally substituted with alkyl, alkoxy, dialkylamino, -OH, $-C(O)-NH_2$, $-C(O)-O-CH_3$, $-C(O)-N(H)(C_1-C_3)$alkyl, heteroarylamino optionally substituted with halogen and $-OCF_3$;

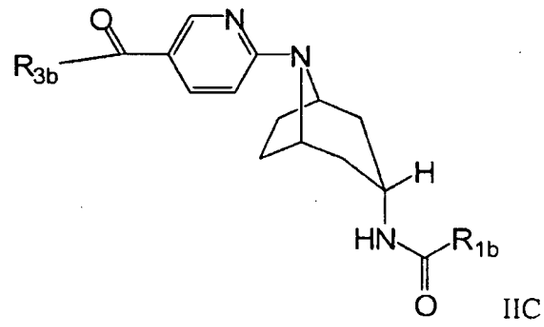
L_{2b} is $-C(O)-NH-R_{3b}$, -CN or $-C(O)-R_{3b}$; and

X is O or S.

[0083] Another embodiment of the compound of Formula II is a compound according to Formula IIB or IIC:



IIB



IIC

wherein R_{1b} is as defined in the compound of Formula II; and R_{3b} is selected from alkyl optionally substituted with 1, 2 or 3 halogens, cycloalkyl and hydrogen.

[0084] In another embodiment of the compound of Formula II, R_{3b} is selected from H, cycloalkyl, and $(C_1\text{-}C_6)$alkyl optionally substituted with one or more halogens.

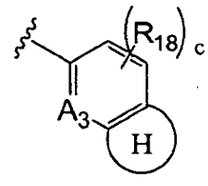
[0085] In another embodiment of Formula II, IIB or IIC, R_{3b} is methyl.

[0086] In another embodiment of Formula II, IIB or IIC, R_{3b} is cyclopropyl.

[0087] In another embodiment of the compound of Formula II, IIB or IIC, R_{3b} is $-CH_2CF_3$.

[0088] In another embodiment of the compound of Formula II, IIB or IIC, R_{3b} is 1-methylethyl.

[0089] In another embodiment of the compound of Formula II, IIB or IIC, R_{1b} is



(O)

wherein:

A_3 is =N- or =CH-;

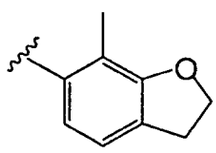
each R_{18} is independently selected from $-NH_2$, halogen and alkyl;

the (H) ring is a 5 or 6 membered heterocyclic ring fused to the two carbon atoms to which the (H) ring is attached, wherein the (H) ring contains 1, 2 or 3 heteroatoms selected from N, O or S; and

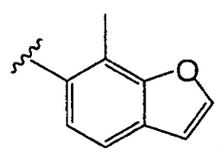
c is 0, 1 or 2.

[0090] In other embodiments of the compound of Formula II, IIB or IIC, R_{1b} is of Formula (O) and is selected from 1H-benzimidazole optionally substituted with 1 or 2 methyl groups, 1H-indole optionally substituted with 1 or 2 methyl groups, benzofuran, 3,4-dihydro-2H-chromenyl optionally substituted with 1 or 2 methyl groups, 2,3-dihydrobenzofuranyl optionally substituted with 1 or 2 methyl groups, 2,3-dihydro-1,4-benzodioxin-6-yl optionally substituted with 1 or 2 methyl groups, 1H-1,2,3-benzotriazole optionally substituted with 1, 2 or 3 methyl groups, 9H-purin-9-yl optionally substituted with 1 or 2 groups selected from halogen and amino, 1,3-benzothiazole optionally substituted with 1 or 2 methyl groups, and 2,3-dihydro-1-benzofuran optionally substituted with 1 or 2 methyl groups.

[0091] In other embodiments of the compound of Formula II, IIB or IIC, R_{1b} is

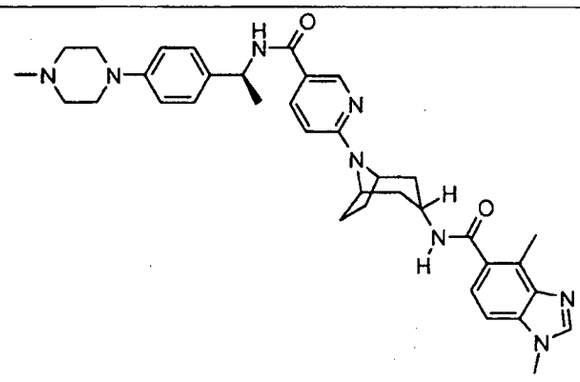
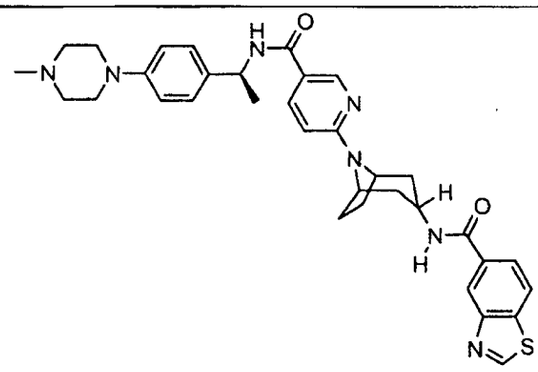
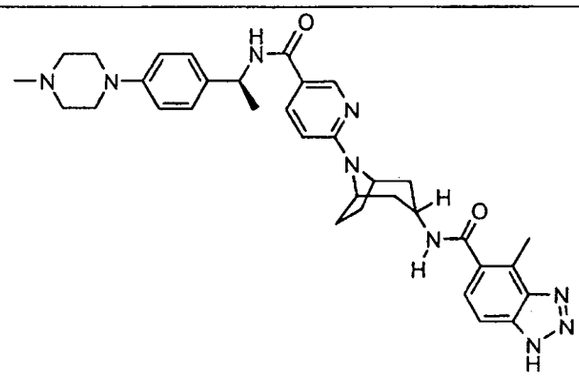


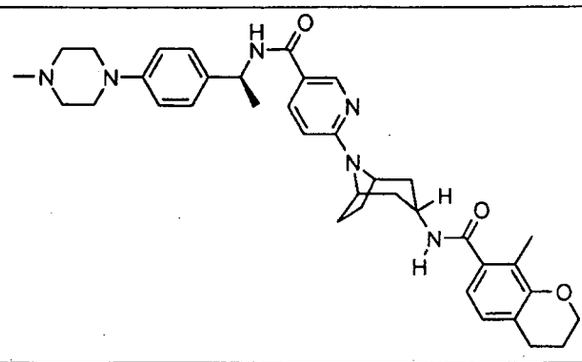
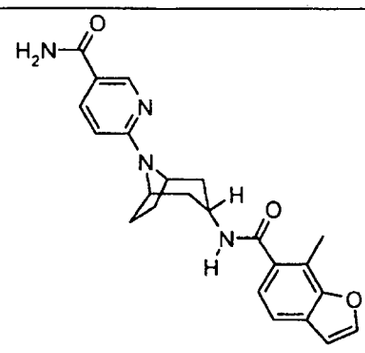
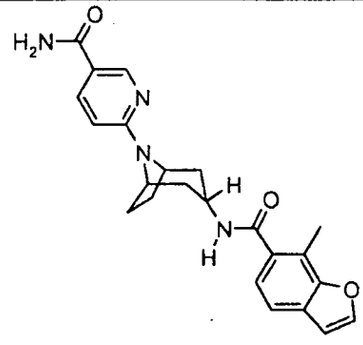
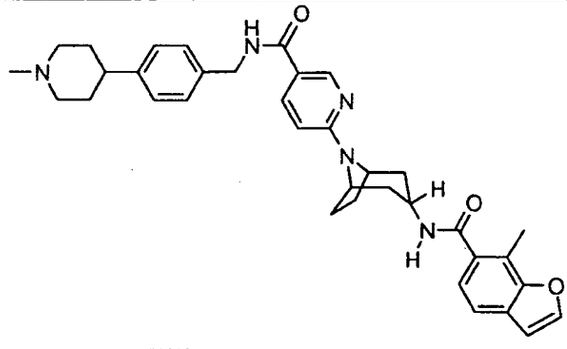
or

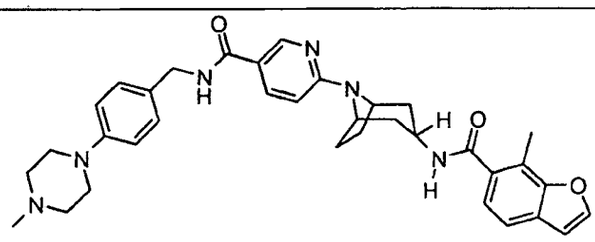
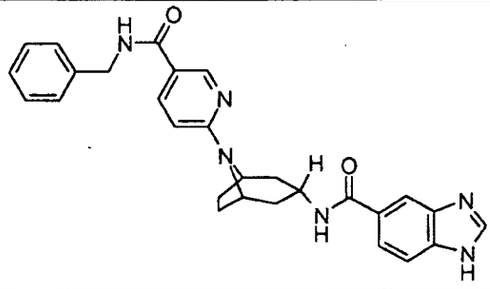
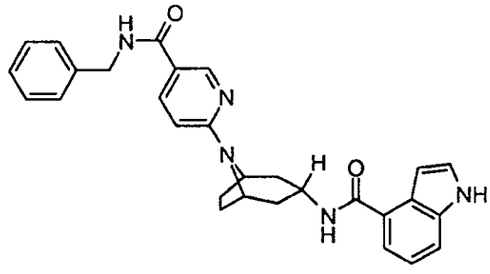
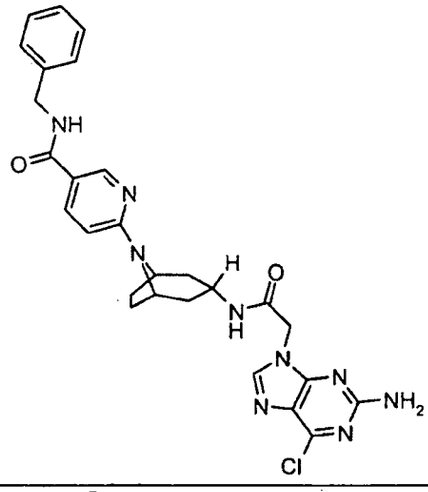
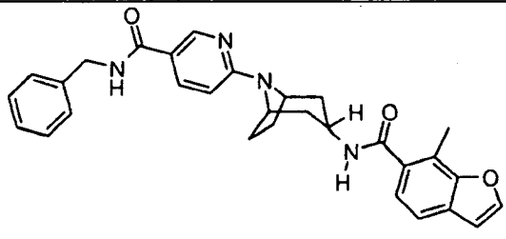


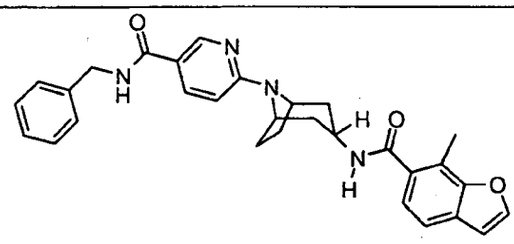
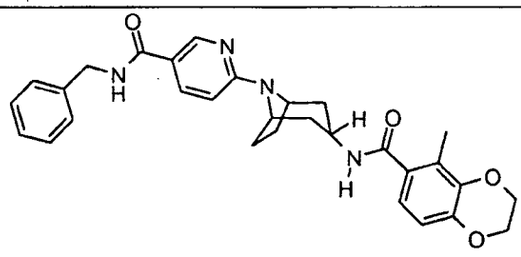
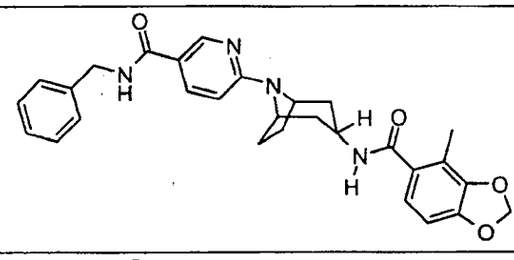
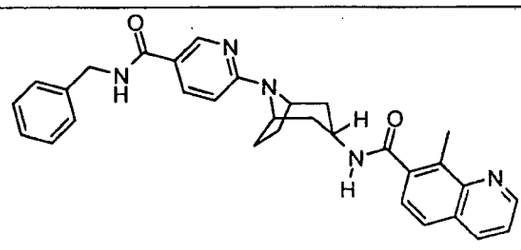
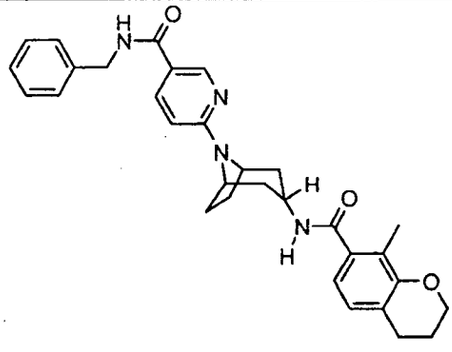
[0092] In another embodiment, the compound of Formula II is selected from one of the following compounds from Table II, or a pharmaceutically acceptable salt of any of the compounds in Table II:

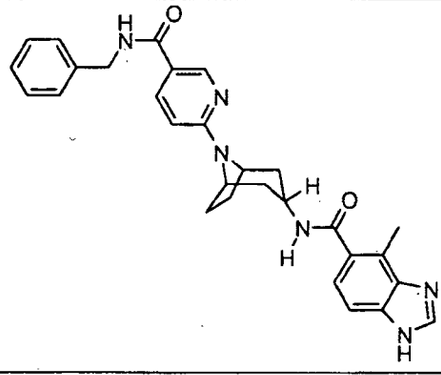
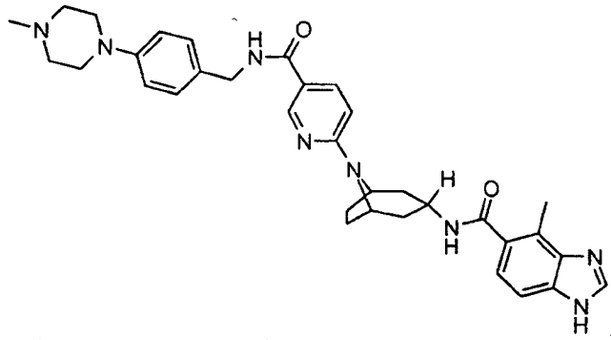
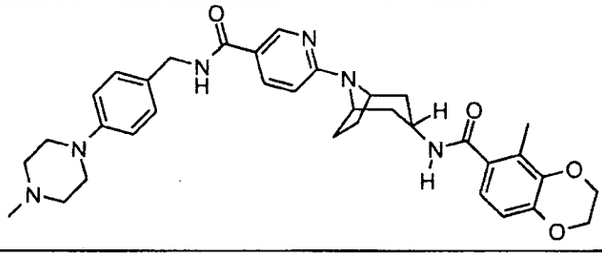
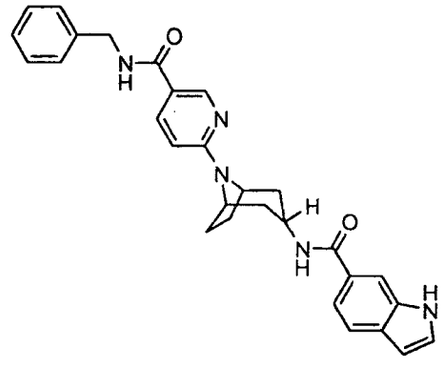
TABLE II

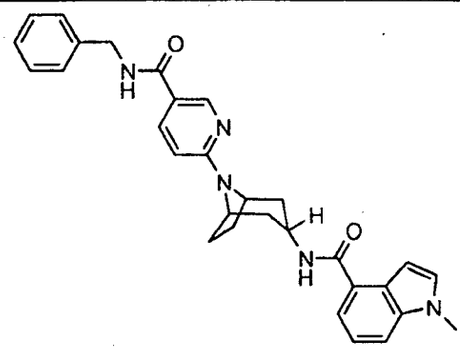
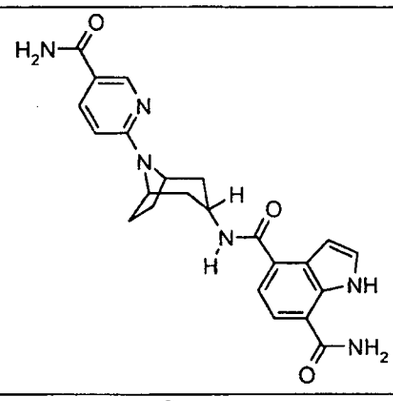
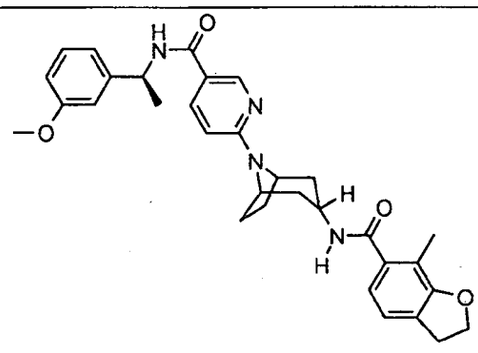
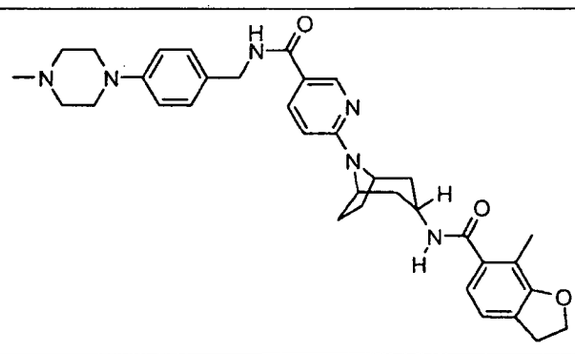
STRUCTURE	NAME
	1,4-dimethyl-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1H-benzimidazole-5-carboxamide
	N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1,3-benzothiazole-5-carboxamide
	4-methyl-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1H-1,2,3-benzotriazole-5-carboxamide

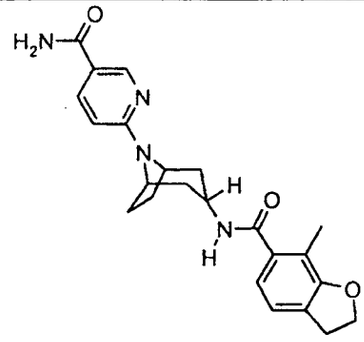
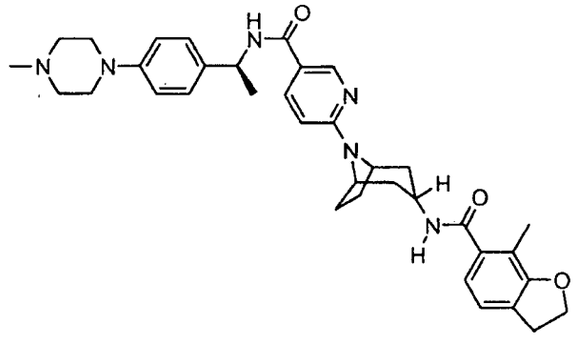
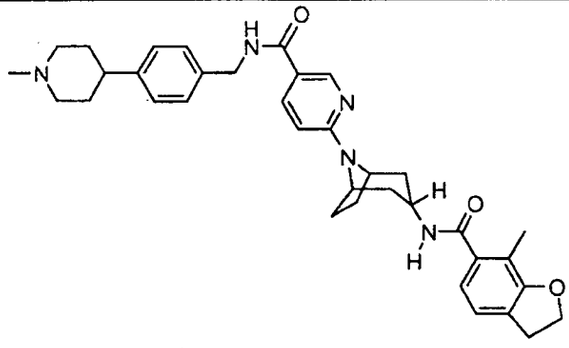
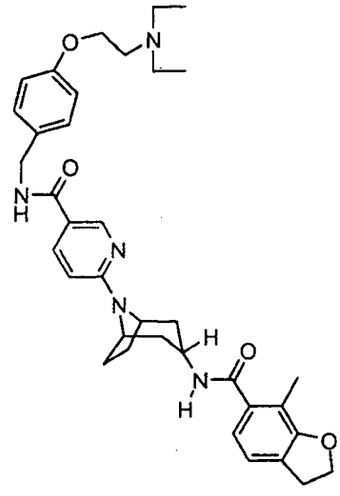
STRUCTURE	NAME
	6-(3-endo-{[(8-methyl-3,4-dihydro-2H-chromen-7-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(1-methylpiperidin-4-yl)phenyl]methyl}pyridine-3-carboxamide

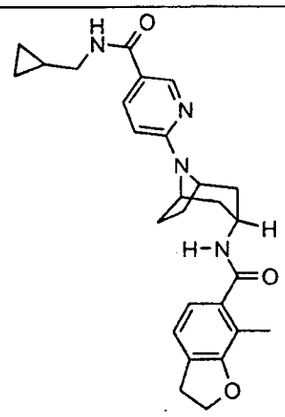
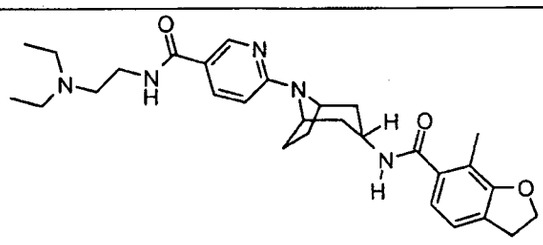
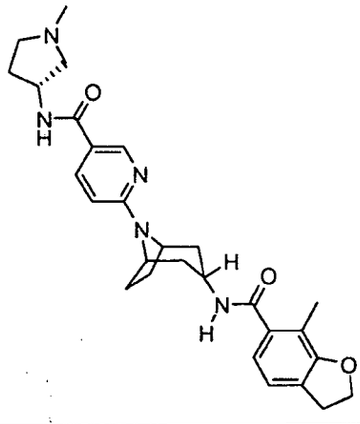
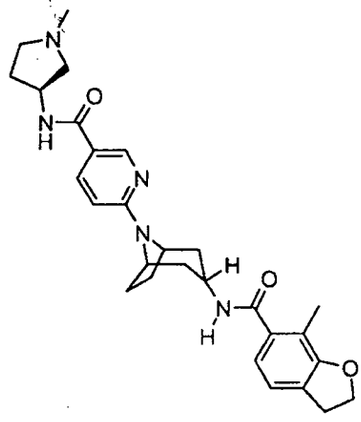
STRUCTURE	NAME
	6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide
	N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-benzimidazole-5-carboxamide
	N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-indole-4-carboxamide
	6-(3-endo-{[(2-amino-6-chloro-9H-purin-9-yl)acetyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide

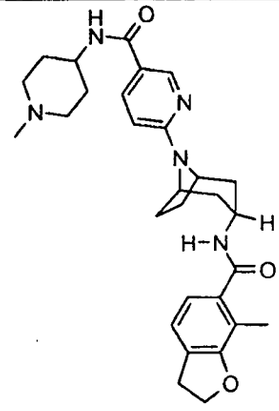
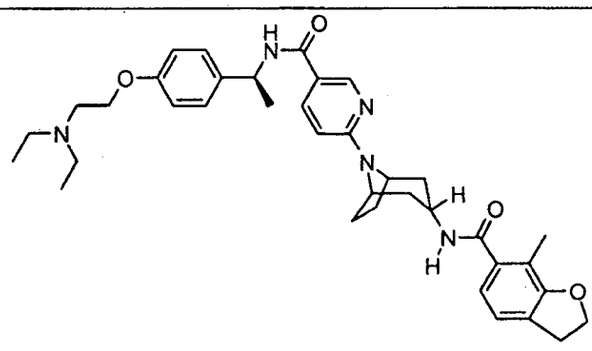
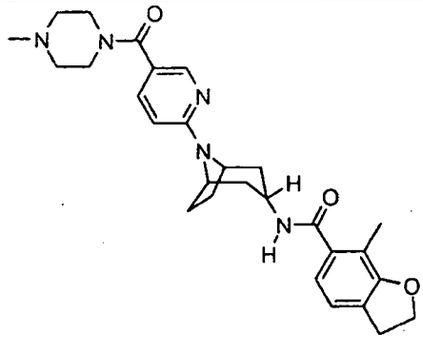
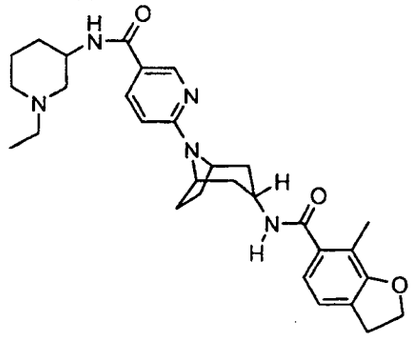
STRUCTURE	NAME
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide
	6-(3-endo-{[(5-methyl-2,3-dihydro-1,4-benzodioxin-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide
	6-(3-endo-{[(4-methyl-1,3-benzodioxol-5-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide
	8-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]quinoline-7-carboxamide
	6-(3-endo-{[(8-methyl-3,4-dihydro-2H-chromen-7-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide

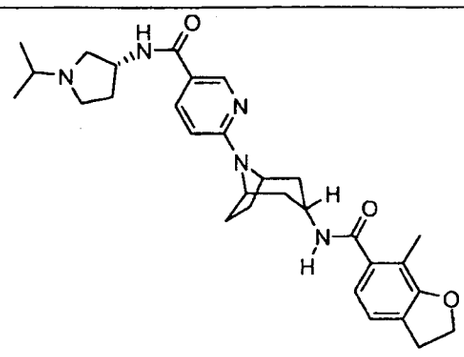
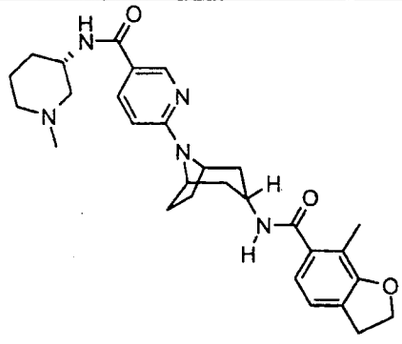
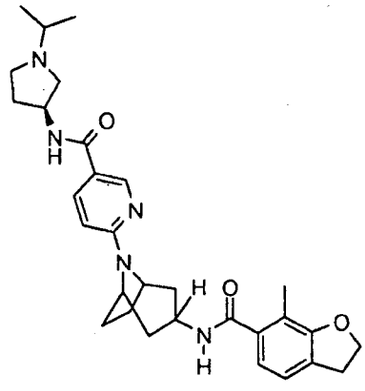
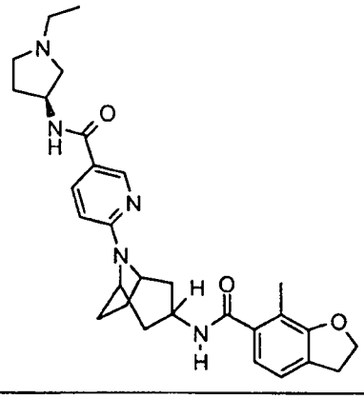
STRUCTURE	NAME
	4-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-benzimidazole-5-carboxamide
	4-methyl-N-(8-{5-[({[4-(4-methylpiperazin-1-yl)phenyl]methyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1H-benzimidazole-5-carboxamide
	6-(3-endo-{[(5-methyl-2,3-dihydro-1,4-benzodioxin-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide
	N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-indole-6-carboxamide

STRUCTURE	NAME
	1-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-indole-4-carboxamide
	N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-1H-indole-4,7-dicarboxamide
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[3-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide

STRUCTURE	NAME
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(1-methylpiperidin-4-yl)phenyl]methyl}pyridine-3-carboxamide
	N-[(4-{[2-(diethylamino)ethyl]oxy}phenyl)methyl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide

STRUCTURE	NAME
	N-(cyclopropylmethyl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide
	N-[2-(diethylamino)ethyl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide

STRUCTURE	NAME
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(1-methylpiperidin-4-yl)pyridine-3-carboxamide
	N-[(1S)-1-(4-{[2-(diethylamino)ethyl]oxy}phenyl)ethyl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide
	7-methyl-N-(8-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2,3-dihydro-1-benzofuran-6-carboxamide
	N-(1-ethylpiperidin-3-yl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide

STRUCTURE	NAME
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-methylpiperidin-3-yl]pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-(1-methylethyl)pyrrolidin-3-yl]pyridine-3-carboxamide
	N-[(3S)-1-ethylpyrrolidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide

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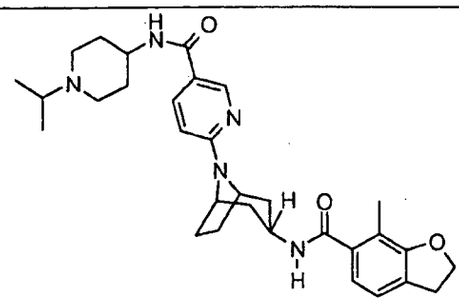
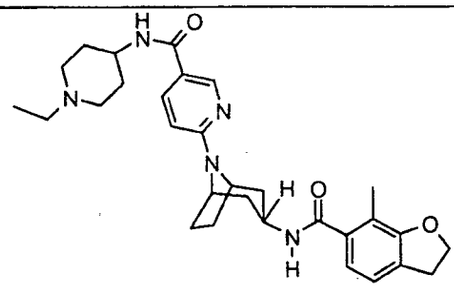
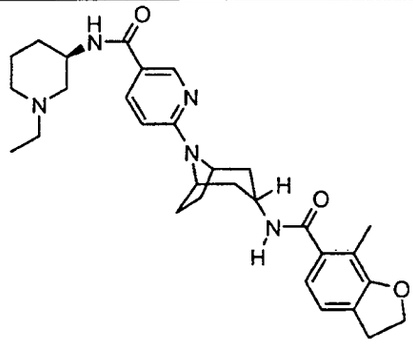
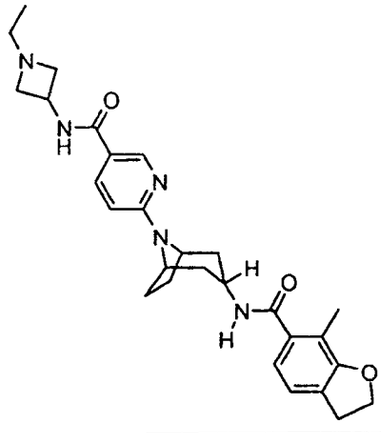
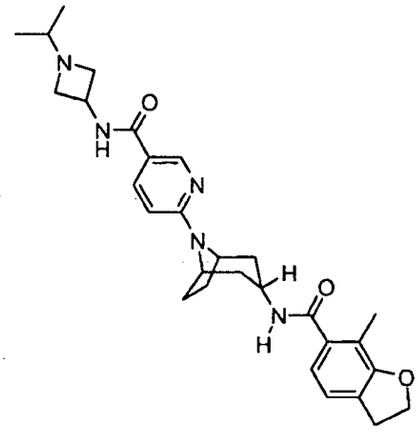
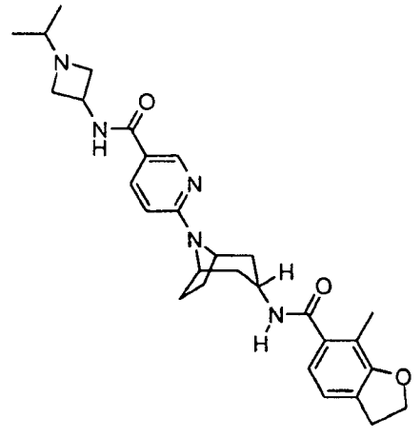
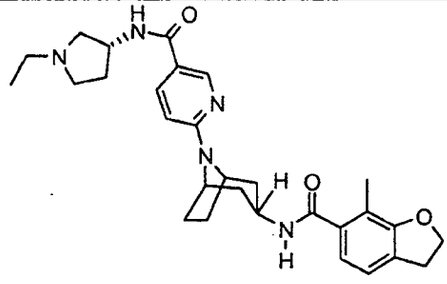
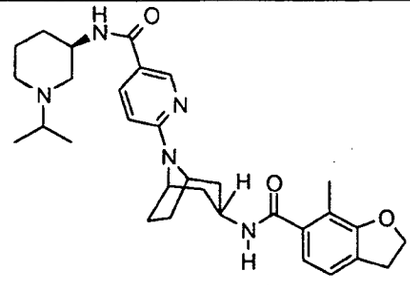
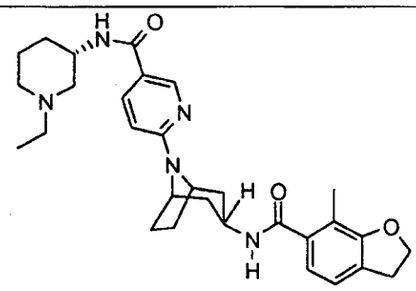
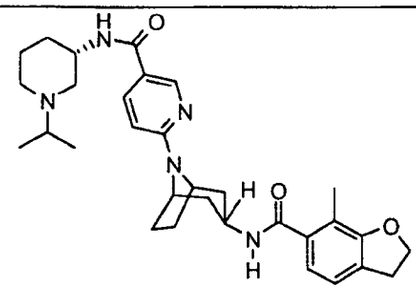
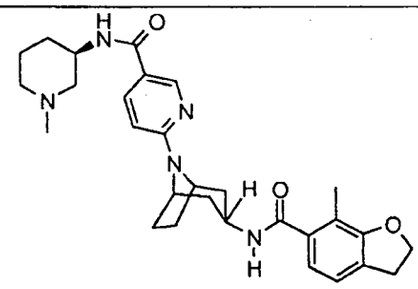
STRUCTURE	NAME
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[1-(1-methylethyl)piperidin-4-yl]pyridine-3-carboxamide
	N-(1-ethylpiperidin-4-yl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide
	N-[(3R)-1-ethylpiperidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide
	N-(1-ethylazetidin-3-yl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide

STRUCTURE	NAME
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[1-(1-methylethyl)azetidin-3-yl]pyridine-3-carboxamide
	N-(1-methylazetidin-3-yl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide
	N-[(3R)-1-ethylpyrrolidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-(1-methylethyl)piperidin-3-yl]pyridine-3-carboxamide

STRUCTURE	NAME
	N-[(3S)-1-ethylpiperidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-(1-methylethyl)piperidin-3-yl]pyridine-3-carboxamide
	6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-methylpiperidin-3-yl]pyridine-3-carboxamide

[0093] Compounds in Tables I and II are named according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS). Names were generated using ACD/Labs naming software 8.00 release, product version 8.08.

[0094] The activity for each of the compounds in Table I is represented by the letters A, B, C and D. These letters are listed next to each of the compounds in Table I in the same row as each of the compounds. The activity that is associated with each of these letters is defined below:

A stands for HSP90 IC_{50} values less than 500 nM.

B stands for HSP90 IC_{50} values ranging from 500 nM to 999 nM.

C stands for HSP90 IC_{50} values ranging from 1000 nM to 1999 nM.

D stands for HSP90 IC_{50} values of ranging from 2000 nM to 10,000 nM.

[0095] HSP90 expression and activity is frequently upregulated in tumor cells [5-8] and is particularly associated with poor prognosis in breast cancer [9, 10]. Furthermore, HSP90 in tumor cells appears to exist in a hyperactivated state with elevated ATPase activity which is highly sensitive to HSP90 inhibition, compared to the largely latent form found in normal cells [11]. This hyperactivated state suggests that HSP90 inhibitors can selectively target tumor cells, with relatively low impact on normal tissues. Many HSP90 client proteins are involved in various aspects of tumor growth and progression [6, 7, 12, 13]. HSP90 promotes the folding and/or stabilization of many oncogenic proteins that confer autonomous growth on cells (eg, EGFR and ErbB2 [14-17], B-Raf [18, 19] and steroid hormone receptors [20]) and also regulates multiple proteins that promote tumor cell survival (eg, IGF 1 receptor [21], PDK1 and Akt [22, 23], RIP [24], IκB [24, 25] and survivin [26]). HSP90 can also promote aberrant cell cycle progression by stabilizing Cdk4, Cdk6 and cyclin D [27], Cdk2, and Plk1 [28, 29]. Conversely, HSP90 inhibitors can downregulate the cell cycle checkpoint kinase Chk1 and sensitize tumors to various forms of chemotherapy [30, 31]. HSP90 inhibition can also blunt tumor angiogenesis, since hypoxia-inducible factor (HIF-1α) and the vascular endothelial growth factor (VEGF) receptor tyrosine kinases are HSP90 clients [32]. The receptor tyrosine kinase Met, which stimulates cellular motility, migration and invasion, is also downregulated in response to HSP90 inhibition, both directly and via inhibition of HIF-1α [33, 34]. Apart from its role as a cellular chaperone, HSP90α has also been implicated in extracellular matrix degradation and tumor cell invasion, via activation (and possibly stabilization) of the matrix metalloproteinase MMP2 [35, 36]. HSP90 depletion or inhibition promotes telomere erosion and apoptosis [37], and can also enable the evolution of heterogenous, metastatic and drug-resistant phenotypes by allowing propagation of metastable mutations [38, 39]. HSP90 has been implicated in activation of the unfolded protein response (UPR, [40, 41]). Failure of the UPR (for example, via inhibition of HSP90) leads to an ER stress signal and apoptosis. Therefore, HSP90 inhibitors can promote tumor cell death indirectly by disrupting the UPR, as well as by directly targeting pro-survival factors.

[0096] In addition to cancer, several other diseases can be amenable to treatment using HSP90 inhibitors. There is substantial data supporting a role for HSP90 inhibitors in treating neurodegenerative and infectious diseases. Other possible HSP90 non-oncology indications include inflammatory diseases, autoimmune disorders, stroke, ischemia, cardiac disorders, sepsis, fibrogenetic disorders (for example, scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis, cystic fibrosis and pulmonary fibrosis) and metabolic diseases.

[0097] Several neurodegenerative diseases ("tauopathies"), including Alzheimer's disease (AD) and frontotemporal lobal dementia, are characterized by accumulation of hyperphosphorylated or mutated forms of the microtubule-associated protein Tau [42]. HSP90 inhibitors can be able to degrade aberrant Tau proteins via two complementary mechanisms. First, HSP90 appears to stabilize p35 (a neuronal protein involved in aberrant Tau phosphorylation) and mutant (but not wild-type) Tau protein [43]. Second, HSP90 inhibition induces expression of HSP70, which can promote productive folding of Tau [44] and/or selective degradation of aberrant Tau proteins [45]. Moreover, HSP90 isolated from brain tissue affected by AD showed markedly higher affinity for an HSP90 inhibitor compared with HSP90 from normal brain tissue [45], concordant with a similar observation in tumor cells [11].

[0098] HSP90 expression in the host organism has been implicated in mediating both infection and replication of a broad range of viral pathogens, including negative strand RNA viruses and influenza virus [46-48], hepatitis B [49], hepatitis C [50, 51] and herpes simplex virus type 1 [52]. Importantly, pharmacological inhibition of HSP90 was found to impair the replication of RNA without selecting for the emergence of drug-resistant mutants [53]. HSP90 also promotes the growth and survival of pathogenic yeast, though in this case the endogenous fungal enzyme is involved. Geldanamycin increases the susceptibility of Candida and Aspergillus species to other antibiotics [54], and an antibody directed against yeast HSP90 (Mycograb) was recently shown to significantly enhance the activity of amphotericin B in a randomized, double blind clinical study [55]. Fungal HSP90 can also help to promote drug resistance [54]. HSP90 inhibition was also recently shown to ameliorate pulmonary damage and inflammation in a mouse model of acute sepsis [56],

suggesting a broader role for HSP90 inhibitors in treating infectious and inflammatory diseases.

[0099] The benzoquinone ansamycin geldanamycin was identified as an inhibitor of HSP90 [57], and several geldanamycin analogs have been evaluated as anticancer agents in clinical trials, with some evidence of activity. However, formulation and administration of these agents remains challenging. An orally available inhibitor of HSP90 would have broad utility in the treatment of a wide range of malignancies and potentially other diseases.

[00100] HSP90 inhibitors have been reported to show synergistic effects on tumor cell growth and survival when combined with various chemotherapeutics. Examples include HSP90 inhibitors in combination with proteosome inhibitors (eg bortezomib) in multiple myeloma, EGFR (eg Iressa) or PI3K (eg LY294002) inhibitors in malignant glioma, DNA damaging agents (eg etoposide or cisplatin) in leukemia and pediatric tumors, and radiation in various tumors including cervical, prostate, glioma and pancreatic. While observed synergy can be hypothesized to be due to loss of stability of specific HSP90 client proteins, it may also be due to loss of general stress buffering capacity of the cell.

[00101] Additionally, several drug-resistant mutant proteins have been shown to be dependent on HSP90 for their stabilization and activity, paving the way for in vivo proof of concept studies and clinical trial design for use of HSP90 inhibitors against certain drug-resistant tumors. Examples include imatinib-resistant c-KIT mutations in GIST (gastrointestinal stromal tumor), gefitinib and erlotinib-resistant EGFR (L858R/T790M) mutants in NSCL, and imatinib-resistant BCR-ABL(T315I) mutant in CML. In fact, the 17-AAG related HSP90 inhibitor IPI-504 was recently granted orphan drug status for GIST after a high rate of response was observed in Gleevec-resistant GIST patients enrolled in a Phase I trial.

[00102] Additionally, inhibition of HSP90 may be in part responsible for the anti-tumor activity of the recently FDA-approved histone deacetylase inhibitor Vorinostat (suberoylanilide hydroxamic acid, or SAHA). HSP90 activity has been reported to be negatively regulated through direct acetylation of the chaperone, and HDAC inhibitors are shown to result in the accumulation of inactive, acetylated HSP90 protein and increased degradation of HSP90 client proteins, implicating HDAC function in the positive control of HSP90 function. Hence, the clinical mechanism of

action of HDAC inhibitors alone or in combination may in certain instances be due to inhibition of HSP90 function.

[00103] HSP90 expression in the host organism has been implicated in mediating both infection and replication of a broad range of viral pathogens. The HSP90 inhibitors geldanamycin and radicicol impair the replication of negative strand RNA viruses and influenza virus by destabilizing the viral RNA polymerase, and geldanamycin can also inhibit replication of hepatitis C virus. HSP90 also directs the folding and intracellular localization of the DNA polymerase from herpes simplex virus type 1 and is required for hepatitis B reverse transcriptase activity. Pharmacological inhibition of HSP90 was found to impair the replication of RNA viruses in cell culture and infected animals, without selecting for the emergence of drug-resistant mutants. Indeed, HSP90 may be broadly implicated in the development of drug resistance in microorganisms, as discussed below.

[00104] HSP90 also promotes the growth and survival of pathogenic yeast, though in this case the endogenous fungal enzyme is involved. Geldanamycin increases the susceptibility of Candida and Aspergillus species to other antibiotics, and an antibody directed against yeast HSP90 (Mycograb) was recently shown to significantly enhance the activity of amphotericin B in a randomized, double blind clinical study. As in the case of tumor cells HSP90 may act via multiple mechanisms, but perhaps most striking is the potential for fungal HSP90 to promote drug resistance. Endogenous HSP90 may support the expression of mutant proteins that confer drug resistance, and HSP90 inhibitors appear to inhibit drug resistance under acute selection conditions, but have less effect on resistance that is acquired by more gradual selection in the presence of antibiotics. Thus, HSP90 inhibitors may have utility early in treatment of fungal infections, before resistance mutations have a chance to emerge. Intriguingly the drug resistance-inducing effects of HSP90 are mediated by calcineurin, which is also implicated in both cyclosporine A resistance and geldanamycin activity in the malarial parasite Plasmodium falciparum.

[00105] HSP90 inhibition was also recently shown to ameliorate pulmonary damage and inflammation in a mouse model of acute sepsis, suggesting a broader role for HSP90 inhibitors in treating infectious and inflammatory diseases.

[00106] In addition to cancer, several other diseases may be amenable to treatment using HSP90 inhibitors. These include neurodegenerative disorders and infectious

diseases. Several neurodegenerative diseases, including Alzheimer's disease (AD) and frontotemporal lobal dementia, are characterized by accumulation of hyperphosphorylated or mutated forms of the microtubule-associated protein Tau. These pathogenic Tau proteins form intracellular aggregates known as neurofibrillary tangles, which have been proposed to have a causative role in disease but may alternatively represent a cellular protective mechanism against the toxic, soluble form of Tau. Selective degradation of aberrant Tau proteins may therefore represent a novel therapeutic strategy. HSP90 inhibitors may achieve this degradation via two complementary mechanisms. First, HSP90 appears to stabilize p35 (a neuronal protein involved in aberrant Tau phosphorylation) and mutant (but not wild-type) Tau protein: the activity of these pathogenic proteins would therefore be reduced by HSP90 inhibition. Second, HSP90 inhibition induces expression of HSP70, which may promote productive folding of Tau and/or selective degradation of aberrant Tau proteins. Moreover, HSP90 isolated from brain tissue affected by AD showed markedly higher affinity for an HSP90 inhibitor compared with HSP90 from normal brain tissue, concordant with a similar observation in tumor cells.

[00107]

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[00108] Another embodiment of the disclosure relates to a pharmaceutical composition comprising the compound of Formula I, IB, IC, ID, IE, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[00109] Another embodiment of the disclosure relates to a method of inhibiting HSP90 in a cell, comprising contacting the cell, in which inhibition of HSP90 is desired, with the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof.

[00110] Another embodiment of the disclosure relates to a method of inhibiting HSP90 in a cell, comprising contacting a cell in which inhibition of HSP90 is desired with a pharmaceutical composition, comprising the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[00111] Another embodiment of the disclosure relates to a method of treating a disease or condition that involves HSP90, comprising administering to an animal, in need of said treatment, the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof.

[00112] Another embodiment of the disclosure relates to a method of treating a disease or condition that involves HSP90, comprising administering to an animal, in need of said treatment, a pharmaceutical composition comprising the compound of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent. In a further embodiment, the disease or condition being treated is cancer.

[00113] In another embodiment, it is contemplated that the HSP90 inhibiting compounds of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, can be used to treat one or more diseases or conditions selected from breast cancer, CML, colorectal carcinoma, glioma, melanoma, multiple myeloma, non-small cell lung cancer, ovarian cancer, prostate cancer, renal cell carcinoma, small cell lung carcinoma, and UPR (unfolded protein response).

[00114] In another embodiment, it is contemplated that the HSP90 inhibiting compounds of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, can be used to treat one or more diseases or conditions selected from neurodegenerative diseases, infectious diseases, inflammatory diseases, autoimmune

disorders, stroke, ischemia, cardiac disorders, sepsis, fibrogenetic disorders (for example, scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis, cystic fibrosis and pulmonary fibrosis) and metabolic diseases.

[00115] Another embodiment of the disclosure relates to a pharmaceutical composition comprising one or more compounds from Table I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[00116] Another embodiment of the disclosure relates to a method of inhibiting HSP90 in a cell, comprising contacting the cell, in which inhibition of HSP90 is desired, with one or more compounds from Table I, or a pharmaceutically acceptable salt thereof.

[00117] Another embodiment of the disclosure relates to a method of inhibiting HSP90 in a cell, comprising contacting a cell in which inhibition of HSP90 is desired with a pharmaceutical composition, comprising one or more compounds from Table I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[00118] Another embodiment of the disclosure relates to a method of treating a disease or condition that involves HSP90, comprising administering to an animal, in need of said treatment, one or more compounds from Table I, or a pharmaceutically acceptable salt thereof.

[00119] Another embodiment of the disclosure relates to a method of treating a disease or condition that involves HSP90, comprising administering to an animal, in need of said treatment, a pharmaceutical composition comprising one or more compounds from Table I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent. In a further embodiment, the disease or condition being treated is cancer.

[00120] In another embodiment, it is contemplated that the HSP90 inhibiting compounds from Table I, or a pharmaceutically acceptable salt thereof, can treat one or more indications selected from breast cancer, CML, colorectal carcinoma, glioma, melanoma, multiple myeloma, non-small cell lung cancer, ovarian cancer, prostate cancer, renal cell carcinoma, small cell lung carcinoma, and UPR (unfolded protein response).

[00121] The HSP90 inhibiting compounds of one or more compounds from Table I, or a pharmaceutically acceptable salt thereof, are also contemplated to be useful as being able to treat one or more diseases or conditions selected from neurodegenerative diseases, infectious diseases, inflammatory diseases, autoimmune disorders, stroke, ischemia, cardiac disorders, sepsis, fibrogenetic disorders (for example, scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis, cystic fibrosis and pulmonary fibrosis) and metabolic diseases.

[00122] Several neurodegenerative diseases ("tauopathies"), including Alzheimer's disease (AD) and frontotemporal lobal dementia, are characterized by accumulation of hyperphosphorylated or mutated forms of the microtubule-associated protein Tau. It is contemplated that the HSP90 inhibiting compounds disclosed herein can degrade aberrant Tau proteins via two complementary mechanisms. First, HSP90 appears to stabilize p35 (a neuronal protein involved in aberrant Tau phosphorylation) and mutant (but not wild-type) Tau protein. Second, HSP90 inhibition induces expression of HSP70, which can promote productive folding of Tau and/or selective degradation of aberrant Tau proteins.

[00123] It is also completed that the HSP90 inhibiting compounds disclosed herein can mediate and treat infection from a broad range of viral pathogens, including negative strand RNA viruses and influenza virus, hepatitis B, hepatitis C and herpes simplex virus type 1.

[00124] In another embodiment, it is contemplated that the HSP90 inhibiting compounds of Formula I, IB, IC, ID or IE, or a pharmaceutically acceptable salt thereof, can be used to treat a neurodegenerative disease characterized by accumulation of hyperphosphorylated or mutated forms of the microtubule-associated protein Tau.

[00125] In another embodiment, it is contemplated that the HSP90 inhibiting compounds of Formula I, IB, IC, ID, IE, or a pharmaceutically acceptable salt thereof, can be used in a method of degrading aberrant Tau proteins in an animal, comprising administering a compound according to claim 1 to said animal.

[00126] In another embodiment, it is contemplated that one or more of the HSP90 inhibiting compounds from Table I, or a pharmaceutically acceptable salt thereof, can be used to treat a neurodegenerative disease characterized by accumulation of hyperphosphorylated or mutated forms of the microtubule-associated protein Tau.

[00127] In another embodiment, it is contemplated that one or more of the HSP90 inhibiting compounds from Table I, or a pharmaceutically acceptable salt thereof, can be used in a method of degrading aberrant Tau proteins in an animal, comprising administering a compound according to claim 1 to said animal.

[00128] In other embodiments, any of the above methods of treating any of the diseases or conditions described herein further comprises administering radiation treatment or one or more therapeutic agents selected from Camptothecin, Topotecan, 9-Nitrocamptothecin, 9-Aminocamptothecin, Karenitecin, Irinotecan, Etoposide, Etoposide Phosphate, Teniposide, Amsacrine, Razoxane, Dexrazoxane, Mechlorethamine, Cyclophosphamide, Ifosfamide, Chlorambucil, Melphalan, Thiotepa, Trenimon, Triethylenemelamine, Dianhydrogalactitol, Dibromodulcitol, Busulfan, dimethylsulfate, Chloroethylnitrosourea, Carmustine, Lomustine, Methyl-Lomustine, Streptozotocin, Chlorozotocin, Prednimustine, Estramustine, Procarbazine, Dacarbazine, Hexamethylmelamine, Pentamethylmelamine, Temozolomide, Cisplatin, Carboplatin, Oxaliplatin, Bleomycin, Dactinomycin, Mithramycin, Rapamycin, Mitomycin C, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Methotrexate, Edatrexate, Trimethoprim, Nolatrexed, Raltitrexed, Hydroxyurea, 5-fluorouracil, Ftorafur, Capecitabine, Furtulon, Eniluracil, ara-C, 5-azacytidine, Gemcitabine, Mercaptopurine, Thioguanine, Pentostatin, antisense DNA, antisense RNA, an antisense DNA/RNA hybrid, a ribozyme, ultraviolet radiation, Vincristine, Vinblastine, Paclitaxel, Docetaxel, L-Asparaginase, a kinase inhibitor, Imatinib, Mitotane, Aminoglutethimide, Diethylstilbestrol, Ethinyl estradiol, Tamoxifen, Anastrozole, Testosterone propionate, Fluoxymesterone, Flutamide, Leuprolide, Prednisone, Hydroxyprogesterone caproate, Medroxyprogesterone acetate, Megestrol acetate, Interferon-alfa, and Interleukin.

Abbreviations and Definitions

[00129] The following abbreviations and terms have the indicated meanings throughout:

Abbreviation	Meaning
Ac	Acetyl
Br	Broad
°C	degrees Celsius
c-	Cyclo

Abbreviation	Meaning
CBZ	CarboBenZoxy = benzyloxycarbonyl
D	Doublet
Dd	doublet of doublet
Dt	doublet of triplet
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EI	Electron Impact ionization
Et	Ethyl
G	gram(s)
GC	gas chromatography
h or hr	hour(s)
HOAc	acetic acid
HOBt	Hydroxybenzotriazole
HPLC	high pressure liquid chromatography
L	liter(s)
M	molar or molarity
M	Multiplet
Me	Methyl
Mesyl	Methanesulfonyl
Mg	milligram(s)
MHz	megahertz (frequency)
Min	minute(s)
mL	milliliter(s)
mM	Millimolar
Mmol	millimole(s)
Mol	mole(s)
MS	mass spectral analysis
MTBE	methyl t-butyl ether
N	normal or normality

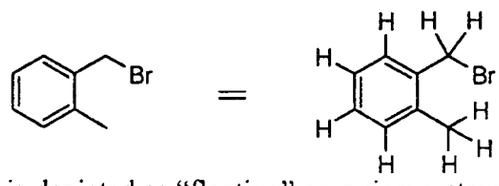
Abbreviation	Meaning
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
nM	Nanomolar
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance spectroscopy
PEG	polyethylene glycol
pEY	poly-glutamine, tyrosine
Ph	Phenyl
PhOH	Phenol
PfP	Pentafluorophenol
PfPy	Pentafluoropyridine
PPTS	Pyridinium p-toluenesulfonate
Py	Pyridine
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
Q	Quartet
RT	Room temperature
Sat'd	Saturated
S	Singlet
s-	Secondary
t-	Tertiary
t or tr	Triplet
TBDMS	*t*-butyldimethylsilyl
TES	Triethylsilyl
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TMOF	trimethyl orthoformate
TMS	Trimethylsilyl
Tosyl	*p*-toluenesulfonyl
Trt	triphenylmethyl
uL	microliter(s)

Abbreviation	Meaning
uM	Micromole(s) or micromolar

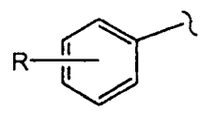
[00130] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

[00131] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond, "- - - -" means a single or double bond. When a group is depicted removed from its parent formula, the "∿∿" symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

[00132] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.

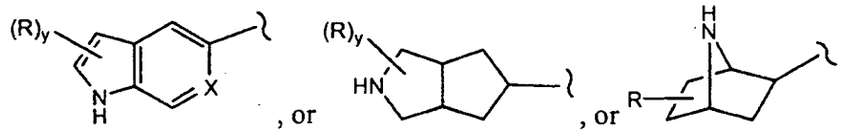


[00133] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



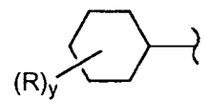
then, unless otherwise defined, a substituent "R" can reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[00134] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:

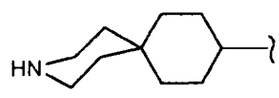


then, unless otherwise defined, a substituent "R" can reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "X" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group can reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two "R's" can reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[00135] When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" can reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon, including that carbon, can form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:



[00136] "Administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of this disclosure (i.e., a compound of formula I, II or III as described herein) means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of this

disclosure or prodrug thereof is provided in combination with one or more other active agents (e.g., surgery, radiation, and chemotherapy, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

[00137] "Alkyl" is intended to include molecules having 1-12 carbons in size (C-C_{12})alkyl, which can be straight chained or branched. For example, alkyl can refer to an n-hexyl, iso-hexyl, cyclobutylethyl, and the like. Alkyl is intended to include lower alkyl groups of from 1-6 carbons in size, such as methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, isobutyl, pentyl, hexyl and the like. An alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus, for example, either "butyl" or "C_4 alkyl" is meant to include n-butyl, sec-butyl, isobutyl, t-butyl; and for example, "propyl" or "C_3 alkyl" each include n-propyl and isopropyl.

[00138] -(C_1-C_6)alkyl is a subset of alkyl groups that are from one to six carbon atoms in length, and can be straight chained or branched.

[00139] -(C_1-C_3)alkyl is a subset of alkyl groups that are from one to three carbon atoms in length, and can be straight chained or branched.

[00140] "Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 14 carbon atoms, including 5 to 10 carbon atoms, or 5 to 7 carbon ring atoms. Non-limiting examples of monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like. Cycloalkyls can be fused or bridge ring systems or spirocyclic systems.

[00141] "Cycloalkylalkyl" means a "cycloalkyl" group, as defined herein, attached to an "alkyl" group, as defined herein, wherein the alkyl group is attached to the parent moiety.

[00142] "Alkyl substituted with one or more halo and hydroxy" means an alkyl group substituted with 1, 2, or 3 hydroxy or 1, 2 or 3 halo.

[00143] "Alkylene" refers to straight or branched chain divalent group consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to ten carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene and the like. Alkylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, fully saturated. Examples of alkylene

include ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), dimethylpropylene ($-CH_2C(CH_3)_2CH_2-$), and cyclohexylpropylene ($-CH_2CH_2CH(C_6H_{13})$).

[00144] "Alkenylene" refers to a straight or branched chain unsaturated divalent group consisting solely of carbon and hydrogen atoms, having from two to ten carbon atoms. Alkenylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, double bond unsaturation. The unsaturation present includes at least one double bond.

[00145] "Alkynylene" refers to a straight or branched chain unsaturated divalent group consisting solely of carbon and hydrogen atoms having from two to ten carbon atoms, for example, propylid-2-ynyl, *n*-butylid-1-ynyl, and the like. Alkylidyne is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, triple bond unsaturation. The unsaturation present includes at least one triple bond.

[00146] Any of the above groups, "alkylene," "alkenylene" and "alkynylene," when optionally substituted, can contain alkyl substitution which itself contains unsaturation. For example, 2-(2-phenylethynyl-but-3-enyl)-naphthalene (IUPAC name) contains an *n*-butylid-3-ynyl group with a vinyl substituent at the 2-position of said group.

[00147] "Alkoxy" or "alkoxyl" both refer to the group -O-alkyl, wherein the term "alkyl" is as defined hereinabove. Examples include methoxy, ethoxy, propoxy, isopropoxy, and the like.

[00148] "Aryl" means a monovalent six- to fourteen-membered mono- or multicyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the multicyclic ring is aromatic. A multicyclic ring that contains only one aryl ring is intended to be included within the definition of aryl. An aryl can also be six- to ten membered, or six membered. Representative non-limiting examples of aryl include phenyl, naphthyl, and the like.

[00149] "Arylalkyl" means a residue in which an aryl moiety, as defined above, is attached to a parent structure via one of an alkyl (i.e, alkylene, alkenylene, or alkynylene). Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. The "alkyl" portion of the group can be one to ten carbons, and in another embodiment, one to six carbons; the latter can also be referred to as C_{1-6} arylalkyl. When a group is referred to as or "-(C_1-C_6)alkylaryl," an aryl moiety is attached to a

parent structure via an alkylene group. Examples include benzyl, phenethyl, and the like.

[00150] In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system can be fused together to form a ring structure. The fused ring structure can contain heteroatoms and can be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (*i.e.* saturated ring structures) can contain two substitution groups.

[00151] "Fused-polycyclic" or "fused ring system" refers to a polycyclic ring system that contains bridged or fused rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems includes non-aromatic and aromatic systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the compounds disclosed herein can themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic.

[00152] "Halogen" or "halo" both refer to fluorine, chlorine, bromine or iodine.

[00153] "Haloalkyl" (which includes alkyl optionally substituted with up to 8 halogens) and "haloaryl" refer generically to alkyl and aryl groups that are substituted with one or more halogens, respectively. Non-limiting examples of "haloalkyl" include 3,3,3-trifluoro-1-methylpropyl, 2-methyl-1-(trifluoromethyl)propyl, $-CH_2F$, $-CHCl_2$ and $-CF_3$.

[00154] "Heteroatom" refers to O, S, N, or P. In another example, the heteroatom is O or N. In another example, the heteroatom is O. In another example, the heteroatom is N.

[00155] "Heterocyclyl" refers to a stable three- to fifteen-membered ring substituent that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this disclosure, the heterocyclyl substituent can be a monocyclic, bicyclic or tricyclic ring system, which can include fused or bridged ring systems as well as spirocyclic systems. The terms "heterocycloalkyl" and "heteroaryl" are groups that are encompassed by the broader term "heterocyclyl." The nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclyl group can be optionally oxidized to various

oxidation states. In a specific example, the group $-S(O)_{0-2}-$, refers to -S- (sulfide), -S(O)- (sulfoxide), and $-SO_2-$ (sulfone) respectively. For convenience, nitrogens, particularly but not exclusively, those defined as annular aromatic nitrogens, are meant to include their corresponding *N*-oxide form, although not explicitly defined as such in a particular example. Thus, for a compound of this disclosure having, for example, a pyridyl ring; the corresponding pyridyl-*N*-oxide is meant to be included as another compound of the disclosure. In addition, annular nitrogen atoms can be optionally quaternized; and the ring substituent can be partially or fully saturated or aromatic. Examples of heterocyclyl groups include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, and tetrahydroquinolinyl.

[00156] "Heterocycloalkyl" refers to a stable 4-12 membered monocyclic or multicyclic ring, wherein at least one of the rings contain at least one heteroatom and wherein there are no aromatic rings. Heterocycloalkyl is meant to include multicyclic rings wherein one ring contains a heteroatom and another ring does not contain a heteroatom.

[00157] "Heterocycloalkylalkyl" refers to a heterocycloalkyl, as defined herein, attached to the parent moiety through an "alkyl," as defined herein. One non-limiting example of heterocycloalkyl includes piperadinyl. Another non-limiting example of

heterocycloalkyl includes piperazinyl. Another non-limiting example of heterocycloalkyl includes furanyl. Another non-limiting example of heterocycloalkyl includes pyrrolidinyl. Another non-limiting example of heterocycloalkyl includes morpholinyl.

[00158] "Amino" refers to $-NH_2$.

[00159] "Alkylamino" refers to -NH(alkyl), wherein "alkyl" is as defined above, and wherein the parent moiety is attached to the nitrogen atom. In one example, alkylamino is (1R)-1,2-dimethylpropylamino. In another example, alkylamino is (1S)-1,2-dimethylpropylamino. . In another example, alkylamino is propylamino. In another example, alkylamino is (1R)-1-methylpropyl]amino. In another example, alkylamino is (1S)-1-methylpropyl]amino. In another example, alkylamino is (1R)-1,2,2-trimethylpropylamino. In another example, alkylamino is (1S)-1,2,2-trimethylpropylamino.In another example, alkylamino is 2-methyl-1-(1-methylethyl)propylamino.

[00160] "Gem-dicycloalkylalkl" refers to a group wherein two cycloalkyl groups are attached to the same carbon atom on an alkyl group, and the alkyl group is attached to the parent moiety. One non-limiting example gem-dicycloalkyl is dicyclopropylmethyl having the following structure:

[00161] "Dialkylamino" refers to $-N(alkyl)_2$, wherein "alkyl" is as defined above, and wherein the parent moiety is attached to the nitrogen atom.

[00162] "Dialkylaminoalkyl" refers to $-(alkyl)N(alkyl)_2$, wherein "alkyl" is as defined above. One such non-limiting example of "dialkylaminoalkyl" includes $-CH_2C(CH_3)_2CH_2N(CH_3)_2$.

[00163] "Aminoalkyl" refers to $-(alkyl)NH_2$, wherein "alkyl" is as defined above, and wherein the parent moiety is attached to the alkyl group. The amino group can be attached at any point along the alkyl group. Non-limiting examples of aminoalkyl include $-CH(NH_2)CH_3$.

[00164] "Heteroaryl" means a 5- to 12-membered, monocyclic aromatic heterocyclyl (where heterocyclyl is defined herein) or bicyclic heterocyclyl ring system (where at least one of the rings in the bicyclic system is aromatic) where the

monocyclic ring and at least one of the rings in the bicyclic ring system contains one, two, three, four, or five heteroatom(s) selected from nitrogen, oxygen, phosphorous, and sulfur. The ring containing the heteroatom can be aromatic or non-aromatic. Representative examples include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzdioxolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Fused, bridged, and spiro moieties are also included within the scope of this definition.

[00165] "Carbonyl" refers to the group "-C(O)-", which is bivalent.

[00166] "Aminocarbonyl" refers to the group "-C(O)-NH_2," wherein the parent moiety is attached to the carbonyl group.

[00167] "Alkoxycarbonyl" refers to the group "-C(O)alkoxy," wherein alkoxy is as defined above, and the parent moiety is attached to the carbonyl. A non-limiting example includes -C(O)-$OC(CH_3)_3$.

[00168] "Hydroxyalkynyl" refers to a group wherein the parent moiety is attached to the alkynyl group, and a hydroxyl group is attached to the alkynyl. A non-limiting example includes 4-hydroxybut-1-yn-1-yl.

[00169] "Hydroxyalkyl" refers to a group wherein the parent moiety is attached to the alkyl group, and a hydroxyl group is attached to the alkyl, and wherein the alkyl porition is as defined herein.

[00170] "Amino(imino)alkyl" refers to a group represented by -alkyl-C(=NH)-NH_2, wherein alkyl is as defined above. A non-limiting example includes amino(imino)methyl.

[00171] "Dihydroxyalkyl" refers to a group wherein the parent moiety is attached to the alkyl group, and a two hydroxyl groups are attached to the alkyl, and wherein the alkyl portion is as defined herein.

[00172] "Alkylaminoalkyl" refers to -(alkyl)NH(alkyl), wherein the "alkyl" portions are as defined above.

[00173] "Alkylaminoalkylamino" refers to -N(H)(alkyl)NH(alkyl), wherein "alkyl" is as defined above.

[00174] "Aminoalkylamino" refers to -N(H)(alkyl)NH_2, wherein "alkyl" is as defined above.

[00175] "Arylalkylamino" refers to -N(H)(alkyl)aryl, wherein "alkyl" and aryl are as defined above.

[00176] "Alkylsulfonylheterocycloalkylamino" refers to -N(H)-alkylheterocycloalkyl-$S(O)_2$-alkyl, wherein the amino is attached to the parent moiety.

[00177] "Cycloalkylalkylamino" refers to -N(H)-alkylcycloalkyl, wherein the amino is attached to the parent moiety.

[00178] "Cycloalkoxy" refers to -O-cycloalkyl, wherein cycloalkyl is as defined above and the oxygen is attached to the parent moiety.

[00179] "Dialkylaminoalkoxy" refers to -(alkoxy)N(alkyl)$_2$, wherein "alkoxy" and "alkyl" are both defined above. One such non-limiting example of "dialkylaminoalkoxy" includes dimethylaminoethyloxy represented by -O-$(CH_2)_2N(CH_3)_2$.

[00180] "Alkylsulfonylalkylamino" refers to -NH_2-$S(O)_2$-alkyl, wherein the amino portion of this group is attached to the parent moieity, and wherein "alkyl" is as defined above. A non-limiting example includes methylsulfonylethylamino.

[00181] When a portion of term (such as the "alkyl" portion of "arylalkyl") is referred to as being defined above or defined herein, this means that this portion has the same meaning as the definition of this term within this specification.

[00182] The phrases "the compounds in this disclosure," the compounds in the disclosure, the compounds disclosed herein, compounds of this disclosure, and similar phrases that contain both of the words "compounds" and "disclosure" are meant to mean compounds of Formula I, II or III, and all of the embodiments for each of these three compounds.

[00183] In the case where there is a point of attachment for a monovalent substituent, such as -CH_3, -NH_2, or -OH, the indication of where the point of attachment is is not necessary. That is, -CH_3 has the same meaning as CH_3, -NH_2 has the same meaning as NH_2, and –OH has the same meaning as OH.

[00184] In Tables 1 and II, where there appears to be an empty valence for oxygen or nitrogen for any of the compounds listed in this table, where the name of the

structure requires that the empty valence is filled with hydrogen, it is assumed that the missing valence is filled with hydrogen for each of these cases.

[00185] When a group is referred to as "-(C_1-C_6)alkyl heterocyclyl" the heterocyclyl is attached to a parent structure via an alkyl group.

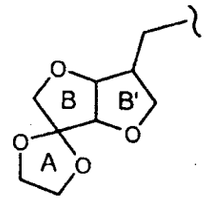
[00186] "Hydroxyalkyl" means -alkyl-OH, wherein alkyl is as defined hereinabove.

[00187] "Optional" or "optionally" means that the subsequently described event or circumstance can or can not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that with respect to any molecule described as containing one or more optional substituents, only sterically practical and/or synthetically feasible compounds are meant to be included. "Optionally substituted" refers to all subsequent modifiers in a term. So, for example, in the term "optionally substituted arylalkyl," both the "alkyl" portion and the "aryl" portion of the molecule can or can not be substituted.

[00188] Unless otherwise specified, the term "optionally substituted" applies to the chemical moiety immediately preceding it. For instance, if a variable group (such as R) is defined as aryl, optionally substituted alkyl, or cycloalkyl, then only the alkyl group is optionally substituted.

[00189] "Saturated bridged ring system" refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system can contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but can have aromatic substitution thereon). For example, hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-aza-bicyclo[2.2.1]-heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class "saturated bridged ring system.

[00190] "Spirocyclyl" or "spirocyclic ring" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B'), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto. A spirocyclyl can be carbocyclic or heteroalicyclic.



[00191] Some of the compounds of the disclosure can have imino, amino, oxo or hydroxy substituents off aromatic heterocyclyl systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents can exist in their corresponding tautomeric form, *i.e.*, amino, imino, hydroxy or oxo, respectively.

[00192] "Animal" for the purposes of this disclosure includes humans (including patients receiving treatment) and other animals, particularly mammals, and other organisms. Thus, the methods are applicable to both human therapy and veterinary applications. In a preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[00193] "Kinase-dependent diseases or conditions" refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion. Diseases associated with kinase activities include tumor growth, the pathologic neovascularization that supports solid tumor growth, and associated with other diseases where excessive local vascularization is involved such as ocular diseases (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

[00194] While not wishing to be bound to theory, phosphatases can also play a role in "kinase-dependent diseases or conditions" as cognates of kinases; that is, kinases phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore compounds of this disclosure, while modulating kinase activity as described herein, can also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, can be synergistic (or not) to activity of compounds of this disclosure toward a related or otherwise interdependent kinase or kinase family. In any case, as stated previously, the compounds of this disclosure are useful for treating diseases characterized in part by abnormal levels of cell

proliferation (*i.e.* tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[00195] "Therapeutically effective amount" is an amount of a compound of this disclosue, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of this disclosure which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their knowledge and to this disclosure.

[00196] "Cancer" as referred to in the specification and in the claims refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinorna, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinorna, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostrate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell

tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis defornians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastorna multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[00197] A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference or S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 both of which are incorporated herein by reference.

[00198] Examples of pharmaceutically acceptable acid addition salts include those formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, 3-(4-

hydroxybenzoyl)benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, p-toluenesulfonic acid, and salicylic acid and the like.

[00199] Examples of a pharmaceutically acceptable base addition salts include those formed when an acidic proton present in the parent compound is replaced by a metal ion, such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferable salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and *tert*iary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Examples of organic bases include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tromethamine, *N*-methylglucamine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

[00200] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this disclosure include, but are not limited to, alkyl esters (for example with between about one and about six carbons) the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this disclosure include, but

are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of this disclosure can be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[00201] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al.. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of this disclosure or its salt can be the biologically active form of the compound in the body. In one example, a prodrug can be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of this disclosure is known to one of skill in the art in light of the present disclosure.

[00202] The compounds of this disclosure also include N-oxide derivatives and protected derivatives of compounds of Formula I, II or III. For example, when compounds of Formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. When compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable "protecting group" or "protective group". A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1991, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of Formula I can be prepared by methods well known in the art.

[00203] "Treating" or "treatment" of a disease, disorder, or syndrome, as used herein, includes (i) preventing the disease, disorder, or syndrome from occurring in a human,

i.e. causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that can be exposed to or predisposed to the disease, disorder, or syndrome but does not yet experience or display symptoms of the disease, disorder, or syndrome; (ii) inhibiting the disease, disorder, or syndrome, *i.e.*, arresting its development; and (iii) relieving the disease, disorder, or syndrome, *i.e.*, causing regression of the disease, disorder, or syndrome. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition can be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

[00204] One of ordinary skill in the art would understand that certain crystallized, protein-ligand complexes, in particular HSP90-ligand complexes, and their corresponding x-ray structure coordinates can be used to reveal new structural information useful for understanding the biological activity of kinases as described herein. As well, the key structural features of the aforementioned proteins, particularly, the shape of the ligand binding site, are useful in methods for designing or identifying selective modulators of kinases and in solving the structures of other proteins with similar features. Such protein-ligand complexes, having compounds of this disclosure as their ligand component, are an aspect of this disclosure.

[00205] As well, one of ordinary skill in the art would appreciate that such suitable x-ray quality crystals can be used as part of a method of identifying a candidate agent capable of binding to and modulating the activity of kinases. Such methods can be characterized by the following aspects: a) introducing into a suitable computer program, information defining a ligand binding domain of a kinase in a conformation (*e.g.* as defined by x-ray structure coordinates obtained from suitable x-ray quality crystals as described above) wherein the computer program creates a model of the three dimensional structures of the ligand binding domain, b) introducing a model of the three dimensional structure of a candidate agent in the computer program, c) superimposing the model of the candidate agent on the model of the ligand binding domain, and d) assessing whether the candidate agent model fits spatially into the ligand binding domain. Aspects a-d are not necessarily carried out in the aforementioned order. Such methods can further entail: performing rational drug

design with the model of the three-dimensional structure, and selecting a potential candidate agent in conjunction with computer modeling.

[00206] Additionally, one skilled in the art would appreciate that such methods can further entail: employing a candidate agent, so-determined to fit spatially into the ligand binding domain, in a biological activity assay for kinase modulation, and determining whether said candidate agent modulates kinase activity in the assay. Such methods can also include administering the candidate agent, determined to modulate kinase activity, to a mammal suffering from a condition treatable by kinase modulation, such as those described above.

[00207] Also, one skilled in the art would appreciate that compounds disclosed herein can be used in a method of evaluating the ability of a test agent to associate with a molecule or molecular complex comprising a ligand binding domain of a kinase. Such a method can be characterized by the following aspects: a) creating a computer model of a kinase binding pocket using structure coordinates obtained from suitable x-ray quality crystals of the kinase, b) employing computational algorithms to perform a fitting operation between the test agent and the computer model of the binding pocket, and c) analyzing the results of the fitting operation to quantify the association between the test agent and the computer model of the binding pocket.

General Administration

[00208] In certain other preferred embodiments, administration can preferably be by the oral route. Administration of the compounds of this disclosure, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[00209] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of this disclosure as the/an active agent, and, in addition, can include carriers and adjuvants, etc.

[00210] Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It can also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00211] If desired, a pharmaceutical composition of the compounds in this disclosure can also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[00212] The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

[00213] Compositions suitable for parenteral injection can comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers,

diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[00214] One preferable route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[00215] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents.

[00216] Solid dosage forms, as described above, can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They can contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[00217] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of this disclosure, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[00218] Suspensions, in addition to the active compounds, can contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[00219] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of this disclosure with, for example, suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[00220] Dosage forms for topical administration of a compound of this disclosure include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as can be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated for the comounds in this disclosure.

[00221] Compressed gases can be used to disperse a compound of this disclosure in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

[00222] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of this disclosure, or a pharmaceutically acceptable salt

thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of this disclosure, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[00223] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of this disclosure, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this disclosure.

[00224] The compounds of this disclosure, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of this disclosure can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

[00225] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of this disclosure as the/an active agent, and, in addition, can include other medicinal agents and pharmaceutical agents. Compositions of the compounds in this disclosure can be used in combination with anticancer and/or other agents that are generally administered to a patient being treated for cancer, e.g. surgery, radiation and/or chemotherapeutic agent(s). Chemotherapeutic agents that can be useful for administration in combination with compounds of Formula I in treating cancer include alkylating agents, platinum containing agents.

[00226] If formulated as a fixed dose, such combination products employ the compounds of this disclosure within the dosage range described above and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of this disclosure can alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

[00227] Representative pharmaceutical formulations containing the compounds disclosed herein are described below.

Synthetic Procedures

[00228] The compounds disclosed herein, or their pharmaceutically acceptable salts, can have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

[00229] The compounds disclosed herein and their pharmaceutically acceptable salts can exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds disclosed herein can also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of the compounds disclosed herein.

[00230] It is assumed that when considering generic descriptions of compounds of the disclosed herein for the purpose of constructing a compound, such construction results in the creation of a stable structure. That is, one of ordinary skill in the art would recognize that theoretically some constructs which would not normally be considered as stable compounds (that is, sterically practical and/or synthetically feasible, *supra*).

[00231] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) can be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which can be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which can be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral

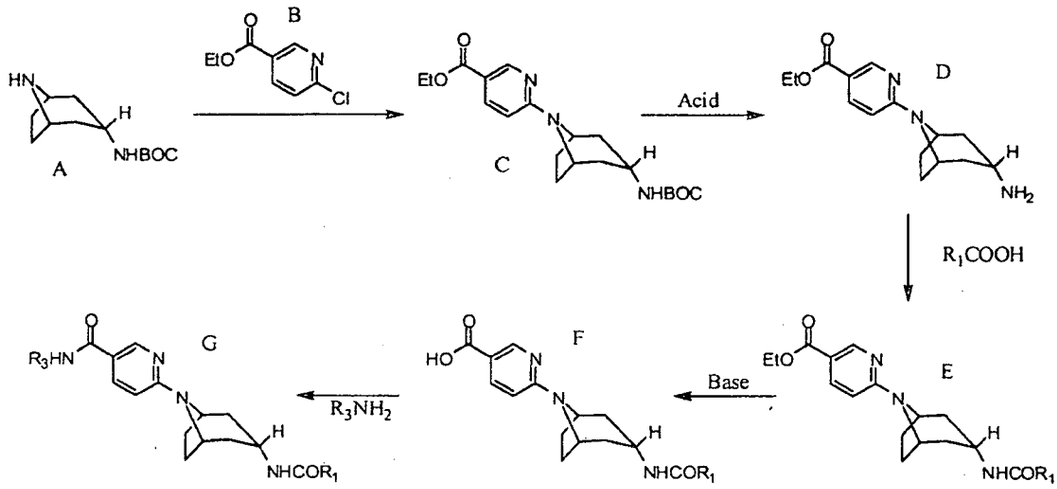
environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step can be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer can be further enriched (with concomitant loss in yield) by recrystallization.

[00232] In addition, the compounds of this disclosure can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds of this disclosure.

[00233] In addition, it is intended that the present disclosure cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry or by biological methods, such as bacterial digestion, metabolism, enzymatic conversion, and the like.

[00234] The examples and scheme below depict the general synthetic procedure for the compounds disclosed herein. Synthesis of the compounds disclosed herein is not limited by these examples and schemes. One skilled in the art will know that other procedures can be used to synthesize the compounds disclosed herein, and that the procedures described in the examples and schemes is only one such procedure. In the descriptions below, one of ordinary skill in the art would recognize that specific reaction conditions, added reagents, solvents, and reaction temperatures can be modified for the synthesis of specific compounds that fall within the scope of this disclosure.

SYNTHETIC SCHEME 1:



[00235] Scheme 1 describes the synthesis of all of the compound(s) listed in Example 1 wherein R_1 and R_3 are as defined in the specification.

[00236] In Scheme 1, compound (B) is added to compound (A) under appropriate reaction conditions to undergo an aromatic nucleophilic substitution reaction to arrive at compound (C). Compound (C) is then deprotected under acidic conditions, such as HCl, to remove BOC and arrive at compound (D). To compound (D), R_1COOH is added under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (E). The carboxylate of compound (E) is then hydrolyzed under basic conditions to yield the carboxylic acid of compound (F). R_3NH_2 is then added to compound F under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (G).

[00237] EXAMPLE 1: 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino) -8-azabicyclo[3.2.1]oct-8-yl]-N-({4-[4-(2-methylpropyl)piperazin-1-yl]phenyl}methyl)pyridine-3-carboxamide.

[00238] STEP 1: 1,1-Dimethylethyl 8-azabicyclo[3.2.1]oct-3-endo-ylcarbamate hydrochloride (synthesized according to the method of reagent preparation 1) (10.44 g, 40 mmol), ethyl 6-chloronicotinate (7.4 g, 40 mmol) and triethylamine (22.4 mL, 160 mmol) were added to 1,2-dimethoxyethane (40 mL) and the resulting suspension was heated at 125 °C for 24 hours in a sealed tube vessel. On cooling to room

temperature, the mixture was diluted with ethyl acetate (200 mL) then washed with water (200 mL). The organic layer was washed twice with 10% aqueous citric acid (2x 100 mL), brine then dried over anhydrous sodium sulfate. Filtration and concentration afforded a solid residue that was then suspended in ethyl ether. The solid was collected by filtration then washed with additional ethyl ether to give ethyl 6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (6.78 g, 45% yield). ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (s, 1H), 7.90 (d, 1H), 6.90 (br s, 1H), 6.73 (d, 1H), 4.53 (br s, 2H), 4.24 (q, 2H), 3.43 (br s, 1H), 2.14-2.10 (m, 2H), 2.00-1.90 (m, 4H), 1.75 (br d, 2H), 1.39 (s, 9H), 1.28 (tr, 3H).

[00239] STEP 2: To a solution of ethyl 6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (2.83 g, 7.54 mmol) in ethanol (20 mL) was added a solution of 4N hydrochloric acid in dioxane (20 mL), and the reaction mixture was refluxed for 2 min. After cooling to room temperature the mixture was diluted with ethyl acetate (100 mL), and saturated aqueous sodium carbonate was added until the aqueous layer reached pH 10. The layers were separated, the aqueous layer was further extracted with ethyl acetate (2 x 50 mL), the combined organic layers were washed with brine (20 mL), dried over sodium sulfate, and concentrated to give ethyl 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylate (1.88 g, 90% yield). ^{1}H NMR (400 MHz, methanol-d_4): 8.65 (d, 1H), 7.98 (dd, 1H), 6.69 (d, 1H), 5.59 (br s, 2H), 4.30 (q, 2H), 3.00 (m, 1H), 2.30-2.05 (m, 6H), 1.58 (d, 2H), 1.35 (t, 3H); MS (EI) for $C_{15}H_{21}N_3O_2$: 276 (MH^+).

[00240] STEP 3: A solution of ethyl 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylate (2.63 g, 9.55 mmol), 3-methoxy-2-methylbenzoic acid (1.59 g, 9.55 mmol), HATU (3.63 g, 9.55 mmol), and diisopropylethylamine (3.70 g, 28.65 mmol) in dimethylformamide (20 mL) was stirred at room temperature for 4 days. The reaction mixture was diluted with ethyl acetate (150 mL), washed with saturated sodium bicarbonate (50 mL), 5% aqueous lithium chloride (2 x 50 mL), and brine (50 mL), dried over sodium sulfate, and dried to provide crude ethyl 6-[3-endo-({[2-methyl-3-methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (4.73 g). MS (EI) for $C_{24}H_{29}N_3O_4$: 424 (MH^+).

[00241] STEP 4: A suspension of crude ethyl 6-[3-endo-({[2-methyl-3-methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (4.72 g, max. 9.55 mmol) and potassium hydroxide (1.07 g, 19.10 mmol) in methanol (90 mL) and water (30 mL) was stirred at 60 °C for 2 hours. After cooling to room temperature, some of the methanol was evaporated, water was added to the resulting mixture, and the pH adjusted to 5 with 1N aqueous hydrochloric acid. The precipitate was filtered, washed with water, and dried to afford 6-[3-endo-({[2-methyl-3-methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (3.14 g, 83% yield over two steps). ^{1}H NMR (400 MHz, DMSO-d_6): 12.45 (s, 1H), 6.83 (br s, 1H), 8.64 (d, 1H), 8.24 (d, 1H), 7.91 (dd, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.75 (d, 1H), 4.60 (br s, 2H), 3.86 (m, 1H), 3.80 (s, 3H), 2.21 (m, 2H), 2.14 (s, 3H), 2.07 (m, 2H), 1.97 (m, 2H), 1.87 (d, 2H); MS (EI) for $C_{22}H_{25}N_3O_4$: 396 (MH^+).

[00242] STEP 5: A solution of tert-butyl 4-[4-(aminomethyl)phenyl]piperazine-1-carboxylate (223 mg, 0.77 mmol), 6-[3-endo-({[2-methyl-3-methyloxy)phenyl]-carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (324 mg, 0.77 mmol), HATU (291 mg, 0.77 mmol), and diisopropylethylamine (302 mg, 2.34 mmol) in dimethylformamide (5 mL) was stirred at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate (50 mL), washed with saturated sodium bicarbonate (25 mL), 5% aqueous lithium chloride (2 x 25 mL), and brine (25 mL), dried over sodium sulfate, and dried to provide 1,1-dimethylethyl 4-(4-{[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-yl}carbonyl)amino]methyl}phenyl)piperazine-1-carboxylate (498 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.58 (d, 1H), 7.90 (dd, 1H), 7.28 (m, 1H),

7.21 (t, 1H), 6.92 (m, 4H), 6.53 (d, 1H), 6.19 (d, 1H), 6.13 (t, 1H), 4.61 (br s, 2H), 4.55 (d, 2H), 4.25 (m, 1H), 3.85 (s, 3H), 3.57 (m, 4H), 3.12 (m, 4H), 2.34 (m, 2H), 2.29 (s, 3H), 2.21 (m, 2H), 2.00 (m, 2H), 1.82 (d, 2H), 1.48 (s, 9H); MS (EI) for $C_{38}H_{48}N_6O_5$: 669 (MH^+).

[00243] STEP 6: To a solution of 1,1-dimethylethyl 4-(4-{[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-yl}carbonyl)amino]methyl}phenyl)piperazine-1-carboxylate (495 mg, 0.74 mmol) in methanol (5 mL) was added a solution of 4N hydrochloric acid in dioxane (5 mL), and the reaction mixture was refluxed for 2 min. Concentration and purification by preparatory HPLC (0.1% aqueous ammonium acetate-acetonitrile) provided 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-piperazin-1-ylphenyl)methyl]pyridine-3-carboxamide acetate salt (45 mg, 9% yield). ^{1}H NMR (400 MHz, methanol-d_4): 8.60 (d, 1H), 7.97 (dd, 1H), 7.27 (d, 2H), 7.23 (t, 1H), 6.99 (m, 3H), 6.90 (d, 1H), 6.75 (d, 1H), 4.60 (br s, 2H), 4.47 (s, 3H), 3.99 (m, 1H), 3.84 (s, 3H), 3.25 (m, 4H), 2.29 (m, 2H), 2.21 (s, 3H), 2.19 (m, 2H), 1.92 (s, 6H), 1.90 (m, 2H); MS (EI) for $C_{33}H_{40}N_6O_3$: 569 (MH^+).

[00244] STEP 7: A mixture of 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]-carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-piperazin-1-ylphenyl)methyl]-pyridine-3-carboxamide (276 mg, 0.30 mmol), 1-iodo-2-methylpropane (62 mg, 0.34 mmol), and cesium carbonate (500 mg, 1.50 mmol) in dimethylformamide (4 mL) was stirred at room temperature for 18 hours. Purification by preparatory HPLC (0.1% aqueous ammonium acetate-acetonitrile) provided 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-({4-[4-(2-methylpropyl)piperazin-1-yl]phenyl}methyl)pyridine-3-carboxamide acetate salt (17 mg, 8% yield). ^{1}H NMR (400 MHz, methanol-d_4): 8.60 (d, 1H), 7.97 (dd, 1H), 7.23 (m, 3H), 7.00 (d, 1H), 6.95 (m, 1H), 6.90 (d, 1H), 6.75 (d, 1H), 4.59 (br s, 2H), 4.46 (s, 2H), 3.99 (m, 1H), 3.84 (s, 3H), 3.17 (m, 4H), 2.62 (m, 4H), 2.29 (m, 2H), 2.23 (m, 5H), 2.12 (m, 2H), 1.90 (m, 4H), 0.94 (d, 6H); MS (EI) for $C_{37}H_{48}N_6O_3$: 625 (MH^+).

[00245] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [1(A)-1(FC)] were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00246] 1(B): N-cyclopropyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-

carboxamide. Prepared according to the method of example 1 by using cyclopropylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{25}H_{30}N_4O_3$: 435 (MH^+).

[00247] 1(C): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(methyloxy)ethyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-methoxyethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{25}H_{32}N_4O_4$: 453 (MH^+).

[00248] 1(D): N-[2-(dimethylamino)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-(dimethylamino)ethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{26}H_{35}N_5O_3$: 466 (MH^+).

[00249] 1(E): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-morpholin-4-ylethyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-(morpholin-4yl)ethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{28}H_{37}N_5O_4$: 507.99 (MH^+).

[00250] 1(F): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyridin-3-ylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-aminomethylpyridine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{28}H_{31}N_5O_3$: 485.97 (MH^+).

[00251] 1(G): N-cyclopentyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using cyclopentylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{27}H_{34}N_4O_3$: 463.02 (MH^+).

[00252] 1(H): N-[(2-chlorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-chlorobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{31}ClN_4O_3$: 519.99 (MH^+).

[00253] 1(I): N-[(4-chlorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-

chlorobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{31}ClN_4O_3$: 519.93 (MH^+).

[00254] 1(J): N-{2-[3,4-bis(methyloxy)phenyl]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3,4-dimethoxyphenethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{32}H_{38}N_4O_5$: 558.94 (MH^+).

[00255] 1(K): N-(furan-2-ylmethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using furfurylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{27}H_{30}N_4O_4$: 474.97 (MH^+).

[00256] 1(L): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-methylpropyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using isobutylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{26}H_{34}N_4O_3$: 451.01 (MH^+).

[00257] 1(M): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(methyloxy)phenyl]methyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-methoxybenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{34}N_4O_4$: 514.97 (MH^+).

[00258] 1(N): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(methyloxy)propyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-methoxypropylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{26}H_{34}N_4O_4$: 497.00 (MH^+).

[00259] 1(O): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-methylphenyl)methyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-methylbenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{34}N_4O_3$: 498.98 (MH^+).

[00260] 1(P): N-(1,3-benzodioxol-5-ylmethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using piperonylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{32}N_4O_5$: 528.94 (MH^+).

[00261] 1(Q): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-prop-2-yn-1-ylpyridine-3-carboxamide. Prepared according to the method of example 1 by using propargylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{25}H_{28}N_4O_3$: 432.98 (MH^+).

[00262] 1(R): N-{[3,4-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3,4-dimethoxybenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{31}H_{36}N_4O_5$: 544.96 (MH^+).

[00263] 1(S): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(4-methylpiperazin-1-yl)propyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-(4-methylpiperazin-1-yl)propylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{42}N_6O_3$: 535.03 (MH^+).

[00264] 1(T): N-[2-(ethylthio)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-(ethylthio)ethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{26}H_{34}N_4O_3S$: 482.97 (MH^+).

[00265] 1(U): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S,2S)-2-[(phenylmethyl)oxy]cyclopentyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using (1S,2S)-2-(benzyloxy)cyclopentylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{34}H_{40}N_4O_4$: 568.98 (MH^+).

[00266] 1(V): N-[(6-chloropyridin-3-yl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (6-chloropyridin-3-yl)methylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{28}H_{30}ClN_5O_3$: 520.92 (MH^+).

[00267] 1(W): N-[(2-chloro-6-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-chloro-6-

fluorobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{30}ClFN_4O_3$: 537.90 (MH^+).

[00268] 1(X): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(methylthio)ethyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-(methylthio)ethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{25}H_{32}N_5O_3S$: 469.45 (MH^+).

[00269] 1(Y): N-butyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]-carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using butylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{26}H_{34}N_4O_3$: 451.08 (MH^+).

[00270] 1(Z): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(3-morpholin-4-ylpropyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-(morpholin-4-yl)propylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{39}N_5O_4$: 522.08 (MH^+).

[00271] 1(AA): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-pyridin-4-ylethyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-(pyridin-4-yl)ethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{33}N_5O_3$: 500.45 (MH^+).

[00272] 1(AB): N-{2-[(1-methylethyl)oxy]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-[(1-methylethyl)oxy]ethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{27}H_{36}N_4O_4$: 481.07 (MH^+).

[00273] 1(AC): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-pyridin-3-ylethyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-(pyridin-3-yl)ethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{33}N_5O_3$: 499.99 (MH^+).

[00274] 1(AD): N-[4,4-bis(methyloxy)butyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4,4-bis(methyloxy)butylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{28}H_{38}N_4O_5$: 511.04 (MH^+).

[00275] 1(AE): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(5-methylpyrazin-2-yl)methyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (5-methylpyrazin-2-yl)methylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{28}H_{32}N_6O_3$: 501.57 (MH^+).

[00276] 1(AF): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(propyloxy)propyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-(propyloxy)propylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{28}H_{38}N_4O_4$: 495.05 (MH^+).

[00277] 1(AG): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[3,4,5-tris(methyloxy)phenyl]methyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3,4,5-tris(methyloxy)benzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{32}H_{38}N_4O_6$: 575.32 (MH^+).

[00278] 1(AH): N-{[3,5-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3,5-bis(methyloxy)benzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{31}H_{36}N_4O_5$: 544.97 (MH^+).

[00279] 1(AI): N-[(1S)-1-(4-{[2-(diethylamino)ethyl]oxy}phenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared as the acetate salt according to the method of example 1 by using 2-({4-[(1S)-1-aminoethyl]phenyl}oxy)-N,N-diethylethanamine (synthesized according to reagent preparation 4) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, methanol-d_4): 8.59 (d, 1H), 7.97 (dd, 1H), 7.31 (m, 2H), 7.23 (t, 1H), 6.99 (d, 1H), 6.90 (m, 3H), 6.74 (d, 1H), 5.18 (q, 1H), 4.59 (br s, 2H), 4.08 (t, 2H), 3.99 (m, 1H), 3.84 (s, 3H), 2.90 (t, 2H), 2.67 (q, 4H), 2.29 (m, 2H), 2.21 (s, 3H), 2.19 (m, 2H), 2.12 (m, 2H), 1.90 (d, 2H), 1.53 (d, 3H), 1.09 (t, 6H); MS (EI) for $C_{36}H_{47}N_5O_4$: 614 (MH^+).

[00280] 1(AJ): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-({4-[(trifluoromethyl)oxy]phenyl}methyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-

trifluoromethoxybenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{31}F_3N_4O_4$: 569.59 (MH^+).

[00281] 1(AK): N-(cyclopropylmethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using cyclopropylmethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{26}H_{32}N_4O_3$: 499.39 (MH^+).

[00282] 1(AL): N-{[2,4-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2,4-bis(methyloxy)benzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{31}H_{36}N_4O_5$: 545.66 (MH^+).

[00283] 1(AM): N-[(4-bromophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-bromobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{31}BrN_4O_3$: 564 (MH^+).

[00284] 1(AN): N-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (2,2-dimethyl-1,3-dioxolan-4-yl)methylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{28}H_{36}N_4O_5$: 509 (MH^+).

[00285] 1(AO): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3S)-1-(phenylmethyl)pyrrolidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (S)-1-benzylpyrrolidin-3-amine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{33}H_{39}N_5O_3$: 554 (MH^+).

[00286] 1(AP): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3R)-1-(phenylmethyl)pyrrolidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (R)-1-benzylpyrrolidin-3-amine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{33}H_{39}N_5O_3$: 554 (MH^+).

[00287] 1(AQ): N-[3-(diethylamino)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-(diethylamino)propylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{41}N_5O_3$: 508 (MH^+).

[00288] 1(AR): N-{3-[(1-methylethyl)oxy]propyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-(1-methylethyloxy)propylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{28}H_{38}N_4O_4$: 495 (MH^+).

[00289] 1(AS): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-propylpyridine-3-carboxamide. Prepared according to the method of example 1 by using propylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{25}H_{32}N_4O_3$: 437 (MH^+).

[00290] 1(AT): N-[2-(diethylamino)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-(diethylamino)ethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{28}H_{39}N_5O_3$: 494 (MH^+).

[00291] 1(AU): N-(3-methylbutyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-methylbutylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{27}H_{36}N_4O_3$: 465 (MH^+).

[00292] 1(AV): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3-methylphenyl)methyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-methylbenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00293] 1(AW): N-[(3-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-fluorobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{31}FN_4O_3$: 503 (MH^+).

[00294] 1(AX): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2-methylphenyl)methyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-methylbenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00295] 1(AY): N-[(3-chlorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-chlorobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{31}ClN_4O_3$: 520 (MH^+).

[00296] 1(AZ): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(tetrahydrofuran-2-ylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using tetrahydrofurfurylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{27}H_{34}N_4O_4$: 479 (MH^+).

[00297] 1(BA): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-(2-oxopyrrolidin-1-yl)propylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{37}N_5O_4$: 520 (MH^+).

[00298] 1(BB): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(1-methylpyrrolidin-2-yl)ethyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-(1-methylpyrrolidin-2-yl)ethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{39}N_5O_3$: 506 (MH^+).

[00299] 1(BC): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-piperidin-1-ylethyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-(piperidin-1-yl)ethylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{39}N_5O_3$: 506 (MH^+).

[00300] 1(BD): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[2-(methyloxy)phenyl]methyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-methoxybenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{34}N_4O_4$: 515 (MH^+).

[00301] 1(BE): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[3-(methyloxy)phenyl]methyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-methoxybenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{34}N_4O_4$: 515 (MH^+).

[00302] 1(BF): N-[(2-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-fluorobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{31}FN_4O_3$: 503 (MH^+).

[00303] 1(BG): N-[(4-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-fluorobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{31}FN_4O_3$: 503 (MH^+).

[00304] 1(BH): N-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-yl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-amino-(1R,2R,4S)-bicyclo[2.2.1]heptane in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{36}N_4O_3$: 489 (MH^+).

[00305] 1(BI): N-(3,3-dimethylbutyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3,3-dimethylbutylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{28}H_{38}N_4O_3$: 479 (MH^+).

[00306] 1(BJ): N-{[2,3-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2,3-dimethoxybenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{31}H_{36}N_4O_5$: 545 (MH^+).

[00307] 1(BK): N-{[2-(ethyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-

ethoxybenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{31}H_{36}N_4O_4$: 529 (MH^+).

[00308] 1(BL): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[1-(phenylmethyl)piperidin-4-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 1-benzyl-4-aminopiperidine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{34}H_{41}N_5O_3$: 463 (MH^+).

[00309] 1(BM): ethyl 4-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino]piperidine-1-carboxylate. Prepared according to the method of example 1 by using ethyl 4-aminopiperidine-1-carboxylate in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{39}N_5O_5$: 550 (MH^+).

[00310] 1(BN): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-thienylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-aminomethylthiophene in step 5, then omission of steps 6 and 7. MS (EI) for $C_{27}H_{30}N_4O_3S$: 491 (MH^+).

[00311] 1(BO): N-cyclobutyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using cyclobutylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{26}H_{32}N_4O_3$: 449 (MH^+).

[00312] 1(BP): N-[3-(ethyloxy)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-(ethyloxy)propylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{27}H_{36}N_4O_4$: 481 (MH^+).

[00313] 1(BQ): N-[3-(dimethylamino)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-(dimethylamino)propylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{27}H_{37}N_5O_3$: 480 (MH^+).

[00314] 1(BR): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(trifluoromethyl)phenyl]methyl}pyridine-3-

carboxamide. Prepared according to the method of example 1 by using 4-trifluoromethylbenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{31}F_3N_4O_3$: 553 (MH^+).

[00315] 1(BS): N-[(2,4-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2,4-difluorobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{30}F_2N_4O_3$: 521 (MH^+).

[00316] 1(BT): N-[(2,5-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2,5-difluorobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{30}F_2N_4O_3$: 521 (MH^+).

[00317] 1(BU): N-[(2,6-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2,6-difluorobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{30}F_2N_4O_3$: 521 (MH^+).

[00318] 1(BV): N-[(3,4-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3,4-difluorobenzylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{29}H_{30}F_2N_4O_3$: 521 (MH^+).

[00319] 1(BW): N-[3-(1H-imidazol-1-yl)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-(1H-imidazol-1-yl)propylamine in step 5, then omission of steps 6 and 7. MS (EI) for $C_{28}H_{34}N_6O_3$: 503 (MH^+).

[00320] 1(BX): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-methylphenyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-methylaniline in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.61 (s, 1H), 8.75 (s, 1H), 8.25 (s,1H), 8.05 (dd, 1H), 7.32 (d, 1H), 7.21 (m, 3H), 7.02 (d, 1H), 6.86 (d, 1H),

6.81 (d, 1H), 4.58 (s, 2H), 3.87 (s, 1H), 3.81 (s, 3H), 3.32 (s, 1H), 2.23 (s, 3H), 2.21 (m, 1H), 2.14 (s, 3H), 2.10 (m, 1H), 1.99 (m, 2H), 1.86 (d, 2H). MS (EI) for $C_{29}H_{32}N_4O_3$: 485.6 (MH^+).

[00321] 1(BY): N-(3,5-dimethylphenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3,5-dimethylaniline in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.83 (s,1H), 8.72 (s,1H), 8.25 (s, 1H), 8.04 (dd, 1H), 7.38 (s, 1H), 7.24 (t, 1H), 7.02 (d, 1H), 6.87 (d, 1H), 6.80 (d, 1H), 6.72 (s, 1H), 4.59 (s, br, 1H), 3.86 (m, 1H), 3.81 (s, 3H), 2.26 (s, 6H), 2.21 (m, 2H), 2.15 (s, 3H), 2.10 (m, 2H), 1.99 (m, 2H), 1.86 (d, 2H). MS (EI) for $C_{30}H_{34}N_4O_3$: 499.4 (MH^+).

[00322] 1(BZ): N-1,3-benzodioxol-5-yl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using benzo[d][1,3]dioxol-5-amine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.90 (s, 1H), 8.70 (s, 1H), 8.25 (s, 1H), 8.02 (dd, 1H), 7.42 (,s, 1H), 7.24 (t, 1H), 7.14 (dd, 1H), 7.02 (d, 1H), 6.88 (t,2H), 6.80 (d, 1H), 6.00 (s, 2H), 4.59 (s, br, 2H), 3.87 (m, 1H), 3.81 (s, 3H), 2.21 (m, 2H), 2.14 (s, 3H), 2.11 (m, 2H), 1.99 (m, 2H), 1.87 (d, 2H). MS (EI) for $C_{29}H_{30}N_4O_5$: 515.5 (MH^+).

[00323] 1(CA): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(4-methylphenyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-methylaniline in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.90 (s, 1H), 8.72 (s, 1h), 8.25 (s, 1H), 8.04 (dd, 1H), 7.63 (m, 2H), 7.23 (t, 1H), 7.13 (d, 2H), 7.02 (d, 1H), 6.86 (d, 1H), 6.80 (d, 1H), 4.58 (s, 2H), 3.87 (m, 1H), 3.81 (s, 3H), 2.27 (m, 5H), 2.12 (m, 5H), 1.99 (m, 2H), 1.87 (d, 2H). MS (EI) for $C_{29}H_{32}N_4O_3$: 485.8 (MH^+).

[00324] 1(CB): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3-methylphenyl)methyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-methylaniline in step 5, then omission of steps 6 and 7. MS (EI) for $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00325] 1(CC): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(methyloxy)phenyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-methoxyaniline in step 5,

then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.22 (s,1H), 8.72 (s, 1H), 8.25 (s, 1H), 8.03 (dd, 1H), 7.75 (dd, 1H), 7.23 (t, 1H), 7.15 (t, 1H), 7.08 (d, 1H), 7.02 (d, 1H), 6.95 (t, 1H), 6.87 (d, 1H), 6.80 (d, 1H), 4.57 (s, br, 2H), 3.83 (m, 4H), 3.81 (s, 3H), 2.17 (m, 2H), 2.15 (m, 3H), 2.11 (m, 1H), 1.99 (m, 2H), 1.87 (m, 3H). MS (EI) for $C_{29}H_{32}N_4O_4$: 501 (MH^+).

[00326] 1(CD): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(methyloxy)phenyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-methoxyaniline in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.93 (s, 1H), 8.70 (s, 1H), 8.23 (s, 1H), 8.03 (dd, 1H), 7.44 (s, 1H), 7.31 (s, 1H), 7.21 (m, 2H), 7.00 (d, 1H), 6.85 (d, 1H), 6.79 (d, 1H), 6.64 (dd, 1H), 4.57 (s, br, 2H), 3.85 (m, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 2.20 (m, 2H), 2.13 (s, 3H), 2.08 (m, 2H), 1.98 (m, 2H), 1.85 (d, 2H). MS (EI) for $C_{29}H_{32}N_4O_4$: 501 (MH^+).

[00327] 1(CE): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[4-(methyloxy)phenyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-methoxyaniline in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.87 (s, 1H), 8.71 (s, 1H), 8.05 (dd, 1H), 7.63 (m, 2H), 7.23 (t, 1H), 7.02 (d, 1H), 6.89 (m, 3H), 6.80 (d, 1H), 4.58 (s, br, 2H), 3.86 (m, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 2.24 (m, 2H), 2.11 (m, 5H), 1.99 (m, 2H), 1.86 (d, 2H). MS (EI) for $C_{29}H_{32}N_4O_4$: 501 (MH^+).

[00328] 1(CF): N-(3-chlorophenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-chloroaniline in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 10.14 (s, 1H), 8.73 (s, 1H), 8.25 (s, 1H), 8.05 (dd, 1H), 7.95 (s, 1H), 7.67 (d, 1H), 7.37 (t, 1H), 7.24 (t, 1H), 7.13 (d, 1H), 7.02 (1H), 6.85 (m, 2H), 4.60 (s, br, 2H), 3.86 (m, 1H), 3.81 (s, 3H), 2.22 (m, 2H), 2.15 (s, 3H), 2.11 (m, 2H), 1.99 (m, 2H), 1.87 (d, 2H). MS (EI) for $C_{28}H_{29}ClN_4O_3$: 506 (MH^+).

[00329] 1(CG): N-(4-fluorophenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-fluoroaniline in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 10.04 (s, 1H), 8.72 (s, 1H), 8.25 (s, 1H), 8.05 (dd, 1H), 7.75 (m, 2H), 7.18

(m, 3H), 7.02 (d, 1H), 6.83 (m, 2H), 4.59 (s, br, 2H), 3.83 (m 1H), 3.80 (s, 3H), 2.21 (m, 2H), 2.14 (m, 5H), 1.99 (m, 2H), 1.87 (d, 2H). MS (EI) for $C_{28}H_{29}FN_4O_3$: 489 (MH^+).

[00330] 1(CH): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[1-(6-piperazin-1-ylpyridin-3-yl)ethyl]pyridine-3-carboxamide. ^{1}H NMR (400 MHz, d6-DMSO): 9.76 (br s, 2H), 9.46 (d, 1H), 8.60 (s, 1H), 8.42 (d, 1H), 8.36 (s, 1H), 8.18 (d, 1H), 8.08 (s, 1H), 7.44-7.38 (m, 2H), 7.24 (tr, 1H), 7.03 (d, 1H), 6.88 (d, 1H), 5.20-5.10 (br m, 1H), 4.01 (br, 4H), 3.92 (br, 2H), 3.81 (s, 2H), 3.58 (s, 3H), 3.24 (br, 4H), 2.35-2.28 (br m, 2H), 2.20-2.00 (br m, 6H), 2.15 (s, 3H), 1.52 (d, 3H). Prepared according to the method of example 1 by using tert-butyl 4-(5-(1-aminoethyl)pyridin-2-yl)piperazine-1-carboxylate in step 5 (synthesized according to reagent preparation 7), then omission of step 6.

[00331] 1(CI): N-[1-(4-bromo-2-fluorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 1-(4-bromo-2-fluorophenyl)ethanamine (synthesized according to reagent preparation 8) in step 5, then omission of steps 6 and 7. ^{1}HNMR (400MHz, $CDCl_3$): 8.59 (d, 1H), 7.88 (dd, 1H), 7.24-7.19 (m, 4H), 6.92 (dd, 1H), 6.52 (d, 1H), 6.41 (d, 1H), 6.20 (d, 1H), 5.38 (m, 1H), 4.61 (br, 2H), 4.25 (q, 1H), 3.86 (s, 3H), 2.36-2.31 (m, 2H), 2.29 (s, 3H), 2.21, (m, 2H), 2.01 (m, 2H), 1.84 (d, 2H), 1.64 (br, 1H), 1.57 (d, 3H); MS (EI) for $C_{30}H_{32}BrFN_4O_3$: 696 (MH^+).

[00332] 1(CJ): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(1-methylpiperidin-4-yl)phenyl]methyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-(1-methylpiperidin-4-yl)benzylamine (synthesized according to reagent preparation 2) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.81 (dd, 1H), 8.63 (d, 1H), 8.22 (d, 1H), 7.96 (dd, 1H), 7.21 (m, 3H), 7.01 (d, 2H), 6.86 (d, 1H), 6.74 (d, 1H), 4.61 (m, 4H), 4.23 (d, 1H), 3.83 (s, 3H), 3.47 (q, 2H), 3.08 (d, 2H), 2.51 (m, 1H), 2.42 (m, 8H), 2.19 (m, 4H), 1.99 (d, 2H), 1.92-1.80 (br m, 6H), 1.21 (m, 4H). MS (EI) for $C_{35}H_{43}N_5O_3$: 582 (MH^+).

[00333] 1(CK): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3R)-pyrrolidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 1,1-dimethylethyl (3R)-

pyrrolidin-3-ylcarbamate in step 5, then omission of step 7. ^{1}H NMR (400 MHz, d_6-DMSO): 9.48 (s, 1H), 9.36 (s, 1H), 9.09 (s, 1H), 8.60 (s, 1H), 8.33-8.38 (m, 2H), 7.29 (d, 1H), 7.24 (t, 1H), 7.03 (d, 1H), 6.88 (d, 1H), 4.86 (br s, 2H), 4.52-4.57 (m, 2H), 3.91 (s, 1H), 3.81 (s, 3H), 3.34-3.42 (m, 2H), 3.19-3.29 (m, 2H), 2.30 (d, 2H), 2.16-2.23 (m, 2H), 2.15 (s, 3H), 1.98-2.06 (m, 4H). MS (EI) for $C_{26}H_{33}N_5O_3$: 464 (MH^+).

[00334] 1(CL): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-piperidin-3-ylpyridine-3-carboxamide. Prepared according to the method of example 1 by using 1,1-dimethylethyl-3-aminopiperidine-1-carboxylate in step 5, then omission of step 7. ^{1}H NMR (400 MHz, d_6-DMSO): 9.43 (s, 1H), 9.17 (s, 1H), 8.98 (s, 1H), 8.78 (s, 1H), 8.61 (d, 1H), 8.39 (d, 1H), 8.34 (d, 1H0, 7.31 (s, 1H), 7.24 (t, 2H), 7.03 (d, 1H), 6.88 (d, 1H), 4.88 (br s, 2H), 4.19-4.27 (m, 1H), 3.88-3.93 (s, 1H), 3.81 (s, 1H), 3.27 (d, 1H), 3.12 (d, 1H), 2.87-2.96 (m, 2H), 2.30 (d, 2H), 2.15 (s, 4H), 1.98-2.06 (m, 3H), 1.87-1.92 (m, 2H), 1.61-1.76 (m, 2H). MS (EI) for $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00335] 1(CM): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-piperidin-4-ylpyridine-3-carboxamide. Prepared according to the method of example 1 by using 1,1-dimethylethyl-4-aminopiperidine-1-carboxylate in step 5, then omission of step 7. ^{1}H NMR (400 MHz, d_6-DMSO): 9.02 (s, 2H), 8.82 (s, 1H), 8.55 (s, 1H), 8.35 (s, 2H), 7.30 (s, 1H), 7.24 (t, 1H), 7.03 (d, 1H), 6.88 (d, 1H), 4.89 (br s, 1H), 4.04-4.09 (m, 1H), 3.91 (s, 1H), 3.81 (s, 3H), 3.65-3.74 (m, 1H), 3.47-3.52 (m, 1H), 3.31 (d, 2H), 3.00 (s, 2H), 2.30 (d, 2H), 2.15 (s, 4H), 1.94-2.10 (m, 5H), 1.80 (q, 2H). MS (EI) for $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00336] 1(CN): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyrrolidin-3-ylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 1,1-dimethylethyl-3-(aminomethyl)pyrrolidine-1-carboxylate in step 5, then omission of step 7. ^{1}H NMR (400 MHz, d_6-DMSO): 9.31 (t, 2H), 9.14 (t, 1H), 8.77 (br s, 1H), 8.54 (d, 1H), 8.35-8.40 (m, 2H), 7.96 (s, 1H), 7.38 (d, 1H), 7.24 (t, 1H), 7.03 (d, 1H), 6.88 (s, 1H), 3.92 (s, 1H), 3.81 (s, 2H), 3.65-3.74 (m, 2H), 3.45-3.52 (m, 2H), 3.32-3.37 (m, 2H), 3.18-3.28 (m, 2H), 3.07-3.13 (m, 1H), 2.89 (s, 4H), 2.73 (s, 3H), 2.31 (d, 2H), 2.15 (s, 4H), 1.98-2.05 (m, 4H0, 1.63-1.70 (m, 1H). MS (EI) for $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00337] 1(CO): N-cyclohexyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-

carboxamide. Prepared according to the method of example 1 by using cyclohexylamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.21 (d, 1H), 7.94 (d, 1H), 7.92 (d, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.73 (d, 1H), 4.54 (s, 2H), 3.80 (s, 4H), 3.73 (s, 1H), 3.34 (s, 3H), 2.19 (d, 2H0, 2.14 (s, 2H), 2.06-2.12 (m, 2H), 1.96-1.99 (m, 2H), 1.72-1.85 (m, 5H), 1.60 (d, 1H), 1.29 (t, 3H), 1.01-1.19 (m, 1H). MS (EI) for $C_{28}H_{36}N_4O_3$: 477 (MH^+).

[00338] 1(CP): N-methyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using methylamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.47 (d, 1H), 8.41 (d, 1H), 8.28 (d, 1H), 8.10 (d, 1H), 7.23 (t, 1H), 7.08 (d, 1H), 7.03 (d, 1H), 6.87 (d, 1H), 4.64 (s, 2H), 3.86-3.92 (m, 1H), 3.81 (s, 3H), 2.78 (d, 2H), 2.23-2.28 (m, 2H), 2.11-2.16 (m, 5H0, 1.99-2.02 (m, 2H), 1.97 (s, 1H), 1.93 (s, 1H). MS (EI) for $C_{23}H_{28}N_4O_3$: 409 (MH^+).

[00339] 1(CQ): N-ethyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using ethylamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.21 (t, 2H), 7.92 (dd, 1H), 7.23 (t, 1H), 7.01 (d, 1H), 6.86 (d, 1H), 6.74 (d, 1H), 4.54 (s, 2H), 3.82 (s, 1H), 3.80 (s, 3H), 3.34 (s, 3H), 3.22-3.29 (m, 2H), 2.17-2.22 (m, 1H), 2.14 (s, 3H), 2.07-2.12 (m, 2H), 1.96-1.99 (m, 2H), 1.86 (s, 1H), 1.82 (s, 1H), 1.10 (t, 3H). MS (EI) for $C_{24}H_{30}N_4O_3$: 423 (MH^+).

[00340] 1(CR): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1R)-1-phenylethyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (1R)-1-phenylethanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.72 (d, 1H), 8.57 (d, 1H), 8.27 (d, 1H), 8.14 (d, 1H), 7.31-7.39 (m, 4H), 7.20-7.25 (m, 2H), 7.00-7.04 (m, 2H), 6.87 (d, 1H), 5.12-5.19 (m, 1H), 4.63 (s, 2H), 3.85-3.90 (m, 1H), 3.81 (s, 3H), 2.24 (d, 2H), 2.14 (s, 4H), 2.11 (s, 1H), 2.00-2.03 (m, 2H), 1.94 (s, 1H), 1.91 (s, 1H), 1.47 (d, 3H). MS (EI) for $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00341] 1(CS): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1S)-1-phenylethyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (1S)-1-phenylethanamine in step 5,

then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.55 (d, 1H), 8.28 (d, 1H), 8.16 (d, 1H), 7.31-7.38 (m, 4H), 7.21-7.25 (m, 2H), 7.02-7.05 (m, 2H), 6.87 (d, 1H), 5.12-5.19 (m, 1H), 4.63 (s, 2H), 3.84-3.91 (m, 1H), 3.81 (s, 3H), 2.25 (d, 2H), 2.14 (s, 4H), 2.11 (s, 1H), 2.00-2.03 (m, 2H), 1.96 (s, 1H), 1.92 (s, 1H), 1.47 (d, 3H). MS (EI) for $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00342] 1(CT): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1S)-1-phenylpropyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (1R)-1-phenylpropan-1-amine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.61 (d, 1H), 8.57 (s, 1H), 8.26 (d, 1H), 8.11 (d, 1H), 7.38 (d, 2H), 7.32 (t, 2H), 7.20-7.25 (m, 2H), 7.02 (d, 1H), 6.96 (s, 1H), 6.87 (d, 1H), 4.86-4.92 (m, 1H), 4.61 (s, 2H), 3.86 (s, 1H), 3.81 (s, 3H), 2.24 (d, 2H), 2.14 (s, 4H), 2.10 (s, 1H), 1.97-2.02 (m, 2H), 1.93 (s, 1H), 1.89 (s, 1H), 1.75-1.86 (m, 2H), 0.90 (t, 3H). MS (EI) for $C_{31}H_{36}N_4O_3$: 513 (MH^+).

[00343] 1(CU): N-[(1S)-1-(4-chlorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (1R)-1-(4-chlorophenyl)ethanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.71 (d, 1H), 8.57 (d, 1H), 8.25 (d, 1H), 8.10 (d, 1H), 7.39 (s, 4H), 7.23 (t, 1H), 7.02 (d, 1H), 6.97 (d, 1H), 6.87 (d, 1H), 5.09-5.17 (m, 1H), 4.62 (s, 2H), 3.85-3.90 (m, 1H), 3.81 (s, 3H), 2.22-2.27 (m, 2H), 2.14 (s, 2H), 2.08-2.12 (m, 2H), 2.00-2.02 (m, 2H), 1.94 (s, 1H), 1.90 (s, 1H), 1.46 (d, 3H). MS (EI) for $C_{30}H_{33}ClN_4O_3$: 533 (MH^+).

[00344] 1(CV): N-[(1S)-2-amino-1-methyl-2-oxoethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using L-alaninamide hydrochloride in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.56 (d, 1H), 8.44 (d, 1H), 8.28 (d, 1H), 8.16 (d, 1H), 7.40 (s, 1H), 7.23 (t, 1H), 7.04-7.07 (m, 1H), 7.01 (d, 1H), 6.87 (d, 1H), 4.65 (s, 2H), 4.37-4.44 (m, 1H), 3.87-3.91 (m, 1H), 3.81 (s, 3H), 2.89 (s, 1H), 2.73 (s, 1H), 2.24-2.29 (m, 2H), 2.15 (s, 4H), 2.09-2.13 (m, 1H), 2.01-2.04 (m, 2H), 1.96 (s, 1H), 1.93 (s, 1H), 1.32 (d, 3H). MS (EI) for $C_{25}H_{31}N_5O_4$: 466 (MH^+).

[00345] 1(CW): N-hydroxy-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using hydroxylamine hydrochloride in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 10.18 (s, 1H), 8.60 (d, 1H), 8.23 (d, 1H), 7.92 (dd, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.76 (d, 1H), 4.56 (br s, 2H), 3.85 (s, 1H), 3.80 (s, 3H), 3.34 (s, 6H), 2.20 (d, 1H), 2.14 (s, 1H), 2.07-2.11 (m, 1H), 1.98 (s, 2H), 1.84-1.87 (m, 2H). MS (EI) for $C_{22}H_{26}N_4O_4$: 410 (MH^+).

[00346] 1(CX): N-{8-[5-(hydrazinocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-3-(methyloxy)benzamide. Prepared according to the method of example 1 by using hydrazine hydrochloride in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 11.11 (br s, 1H), 8.42 (d, 1H), 8.26 (d, 1H), 7.95 (d, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.96 (d, 1H), 6.87 (d, 1H), 4.60 (s, 2H), 3.87 (s, 1H), 3.81 (s, 3H), 2.21-2.26 (m, 2H), 2.14 (s, 3H), 2.07-2.12 (m, 1H), 1.98-2.00 (m, 2H), 1.93 (s, 1H), 1.89 (s, 1H). MS (EI) for $C_{22}H_{27}N_5O_3$: 411 (MH^+).

[00347] 1(CY): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(1-methylpiperidin-4-yl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 1-methylpiperidin-4-amine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 10.47 (br s, 1H), 8.71 (d, 1H), 8.54 (d, 1H), 8.32 (d, 1H), 8.25 (d, 1H), 7.20-7.26 (m, 2H), 1.03 (d, 1H), 6.88 (d, 1H), 4.81 (br s, 2H), 3.86-3.94 (m, 1H), 3.81 (s, 3H), 3.43 (d, 2H), 3.30-3.36 (m, 1H), 2.98-3.11 (m, 3H), 2.76 (t, 1H), 2.71-2.74 (m, 3H), 2.28 (d, 2H), 2.15 (s, 4H), 1.84-2.05 (m, 6H). MS (EI) for $C_{28}H_{37}N_5O_3$: 492 (MH^+).

[00348] 1(CZ): N-(1-methylethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using propan-2-amine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.22 (d, 1H), 7.95 (t, 1H), 7.93 (d, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.73 (d, 1H), 4.54 (s, 2H), 4.05-4.10 (m, 1H), 3.84 (s, 1H), 3.80 (s, 3H), 3.34 (s, 4H), 2.17-2.22 (m, 2H), 2.14 (s, 2H), 2.06-2.12 (m, 1H), 1.96-1.99 (m, 2H), 1.85 (s, 1H), 1.82 (s, 1H), 1.14 (d, 6H). MS (EI) for $C_{25}H_{32}N_4O_3$: 437 (MH^+).

[00349] 1(DA): 2-[(1-ethylpropyl)amino]-N4-[8-(5-{[3R]-pyrrolidin-3-ylaminocarbonyl}pyridine-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide. Prepared according to the method of example 1 by using 4-(aminocarbonyl)-3-[(1-ethylpropyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 3 and 1,1-dimethylethyl (3R)-3-aminopyrrolidine-1-carboxylate in step 5, then omission of step 7. MS (EI) for $C_{30}H_{41}N_7O_3$: 548.4 (MH^+).

[00350] 1(DB): 2-[(1-ethylpropyl)amino]-N4-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridine-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 1 by using 4-(aminocarbonyl)-3-[(1-ethylpropyl)amino]benzoic acid in step 3 (synthesized according to reagent preparation 39) and (3R)-1-(1-methylethyl)pyrrolidine-3-amine hydrochloride (synthesized according to reagent preparation 9) in step 5, then omission of steps 6 and 7. MS (EI) for $C_{33}H_{47}N_7O_3$: 590.4 (MH^+).

[00351] 1(DC): 2-[(1-ethylpropyl)amino]-N4-{8-[5-({[(3S)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridine-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 1 by using 4-(aminocarbonyl)-3-[(1-ethylpropyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 3 and (3S)-1-(1-methylethyl)pyrrolidine-3-amine hydrochloride (synthesized according to reagent preparation 9) in step 5, then omission of steps 6 and 7. MS (EI) for $C_{33}H_{47}N_7O_3$: 590.4 (MH^+).

[00352] 1(DD): 2-[(1-ethylpropyl)amino]-N4-{8-[5-({[(3R)-1-ethylpyrrolidin-3-yl]amino}carbonyl)pyridine-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 1 by using 4-(aminocarbonyl)-3-[(1-ethylpropyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 3 and (3R)-1-ethylpyrrolidine-3-amine (synthesized according to reagent preparation 9) in step 5, then omission of steps 6 and 7. MS (EI) for $C_{33}H_{47}N_7O_3$: 590.4 (MH^+).

[00353] 1(DE): 2-[(1-ethylpropyl)amino]-2-methyl-N4-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridine-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 1 by using 4-(aminocarbonyl)-5-[(1-ethylpropyl)amino]-2-methyl benzoic acid (synthesized according to reagent preparation 42) in step 3 and (3R)-1-(1-

methylethyl)pyrrolidine-3-amine hydrochloride (synthesized according to reagent preparation 9) in step 5, then omission of steps 6 and 7. MS (EI) for $C_{34}H_{49}N_7O_3$: 604.4 (MH^+).

[00354] 1(DF): 2-[(1-ethylpropyl)amino]-N4-{8-(5-{[(3S)-pyrrolidin-3-ylamino]carbonyl}pyridine-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 1 by using 4-(aminocarbonyl)-5-[(1-ethylpropyl)amino]-2-methyl benzoic acid in step 3 (synthesized according to reagent preparation 42) and 1,1-dimethylethyl (3S)-3-aminopiperidine-1-carboxylate in step 5, then omission of step 7. MS (EI) for $C_{34}H_{49}N_7O_3$: 562.2 (MH^+).

[00355] 1(DG): 5-[(1-ethylpropyl)amino]-2-methyl-N4-{8-(5-({[(3R)-1-(1-methylethyl)piperidin-3-yl]amino}carbonyl)pyridine-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 1 by using 4-(aminocarbonyl)-5-[(1-ethylpropyl)amino]-2-methyl benzoic acid (synthesized according to reagent preparation 42) in step 3 and (3*R*)-1-(1-methylethyl)piperidine-3-amine (synthesized according to reagent preparation 9) in step 5, then omission of steps 6 and 7. MS (EI) for $C_{35}H_{51}N_7O_3$: 618.3 (MH^+).

[00356] 1(DH): N-[(4-{[2-(diethylamino)ethyl]oxy}phenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-{4-(aminomethyl)phenyl]oxy}-N,N-diethylethanamine (synthesized according to reagent preparation 4) in step 5, then omission of steps 6 and 7. ^{1}H-NMR(CD_3OD): 8.50 (d, 1H), 8.35(d, 1H), 7.35(s, 1H), 7.35-7.33 (m, 1H), 7.32 (s, 1H), 7.23(t, 1H), 7.02-6.98(m, 3H), 6.89(d, 1H), 4.83(s, 2H), 4.51(s, 2H), 4.33(t, 3H), 4.21-418(m, 1H), 3.85 (s, 3H), 3.61(t, 2H), 3.38-3.36(m, 2H), 3.30-3.29(m, 4H), 2.10(s, 3H), 2.03(s, 2H), 2.00(s, 2H), 1.36(t, 6H). MS (EI) for $C_{35}H_{45}N_5O_4$: 601 (MH^+).

[00357] 1(DI): N-[(3-{[2-(diethylamino)ethyl]oxy}phenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2-{3-(aminomethyl)phenyl]oxy}-N,N-diethylethanamine (synthesized according to reagent preparation 4) in step 5, then omission of steps 6 and 7. ^{1}H-NMR (CD_3OD): 8.50(s, 1H), 8.49 (s, 1H), 8.21(dd, 1H), 7.32 (t, 1H), 7.26(t, 1H), 7.16 (d, 1H), 7.01-6.94 (m, 3H), 6.93-6.90(m, 2H), 4.68(s, 2H), 4.55(s, 2H), 4.34(t, 2H), 4.06-

4.05(m,1H), 3.84(s, 3H), 3.59(t, 2H), 3.37-3.35(m, 2H), 3.35-2.33 (m, 4H), 2.31 (s, 3H), 2.28(s, 2H), 2.21 (s, 2H), 1.38 (t, 6H). MS (EI) for $C_{35}H_{45}N_5O_4$: 601 (MH^+).

[00358] 1(DJ): N-(8-{5-[({[4-(4-methylpiperazin-1-yl)phenyl]methyl}amino)-carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared according to the method of example 1 by using terephthalic acid monoamide in step 3 and 4-(4-methylpiperazin-1-yl)benzylamine in step 5, then omission of steps 6 and 7.

^{1}H-NMR (CD_3OD): 8.60(s, 1H), 8.00-7.95(m, 3H), 7.83(d, 2H), 7.25(d, 2H), 6.95(d, 2H), 6.75(s, 1H), 4.62(s, 2H), 4.47(s, 2H), 4.00-4.01(m, 1H), 3.28- 3.21 (m, 4H), 2.87-2.82 (m, 4), 2.51(s, 3H), 2.31-2.16(m, 8H). MS (EI) for $C_{33}H_{39}N_7O_3$: 583(MH^+).

[00359] 1(DK): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[4-(4-methylpiperazin-1-yl)phenyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-(4-methylpiperazin-1-yl)aniline in step 5, then omission of steps 6 and 7. ^{1}H-NMR (DMSO-d_6): 9.79(s, 1H), 8.71(d, 1H), 8.23(d, 1H), 8.03(d, 1H), 7.58(d, 2H), 7.23(t, 1H), 7.02(d, 1H), 6.92-6.90(m, 2H), 6.80(d, 1H), 4.58(s, 2H), 3.82(s, 1H), 3.81(s, 3H), 3.09-2.98(m, 4H), 2.46-2.23 (m, 4H), 2.25(s, 3H), 2.20 (s, 2H), 2.15(s, 3H), 2.11-1.98(m, 4H), 1.86(d, 2H). MS (EI) for $C_{33}H_{40}N_6O_3$: 569 (MH^+).

[00360] 1(DL): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[4-(1-methylpiperidin-4-yl)phenyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-(1-methylpiperidin-4-yl)aniline in step 5, then omission of steps 6 and 7. ^{1}H-NMR (CD_3OD): 8.59(s, 1H), 8.45(d, 1H), 8.35(dd, 1H), 7.64(d, 2H), 7.28-7.23(m, 3H), 7.02(d, 1H), 6.91(d, 1H), 4.73(s, 2H), 3.85-3.82(m, 1H), 3.62(s, 3H), 3.31(s, 1H), 3.30(s, 1H), 3.15(t, 2H), 2.99(s, 1H), 2.92(s, 3H), 2.85(s, 1H), 2.36-2.34(m, 4H), 2.26(s, 3H), 2.15-2.09(m, 2H), 1.96-1.93(m, 2H). MS (EI) for $C_{34}H_{41}N_5O_3$: 569 (MH^+).

[00361] 1(DM): N-(4-{[2-(dimethylamino)ethyl]oxy}phenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 4-[2-(diethylamino)ethoxy]aniline in step 5, then omission of steps 6 and 7. ^{1}H-NMR (CD_3OD): 8.57(d, 1H), 8.46(d, 1H), 8.34(d, 1H), 7.64(s, 1H), 7.62(s, 1H), 7.24(t, 2H), 7.07-7.03(m, 3H), 6.91(d, 2H), 4.73(s, 2H), 4.36(t, 2H), 4.04-4.02(m, 1H), 3.85(s,

3H), 3.60(t,2H), 2.99(s, 6H), 2.35-2.33(m, 4H), 2.22(s, 3H), 2.13-2.12(m, 4H). MS (EI) for $C_{32}H_{39}N_5O_4$: 559 (MH^+).

[00362] 1(DN): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1S)-1-methylpropyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (S)-(+)-2-butylamine in step 5, then omission of steps 6 and 7.

^{1}H-NMR (DMSO-d_6): 8.49(s, 1H), 8.31(d, 1H), 8.27-8.24(m, 1H), 7.22(t, 2H), 7.04(d, 1H), 6.88(d, 1H), 4.72(s, 2H), 3.92-3.91(m, 1H), 3.81(s, 3H), 2.27-2.15(m, 4H), 2.06(s, 3H), 2.01-1.99(m, 4H), 1.52-147(m, 2H), 1.14(d, 2H), 0.88(t, 2H). MS (EI) for $C_{26}H_{34}N_4O_3$: 451 (MH^+).

[00363] 1(DO): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3R)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (3R)-1-methylpyrrolidin-3-amine in step 5, then omission of steps 6 and 7. ^{1}H-NMR (CD_3OD):8.51-8.50(m, 1H), 8.39(d, 1H), 7.39(d, 1H), 7.24(t, 1H), 7.03(d, 1H), 6.91(d, 1H), 4.77(s, 2H), 4.70(s, 1H), 4.11-4.07(m, 1H), 3.92-3.90(m,1H0, 3.85(s,3H), 3.81-3.78(m,1H), 3.51-3.49(m, 2H), 3.21-3.19(m, 1H), 3.04(s, 2H), 2.98(s, 3H), 2.42-2.40(m, 1H), 2.37-2.34(m, 4H), 2.22(s, 3H), 2.19-2.15(m, 4H). MS (EI) for $C_{27}H_{35}N_5O_3$: 479 (MH^+).

[00364] 1(DP): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3S)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (3S)-1-methylpyrrolidin-3-amine in step 5, then omission of steps 6 and 7. ^{1}H-NMR (CD_3OD): 8.47(s,1H), 8.38(d, 1H), 7.39(d, 1H), 7.25(t, 1H), 7.03(d, 1H), 6.91(d, 1H), 4.75 (s, 2H), 4.65-4.60(m, 1H), 4.11-4.01(m, 2H), 3.84(s, 3H), 3.81-3.78(m, 1H), 3.45-3.40(m, 1H), 3.22-3.20(m, 1H), 3.11(s, 2H), 2.28(s, 3H), 2.65-2.60(m, 1H), 2.44-2.40(m, 4H), 2.21(s, 3H), 2.18-2.16(m, 4H). MS (EI) for $C_{27}H_{35}N_5O_3$: 479 (MH^+).

[00365] 1(DQ): N-[(2-chloro-3,6-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 1 by using 2-chloro-3,6-difluorobenzylamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.71 (br s, 1H), 8.51 (s, 1H), 8.25 (d,

1H), 8.04 (d, 1H), 7.50-7.42 (m, 1H), 7.35-7.29 (m, 2H), 7.03-6.85 (m, 3H), 4.62-4.56 (m, 4H), 3.89-3.83 (m, 1H), 3.80 (s, 3H), 2.26-2.20 (m, 2H), 2.15-1.86 (m, 9H). MS (EI) for $C_{29}H_{29}ClF_2N_4O_3$: 556 (MH^+).

[00366] 1(DR): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide. Prepared as the hydrochloride salt according to the method of example 1 by using (1*S*)-1-[4-(4-methylpiperazine-1-yl)phenyl]ethanamine dihydrochloride (synthesized according to reagent preparation 3) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 10.99 (br s, 1H), 9.11 (d, 1H), 8.56 (s, 1H), 8.38-8.33 (m, 2H), 7.38-7.22 (m, 4H), 7.04-6.87 (m, 4H), 5.13-5.05 (m, 1H), 3.94-3.89 (m, 1H), 3.82-3.73 (m, 5H), 3.49-3.43 (m, 2H), 3.16-3.04 (m, 4H), 2.79 (d, 3H), 2.34-1.98 (m, 8H), 1.45 (d, 3H). MS (EI) for $C_{35}H_{44}N_6O_3$: 597 (MH^+).

[00367] 1(DS): N-{[4-fluoro-3-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 1 by using 4-fluoro-3-methoxybenzylamine (synthesized according to reagent preparation 6) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.95 (br s, 1H), 8.55 (s, 1H), 8.27 (d, 1H), 8.13 (d, 1H), 7.25-7.11 (m, 3H), 7.08-7.01 (m, 2H), 6.89-6.83 (m, 2H), 4.63 (br s, 2H), 4.44 (d, 2H), 3.91-3.86 (m, 1H), 3.83-3.79 (m, 6H), 2.28-2.22 (m, 2H), 2.17-2.09 (m, 5H), 2.05-1.90 (m, 4H). MS (EI) for $C_{30}H_{33}FN_4O_4$: 533 (MH^+).

[00368] 1(DT): N-{[3-fluoro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 1 by using 3-fluoro-4-methoxybenzylamine (synthesized according to reagent preparation 6) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.93 (br s, 1H), 8.55 (s, 1H), 8.27 (d, 1H), 8.11 (d, 1H), 7.26-7.21 (m, 1H), 7.17-7.00 (m, 5H), 6.87 (d, 1H), 4.61 (br s, 2H), 4.40 (d, 2H), 3.91-3.85 (m, 1H), 3.82-3.78 (m, 6H), 2.28-2.20 (m, 2H), 2.17-1.89 (m, 9H). MS (EI) for $C_{30}H_{33}FN_4O_4$: 533 (MH^+).

[00369] 1(DU): N-{[2-chloro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-

3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 1 by using 2-chloro-4-methoxybenzylamine (synthesized according to reagent preparation 6) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (br s, 1H), 8.56 (s, 1H), 8.27 (d, 1H), 8.14 (d, 1H), 7.30-7.21 (m, 2H), 7.06-7.00 (m, 3H), 6.93-6.85 (m, 2H), 4.63 (br s, 2H), 4.47 (d, 2H), 3.92-3.85 (m, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 2.28-2.25 (m, 2H), 2.17-2.09 (m, 5H), 2.04-1.90 (m, 4H). MS (EI) for $C_{30}H_{33}ClN_4O_4$: 549 (MH^+).

[00370] 1(DV): N-{[2,6-difluoro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 1 by using 2,6-Difluoro-4-methoxybenzylamine (synthesized according to reagent preparation 6) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.78 (br s, 1H), 8.49 (s, 1H), 8.28 (d, 1H), 8.13 (d, 1H), 7.26-7.21 (m, 1H), 7.10-7.01 (m, 2H), 6.87 (d, 1H), 6.77-6.71 (m, 2H), 4.64 (br s, 2H), 4.42 (d, 2H), 3.92-3.85 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 2.28-2.22 (m, 2H), 2.17-2.08 (m, 5H), 2.04-1.91 (m, 4H). MS (EI) for $C_{30}H_{32}F_2N_4O_4$: 551 (MH^+).

[00371] 1(DW): N-{[2-fluoro-6-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 1 by using 2-fluoro-6-methoxybenzylamine (synthesized according to reagent preparation 6) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.52 (br s, 1H), 8.47 (s, 1H), 8.27 (d, 1H), 8.15 (d, 1H), 7.36-7.21 (m, 2H), 7.10-7.00 (m, 2H), 6.90-6.78 (m, 3H), 4.64 (br s, 2H), 4.46 (d, 2H), 3.91-3.85 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.28-2.20 (m, 2H), 2.16-2.08 (m, 5H), 2.04-1.90 (m, 4H). MS (EI) for $C_{30}H_{33}FN_4O_4$: 533 (MH^+).

[00372] 1(DX): N-{[4-fluoro-2-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 1 by using 4-fluoro-2-methoxybenzylamine (synthesized according to reagent preparation 6) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.82 (br s, 1H), 8.54 (s, 1H), 8.28 (d, 1H), 8.17 (d, 1H), 7.26-7.17 (m, 2H), 7.11-7.01 (m, 2H), 6.94-6.86 (m, 2H), 6.76-6.70 (m, 1H), 4.65 (br s, 2H), 4.38

(d, 2H), 3.92-3.87 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.28-2.23 (m, 2H), 2.17-2.10 (m, 5H), 2.05-1.92 (m, 4H). MS (EI) for $C_{30}H_{33}FN_4O_4$: 533 (MH^+).

[00373] 1(DY): N-[(2-chloro-6-fluoro-3-methylphenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 1 by using 1-(2-chloro-6-fluoro-3-methylphenyl)methanamine (synthesized according to reagent preparation 6) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.68 (br s, 1H), 8.49 (d, 1H), 8.27 (d, 1H), 8.11 (d, 1H), 7.40-7.35 (m, 1H), 7.25-7.14 (m, 2H), 7.03-7.00 (m, 2H), 6.86 (d, 1H), 4.62 (br s, 2H), 4.57 (d, 2H), 3.90-3.84 (m, 1H), 3.80 (s, 3H), 2.32 (s, 3H), 2.28-2.21 (m, 2H), 2.15-2.08 (m, 5H), 2.04-1.90 (m, 4H). MS (EI) for $C_{30}H_{32}ClFN_4O_3$: 551 (MH^+).

[00374] 1(DZ): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2,3,6-trifluorophenyl)methyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2,3,6-trifluorobenzylamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.73-8.67 (m,1H), 8.58 (s,1H), 8.22 (s, 1H), 7.95-7.90 (d, 1H), 7.50-7.40 (m, 1H), 7.25-7.19 (m, 1H), 7.17-7.09 (m, 1H), 7.03-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.75-6.71 (d, 1H), 4.57-4.47 (m, 4H), 3.87-3.77 (m, 4H), 2.23-2.16 (d, 2H), 2.14 (s, 3H), 2.11-2.03 (m, 2H), 2.01-1.93 (m, 2H), 1.88-1.79 (d, 2H). MS (EI) for $C_{29}H_{29}F_3N_4O_3$: 539 (MH^+).

[00375] 1(EA): N-{[3-fluoro-4-(4-methylpiperazin-1-yl)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-fluoro-4-(4-methylpiperazin-1-yl)benzylamine (synthesized according to the method of reagent preparation 5) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.79-8.73 (m,1H), 8.64 (s,1H), 8.24-8.20 (m, 1H), 7.99-7.90 (m, 2H), 7.26-7.20 (m, 1H), 7.10-6.98 (m, 3H), 6.88-6.84 (d, 1H), 6.78-6.72 (d, 1H), 4.61-4.50 (m, 2H), 4.40-4.35 (d, 2H), 3.88-3.78 (m, 4H), 3.32-3.30 (m, 4H), 3.11-2.96 (br. s, 4H), 2.59 (s, 3H), 2.24-2.16 (m, 2H), 2.14 (s, 3H), 2.13-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.89-1.79 (d, 2H). MS (EI) for $C_{34}H_{41}FN_6O_3$: 601 (MH^+).

[00376] 1(EB): N-(2,3-dihydroxypropyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 3-

aminopropane-1,2-diol in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.61 (s,1H), 8.23-8.18 (m, 2H), 7.97-7.92 (d, 1H), 7.26-7.20 (m, 1H), 7.04-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.76-6.72 (d, 1H), 4.84-4.81 (d, 2H), 4.60-4.50 (m, 4H), 3.88-3.78 (m, 4H), 3.63-3.57 (m, 1H), 3.21-3.11 (m, 2H), 2.24-2.16 (m, 2H), 2.14 (s, 3H), 2.10-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.89-1.79 (d, 2H). MS (EI) for $C_{25}H_{32}N_4O_5$: 469 (MH^+).

[00377] 1(EC): N-[(1S,2S)-2-hydroxycyclopentyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (1S,2S)-2-aminocyclopentanol in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.60 (s,1H), 8.24-8.20 (d, 1H), 8.00-7.90 (m, 2H), 7.27-7.19 (m, 1H), 7.04-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.77-6.71 (d, 1H), 4.80-4.76 (d, 2H), 4.60-4.50 (br. s, 2H), 4.01-3.90 (m, 2H), 3.87-3.78 (m, 4H), 2.24-2.16 (m, 2H), 2.14 (s, 3H), 2.10-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.89-1.79 (d, 2H), 1.70-1.60 (m, 4H), 1.51-1.40 (m, 2H). MS (EI) for $C_{27}H_{34}N_4O_4$: 479 (MH^+).

[00378] 1(ED): N-[(1S,2S)-2-hydroxycyclohexyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (1S,2S)-2-aminocyclohexanol in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.60 (s,1H), 8.24-8.20 (d, 1H), 7.98-7.93 (d, 1H), 7.88-7.84 (d, 1H), 7.26-7.20 (m, 1H), 7.04-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.77-6.71 (d, 1H), 4.64-4.59 (m, 1H), 4.58-4.50 (br. s, 2H), 3.87-3.78 (m, 4H), 3.66-3.54 (m, 1H), 2.24-2.16 (m, 2H), 2.14 (s, 3H), 2.10-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.90-1.78 (m, 3H), 1.69-1.59 (m, 4H), 1.27-1.16 (m, 4H). MS (EI) for $C_{28}H_{36}N_4O_4$: 493 (MH^+).

[00379] 1(EE): N-azetidin-3-yl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 1,1-dimethylethyl-3-aminoazetidine-1-carboxylate in step 5, then omission of step 7. ^{1}H NMR (400 MHz, d_6-DMSO): 9.25 (s, 1H), 8.98 (s, 2H), 8.61 (d, 1H), 8.29 (d, 1H), 8.12 (d, 1H), 7.24 (t, 1H), 7.05 (s, 1H), 7.03 (d, 1H), 6.87 (d, 1H), 4.75-4.84 (m, 2H), 4.70 (s, 2H), 4.07-4.19 (m, 4H), 3.87 (s, 1H), 3.81 (s, 3H), 2.25 (d, 2H), 2.08-2.14 (m, 4H), 2.00-2.03 (m, 2H), 1.95 (s, 1H), 1.92 (s, 1H). MS (EI) for $C_{25}H_{31}N_5O_3$: 450 (MH^+).

[00380] 1(EF): N-[(1S)-2-hydroxy-1-methylethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (S)-2-aminopropan-1-ol in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.60 (s,1H), 8.25-8.20 (d, 1H), 7.97-7.92 (d, 1H), 7.87-7.81 (d, 1H), 7.26-7.20 (m, 1H), 7.04-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.76-6.72 (d, 1H), 4.75-4.67 (m, 1H), 4.60-4.50 (br. s, 2H), 4.05-3.94 (m, 2H), 3.87-3.78 (m, 4H), 3.48-3.40 (m, 1H), 2.24-2.16 (m, 2H), 2.14 (s, 3H), 2.10-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.89-1.79 (d, 2H), 1.14-1.08 (d, 3H). MS (EI) for $C_{25}H_{32}N_4O_4$: 453 (MH^+).

[00381] 1(EG): N-[(2S)-2-hydroxypropyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (S)-1-aminopropan-2-ol in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.60 (s,1H), 8.24-8.16 (m, 2H), 7.97-7.92 (d, 1H), 7.26-7.20 (m, 1H), 7.04-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.76-6.72 (d, 1H), 4.76-4.73 (d, 1H), 4.57-4.52 (br. s, 2H), 3.87-3.79 (m, 4H), 3.78-3.72 (m, 1H), 3.21-3.13 (m, 2H), 2.24-2.16 (m, 2H), 2.14 (s, 3H), 2.10-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.89-1.79 (d, 2H), 1.07-1.03 (d, 3H). MS (EI) for $C_{25}H_{32}N_4O_4$: 453 (MH^+).

[00382] 1(EH): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[3-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using (S)-1-(3-methoxyphenyl)ethanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.64 (d, 1H), 8.52 (d, 1H), 8.23 (d, 1H), 7.98 (dd, 1H), 7.22 (t, 2H), 7.02 (d, 1H), 6.94 (m, 2H), 6.86 (d, 1H), 6.80 (m, 1H), 6.76 (d, 1H), 5.12 (m, 1H), 4.54 (bs, 2H), 3.85 (m, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 2.20 (m, 2H), 2.15 (s, 3H), 2.08 (m, 2H), 1.98 (m, 2H), 1.84 (m, 2H), 1.44 (d, 3H). MS (EI) for $C_{31}H_{36}N_4O_4$: 529 (MH^+).

[00383] 1(EI): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-morpholin-4-ylphenyl)methyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (4-morpholinophenyl)methanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.70 (t, 1H), 8.63 (d, 1H), 8.22 (d, 1H), 7.96 (dd, 1H), 7.22 (t, 1H), 7.18 (d, 2H), 7.02 (d, 1H), 6.89 (d, 2H), 6.86 (d, 1H), 6.74 (d, 1H), 4.54 (bs, 2H),

4.32 (d, 2H), 3.83 (m, 1H), 3.80 (s, 3H), 3.72 (m, 4H), 3.02 (m, 4H), 2.20 (m, 2H), 2.15 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H). MS (EI) for $C_{33}H_{39}N_5O_4$: 570 (MH^+).

[00384] 1(EJ): N-[(1S)-1,2-dimethylpropyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (S)-3-methylbutan-2-amine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.61 (d, 1H), 8.21 (d, 1H), 7.94 (dd, 1H), 7.84 (d, 1H), 7.22 (t, 1H), 7.02 (d, 1H), 6.86 (d, 2H), 6.74 (d, 1H), 4.52 (bs, 2H), 3.82 (m, 2H), 3.80 (s, 3H), 2.20 (m, 2H), 2.14 (s, 3H), 2.09 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H), 1.74 (m, 1H), 1.08 (d, 3H), 0.88 (d, 3H), 0.86 (d, 3H). MS (EI) for $C_{27}H_{36}N_4O_3$: 465 (MH^+).

[00385] 1(EK): N-[(1R)-1,2-dimethylpropyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (R)-3-methylbutan-2-amine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (d, 1H), 8.21 (d, 1H), 7.94 (dd, 1H), 7.85 (d, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 2H), 6.74 (d, 1H), 4.53 (bs, 2H), 3.82 (m, 2H), 3.80 (s, 3H), 2.20 (m, 2H), 2.15 (s, 3H), 2.10 (m, 2H), 1.97 (m, 2H), 1.84 (d, 2H), 1.74 (m, 1H), 1.08 (d, 3H), 0.88 (d, 3H), 0.86 (d, 3H). MS (EI) for $C_{27}H_{36}N_4O_3$: 465 (MH^+).

[00386] 1(EL): N-[(1S)-1-methyl-2-(methyloxy)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (S)-1-methoxypropan-2-amine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.59 (d, 1H), 8.21 (d, 1H), 7.94 (m, 2H), 7.22 (t, 1H), 7.02 (d, 1H), 6.86 (d, 2H), 6.74 (d, 1H), 4.54 (bs, 2H), 4.17 (m, 1H), 3.84 (m, 1H), 3.80 (s, 3H), 3.39 (d, 0.5H), 3.37 (d, 0.5H), 3.26 (d, 0.5H), 3.26 (s, 3H), 3.24 (d, 0.5H), 2.19 (m, 2H), 2.14 (s, 3H), 2.09 (m, 2H), 1.97 (m, 2H), 1.84 (d, 2H), 1.07 (d, 3H). MS (EI) for $C_{26}H_{34}N_4O_4$: 467 (MH^+).

[00387] 1(EM): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using (S)-1-(4-methoxyphenyl)ethanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (d, 1H), 8.45 (d, 1H), 8.21 (d, 1H), 7.96 (dd, 1H), 7.29 (d,

2H), 7.23 (t, 1H), 7.02 (d, 1H), 6.87 (m, 3H), 6.74 (d, 1H), 5.10 (m, 1H), 4.52 (bs, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.81 (m, 1H), 2.20 (m, 2H), 2.14 (s, 3H), 2.06 (m, 2H), 1.97 (m, 2H), 1.83 (d, 2H), 1.42 (d, 3H). MS (EI) for $C_{31}H_{36}N_4O_4$: 528 (M).

[00388] 1(EN): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1R)-1-[4-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using (R)-1-(4-methoxyphenyl)ethanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (d, 1H), 8.45 (d, 1H), 8.21 (d, 1H), 7.96 (dd, 1H), 7.29 (d, 2H), 7.23 (t, 1H), 7.01 (d, 1H), 6.86 (m, 3H), 6.74 (d, 1H), 5.10 (m, 1H), 4.53 (bs, 2H), 3. 82 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.19 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.97 (m, 2H), 1.83 (d, 2H), 1.43 (d, 3H). MS (EI) for $C_{31}H_{36}N_4O_4$: 529 (MH^+).

[00389] 1(EO): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-((1-phenylethyl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 1-phenylethanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.65 (d, 1H), 8.53 (d, 1H), 8.21 (d, 1H), 7.98 (dd, 1H), 7.38 (m, 2H), 7.32 (m, 2H), 7.22 (m, 2H), 7.02 (d, 1H), 6.86 (d, 1H), 6.75 (d, 1H), 5.12 (m, 1H), 4.54 (bs, 2H), 3. 82 (m, 1H), 3.80 (s, 3H), 2.20 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.97 (m, 2H), 1.84 (d, 2H), 1.45 (d, 3H). MS (EI) for $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00390] 1(EP): N-[1-(4-chlorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 1-(4-chlorophenyl)ethanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (d, 1H), 8.55 (d, 1H), 8.21 (d, 1H), 7.96 (dd, 1H), 7.39 (m, 4H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.75 (d, 1H), 5.12 (m, 1H), 4.54 (bs, 2H), 3. 84 (m, 1H), 3.80 (s, 3H), 2.20 (m, 2H), 2.13 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H), 1.44 (d, 3H). MS (EI) for $C_{30}H_{33}ClN_4O_3$: 535 (MH^+).

[00391] 1(EQ): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(1-phenylpiperidin-4-yl)pyridine-3-carboxamide. Prepared according to the method of example 1 by using 1-phenylpiperidin-4-amine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.61 (d, 1H), 8.21 (d, 1H), 8.03 (d, 1H), 7.94 (dd, 1H), 7.21 (m, 3H), 7.02 (d, 1H), 6.96 (m, 2H), 6.86 (d, 1H), 6.74 (m, 2H), 4.54 (bs, 2H), 3.94 (m, 1H), 3. 83 (m, 1H), 3.80 (s,

3H), 3.72 (m, 2H), 2.80 (m, 2H), 2.19 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 4H), 1.64 (m, 2H). MS (EI) for $C_{33}H_{39}N_5O_3$: 554 (MH^+).

[00392] 1(ER): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-pyrrolidin-1-ylphenyl)methyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (4-(pyrrolidin-1-yl)phenyl)methanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.62 (m, 2H), 8.21 (d, 1H), 7.95 (dd, 1H), 7.22 (t, 1H), 7.11 (m, 2H), 7.01 (d, 1H), 6.85 (d, 1H), 6.73 (d, 1H), 6.47 (m, 2H), 4.52 (bs, 2H), 4.32 (d, 2H), 3. 83 (m, 1H), 3.79 (s, 3H), 3.17 (m, 4H), 2.19 (m, 2H), 2.13 (s, 3H), 2.08 (m, 2H), 1.92-1.98 (m, 6H), 1.84 (d, 2H). MS (EI) for $C_{33}H_{39}N_5O_3$: 553 (M).

[00393] 1(ES): N-[(1S)-1-(4-{[2-(diethylamino)ethyl]oxy}-2-fluorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (S)-2-(4-(1-aminoethyl)-3-fluorophenoxy)-N,N-diethylethanamine (synthesized according to reagent preparation 4) in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.64 (d, 1H), 8.52 (d, 1H), 8.21 (d, 1H), 7.97 (dd, 1H), 7.34 (t, 1H), 7.23 (t, 1H), 7.01 (d, 1H), 6.86 (d, 1H), 6.73-6.79 (m, 3H), 5.30 (m, 1H), 4.54 (bs, 2H), 4.00 (t, 2H), 3. 83 (m, 1H), 3.80 (s, 3H), 2.74 (t, 2H), 2.52 (dd, 4H), 2.20 (m, 2H), 2.13 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H) 1.41 (d, 3H), 0.96 (t, 6H). MS (EI) for $C_{36}H_{46}FN_5O_3$: 633 (MH^+).

[00394] 1(ET): N-{1-[3,4-bis(methyloxy)phenyl]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using 1-(3,4-dimethoxyphenyl)ethanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (d, 1H), 8.44 (d, 1H), 8.21 (d, 1H), 7.94 (dd, 1H), 7.23 (t, 1H), 7.02 (d, s, 2H), 6.86 (m, 3H), 6.74 (d, 1H), 5.10 (m, 1H), 4.54 (bs, 2H), 3.83 (m, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 2.19 (m, 2H), 2.13 (s, 3H), 2.08 (m, 2H), 1.97 (m, 2H), 1.84 (d, 2H), 1.43 (d, 3H). MS (EI) for $C_{32}H_{38}N_4O_5$: 559 (MH^+).

[00395] 1(EU): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using (4-(4-

methylpiperazin-1-yl)phenyl)methanamine in step 5 then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.68 (t, 1H), 8.63 (d, 1H), 8.21 (d, 1H), 7.96 (dd, 1H), 7.22 (t, 1H), 7.15 (m, 2H), 7.02 (d, 1H), 6.87 (m, 3H), 6.74 (d, 1H), 4.53 (bs, 2H), 4.33 (d, 2H), 3.82 (m, 1H), 3.79 (s, 3H), 3.06 (m, 4H), 2.42 (m, 4H), 2.20 (s, m, 5H), 2.14 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H). MS (EI) for $C_{34}H_{42}N_6O_3$: 583 (MH^+).

[00396] 1(EV): N-{(1S)-1-[2-fluoro-4-(methyloxy)phenyl]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared as the hydrochloride salt according to the method of example 1 by using (1S)-1-(2-fluoro-4-methoxyphenyl)ethanamine hydrochloride in step 5, and then omission of steps 6 and 7. ^{1}H NMR (400 MHz, Methanol-d_4): 8.60 (d, 1H), 7.97 (dd, 1H), 7.31 (t, 1H), 7.23 (t, 1H), 6.99 (d, 1H), 6.90 (d, 1H), 6.77-6.64 (m, 3H), 5.43-5.35 (m, 1H), 4.60 (br s, 2H), 4.03-3.96 (m, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 2.35-2.06 (m, 9H), 1.90 (d, 2H), 1.52 (d, 3H); MS (EI) for $C_{31}H_{35}FN_4O_4$: 547 (MH^+).

[00397] 1(EW): N-{[2-fluoro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (2-fluoro-4-methoxyphenyl)methanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, Methanol-d_4): 8.60 (d, 1H), 7.96 (dd, 1H), 7.29 (t, 1H), 7.22 (t, 1H), 6.99 (d, 1H), 6.90 (d, 1H), 6.77-6.66 (m, 3H), 4.60 (br s, 2H), 4.52 (s, 2H), 4.04-3.95 (m, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 2.35-2.07 (m, 9H), 1.91 (d, 2H); MS (EI) for $C_{30}H_{33}FN_4O_4$: 533 (MH^+).

[00398] 1(EX): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2,4,6-trifluorophenyl)methyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using (2,4,6-trifluorophenyl)methanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (t, 1H), 8.56 (d, 1H), 8.19 (d, 1H), 7.90 (dd, 1H), 7.23-7.11 (m, 3H), 6.99 (d, 1H), 6.83 (d, 1H), 6.70 (d, 1H), 4.51 (br s, 2H), 4.41 (d, 2H), 3.85-3.74 (m, 4H), 2.23-1.99 (m, 7H), 1.98-1.88 (m, 2H), 1.81 (d, 2H); MS (EI) for $C_{29}H_{29}F_3N_4O_3$: 537 (M-H).

[00399] 1(EY): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[3-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-

3-carboxamide. Prepared as the acetate salt according to the method of example 1 by using 1-[3-(4-methylpiperazin-1-yl)phenyl]methanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, Methanol-d_4): 8.61 (d, 1H), 7.98 (dd, 1H), 7.26-7.20 (m, 2H), 7.02-6.97 (m, 2H), 6.93-6.85 (m, 3H), 6.76 (d, 1H), 4.60 (br s, 2H), 4.51 (s, 2H), 4.04-3.96 (m, 1H), 3.84 (s, 3H), 3.39-3.22 (m, 4H), 2.89-2.81 (m, 4H), 2.54-2.51 (m, 3H), 2.34-2.25 (m, 2H), 2.23-2.08 (m, 7H), 1.96 (s, 3H), 1.90 (d, 2H); MS (EI) for $C_{34}H_{42}N_6O_3$: 583 (MH^+).

[00400] 1(EZ): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[2-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide. Prepared according to the method of example 1 by using 1-[2-(4-methylpiperazin-1-yl)phenyl]methanamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.65-8.58 (m, 2H), 8.16 (d, 1H), 7.92 (dd, 1H), 7.19-7.12 (m, 3H), 7.07-6.93(m, 3H), 6.79 (d, 1H), 6.69 (d, 1H), 4.53-4.41 (m, 4H), 3.82-3.75 (m, 1H), 3.73 (s, 3H), 2.89-2.81 (m, 4H), 2.68-2.56 (m, 4H), 2.31 (br s, 3H), 2.18-1.98 (m, 7H), 1.95-1.86 (m, 2H), 1.78 (d, 2H); MS (EI) for $C_{34}H_{42}N_6O_3$: 583 (MH^+).

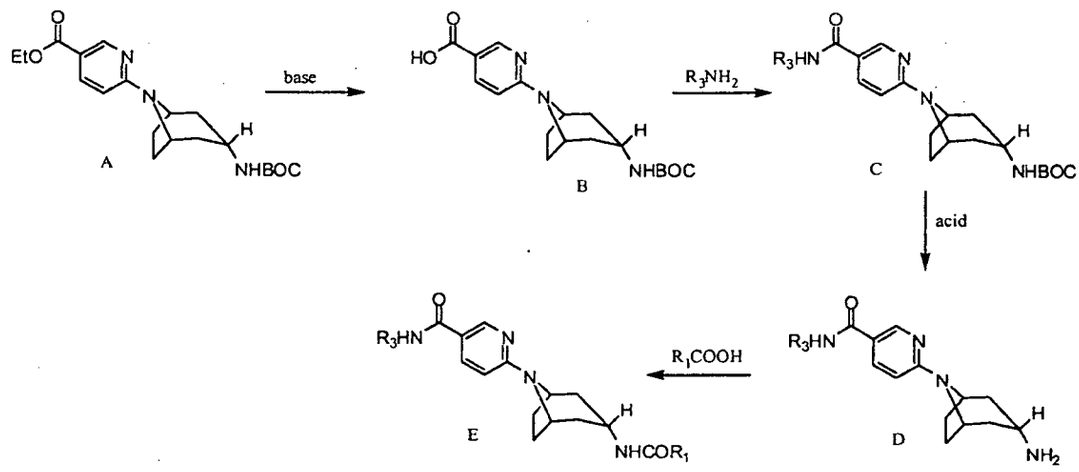
[00401] 1(FA): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2,4,5-trifluorophenyl)methyl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using 2,4,5-trifluorobenzylamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.77 (t, 1H), 8.62 (d, 1H), 8.21 (d, 1H), 7.94 (dd, 1H), 7.57-7.48 (m, 1H), 7.44-7.34 (m, 1H), 7.20 (t, 1H), 6.99 (d, 1H), 6.84 (d, 1H), 6.74 (d, 1H), 4.53 (br s, 2H), 4.41 (d, 2H), 3.87-3.74 (m, 4H), 2.25-1.75 (m, 11H); MS (EI) for $C_{29}H_{29}F_3N_4O_3$: 537 (M-H).

[00402] 1(FB): N-(2-hydroxyethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 1 by using ethanolamine in step 5, then omission of steps 6 and 7. ^{1}H NMR (400 MHz, Methanol-d_4): 8.46 (d, 1H), 8.41 (d, 1H), 8.31 (dd, 1H), 7.32 (d, 1H), 7.24 (t, 1H), 7.01 (d, 1H), 6.91(d, 1H), 4.71 (br s, 2H), 4.13-4.07 (m, 1H), 3.85 (s, 3H), 3.71 (t, 2H), 3.50 (t, 2H), 32.41-2.18 (m, 9H), 2.14 (d, 2H); MS (EI) for $C_{24}H_{30}N_4O_4$: 439 (MH^+).

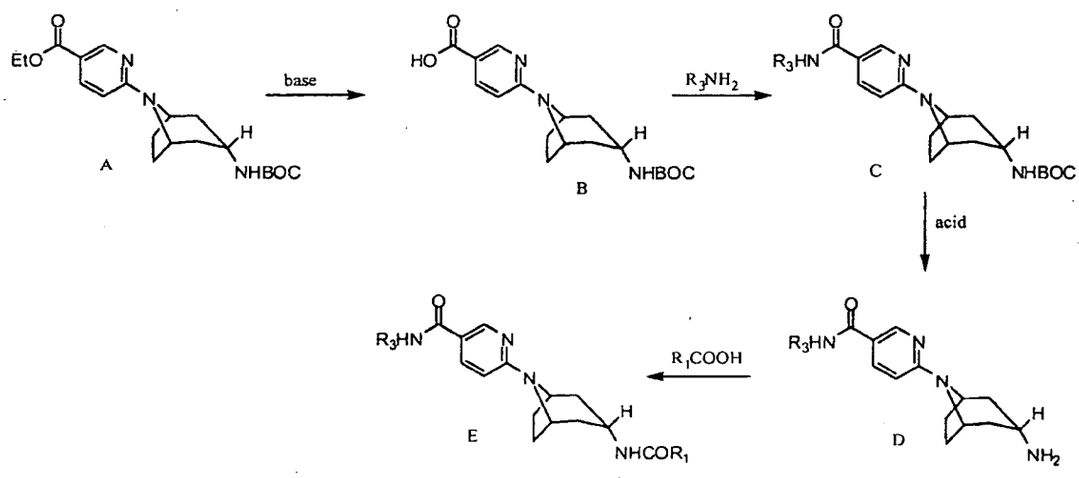
[00403] 1(FC): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-piperazin-1-ylphenyl)methyl]pyridine-3-

carboxamide. Prepared as the acetate salt in example 1 step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.60 (d, 1H), 7.97 (dd, 1H), 7.27 (d, 2H), 7.23 (t, 1H), 6.99 (m, 3H), 6.90 (d, 1H), 6.75 (d, 1H), 4.60 (br s, 2H), 4.47 (s, 3H), 3.99 (m, 1H), 3.84 (s, 3H), 3.25 (m, 4H), 2.29 (m, 2H), 2.21 (s, 3H), 2.19 (m, 2H), 1.92 (s, 6H), 1.90 (m, 2H); MS (EI) for $C_{33}H_{40}N_6O_3$: 569 (MH^+).

SYNTHETIC SCHEME 2:



SYNTHETIC SCHEME 2:



[00404] Scheme 2 generally describes the synthesis of all of the compound(s) listed in Example 2, wherein R_1 and R_3 are as defined in the specification.

[00405] In Scheme 2, the carboxylate of compound (A) is hydrolyzed to form compound (B) under acidic conditions, such as with the use of KOH. R_3NH_2 is then added to compound (B) under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (C). Compound (C) is then deprotected under acid conditions, such as with the use of HCl, to remove BOC and form compound (D). To compound (D) is added R_1COOH under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (E).

[00406] EXAMPLE 2: 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}-amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide.

[00407] STEP 1: A mixture of ethyl 6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}-amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (prepared in example 1) (13.56 g, 36.12 mmol) and potassium hydroxide (4.05 g, 72.23 mmol) in methanol (120 mL) and water (40 mL) was stirred at 70 °C for 1 h. The reaction mixture was concentrated and then acidified to pH5 with 1N aqueous hydrochloric acid. The precipitate was collected by filtration, washed with water and dried to give 6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (11.69 g, 93% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.46 (br s, 1H), 8.61 (d, 1H), 7.89 (dd, 1H), 6.90 (br s, 1H), 6.71 (d, 1H), 4.52 (br s, 2H), 3.44 (m, 1H), 2.12 (m, 2H), 1.94 (m, 4H), 1.75 (d, 2H), 1.39 (s, 9H); MS (EI) for $C_{18}H_{25}N_3O_4$: 348 (MH^+).

[00408] STEP 2: A mixture of 6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (643 mg, 1.85 mmol), benzylamine (198 mg, 1.85 mmol), HATU (704 mg, 1.85 mmol), and diisopropylethylamine (598 mg, 4.63 mmol) in DMF (10 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (50 mL), 5% lithium chloride (2 x 50 mL), and brine (50 mL), dried over sodium sulfate then filtered and concentrated. The resulting solid was triturated with ethyl acetate (10 mL) then dried to afford 1,1-

dimethylethyl [8-(5-{[(phenylmethyl)amino]carbonyl}pyridine-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]carbamate (612 mg, 76% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.79 (t, 1H), 8.63 (d, 1H), 7.96 (dd, 1H), 7.31 (m, 5H), 7.23 (m, 1H), 6.87 (br s, 1H), 6.72 (d, 1H), 4.49 (br s, 2H), 4.45 (d, 2H), 3.42 (m, 1H), 2.11 (m, 2H), 1.95 (m, 4H), 1.72 (d, 2H), 1.39 (s, 9H); MS (EI) for $C_{25}H_{32}N_4O_3$: 437 (MH^+).

[00409] STEP 3: A solution of 1,1-dimethylethyl [8-(5-{[(phenylmethyl)amino]carbonyl}pyridine-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]carbamate (13.49 g, 30.90 mmol) in methanol (75 mL) and 4M HCl in dioxane (75 mL) was refluxed for 2 min. The reaction mixture was concentrated, and water (500 mL) was added. The aqueous solution was washed with ethyl acetate (2 x 150 mL), and then basified to pH 11 with 50% sodium hydroxide. The aqueous layer was extracted with ethyl acetate (3 x 250 mL), and the organic extracts were washed with brine (50 mL). The organic solution was dried over sodium sulfate, filtered and concentrated to give 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide (9.40 g, 90% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.76 (t, 1H), 8.62 (d, 1H), 7.94 (dd, 1H), 7.30 (m, 5H), 7.23 (m, 1H), 6.63 (d, 1H), 4.49 (br s, 2H), 4.45 (d, 2H), 3.14 (m, 1H), 2.34 (m, 2H), 1.92 (m, 4H), 1.57 (br s, 2H), 1.42 (d, 2H).

[00410] STEP 4: A mixture of 3-(methyloxy)-2-methylbenzoic acid (22 mg, 0.13 mmol), 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide (44 mg, 0.13 mmol), HATU (50 mg, 0.13 mmol), and diisopropylethylamine (52 mg, 0.40 mmol) in DMF (2 mL) was stirred at room temperature for 5 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with saturated sodium bicarbonate (2 x 30 mL), 5% lithium chloride (20 mL), and brine (20 mL), dried over sodium sulfate then filtered and concentrated. The resulting solid was suspended in acetonitrile and the insoluble product collected by filtration then washed with methanol (3x) to afford the title compound (19 mg, 22% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.80 (t, 1H), 8.65 (s, 1H), 8.23 (d, 1H), 7.98 (m, 1H), 7.31 (m, 4H), 7.23 (m, 2H), 7.02 (d, 1H), 6.86 (d, 1H), 6.76 (d, 1H), 4.55 (br s, 2H), 4.46 (d, 2H), 3.84 (m, 1H), 3.80 (s, 3H), 2.26 (m, 2H), 2.14 (s, 3H), 2.09 (m, 2H), 1.97 (m, 2H), 1.85 (d, 2H); MS (EI) for $C_{29}H_{32}N_4O_3$: 485 (MH^+).

[00411] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [2(A)-2(AU)] were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00412] (2B): N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-indole-4-carboxamide. Prepared according to the method of example 2 by using indole-4-carboxylic acid in step 4. ^{1}H-NMR(400 MHz, DMSO-d_6): 11.31(s, 1H), 8.87 (s, 1H), 8.64 (s, 1H), 8.12-8.03 (m, 2H), 7.54(d, 2H), 7.45(t, 1H), 7.35-7.30 (m, 4H), 7.24-7.19 (m,1H), 7.15 (t, 1H), 6.85 (br s, 1H), 6.78 (t, 1H), 4.62 (br s, 2H), 4.47 (d, 2H), 3.94 (br s, 1H), 2.33-2.31 (m, 2H), 2.08-1.96 (m, 6H). MS(EI) for $C_{29}H_{29}N_5O_2$: 478 (M^-).

[00413] (2C): 6-(3-endo-{[(3-hydroxy-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 3-hydroxy-2-methylbenzoic acid in step 4. ^{1}H-NMR (400 MHz, DMSO-d_6): 9.50 (br s, 1H), 8.95 (br s, 1H), 8.57 (s, 1H), 8.22 (d, 1H), 8.10 (s, 1H), 7.35- 7.26 (m, 2H), 7.25-7.07 (m, 1H), 7.01 (t, 1H), 6.84 (d, 1H), 6.72 (d, 1H), 4.62 (br s, 2H), 4.47 (d, 2H), 3.86 (br s, 1H), 2.26-2.24 (m, 2H), 2.11 (s, 3H), 2.08- 1.99 (m, 2H), 1.94-1.90 (m, 4H). MS(EI) for $C_{28}H_{30}N_4O_3$: 471 (MH^+).

[00414] (2D): 6-(3-endo-{[(3-amino-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 3-amino-2-methylbenzoic acid in step 4. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.80 (t, 1H), 8.65 (br s, 1H), 8.09 (d, 1H), 7.99-7.96 (m, 1H), 7.33-7.31 (m, 3H), 7.25-7.24 (m, 1H), 6.91 (t, 1H), 6.75 (d, 1H), 6.67 (d, 1H), 6.48 (d, 1H), 4.97 (br s, 2H), 4.55 (s, 1H), 4.46 (d, 2H), 3.82 (s, 1H), 2.21-2.08 (m, 2H), 2.07-1.98 (m, 7H), 1.97-1.84 (m, 2H). MS(EI) for $C_{28}H_{31}N_5O_2$: 468 (M^-).

[00415] (2E): N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using terephthalic acid monoamide in step 4. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.80 (t, 1H), 8.66 (s, 1H), 8.32 (d, 1H), 8.10 (s, 1H), 8.00-7.95 (m, 2H), 7.84-7.82 (m, 2H), 7.53 (s, 1H), 7.33-7.31 (m, 2H), 6.78 (d, 1H), 4.58 (s, 2H), 4.46 (d, 2H), 3.86 (s, 1H), 2.23-2.21 (m, 2H), 2.11-1.90 (m, 6H). MS(EI) for $C_{28}H_{29}N_5O_3$: 484 (MH^+).

[00416] (2F): 2-methyl-N1-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using 4-(aminocarbonyl)-2-methylbenzoic acid (synthesized according to reagent preparation 11) in step 4. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.82 (t, 1H), 8.66 (s, 1H), 8.34 (d, 1H), 8.01-7.98 (m, 2H), 7.75-7.72 (m, 2H), 7.43 (s, 1H), 7.43-7.31 (m, 3H), 7.29-7.14 (m, 2H), 6.77 (d, 1H), 6.59 (s, 1H), 4.56 (s, 2H), 4.46 (d, 2H), 3.87 (s, 1H), 2.37 (s, 3H), 2.22-2.20 (m, 2H), 2.12-2.08 (m, 2H), 1.99-1.87 (m, 4H). MS(EI) for $C_{29}H_{31}N_5O_3$: 496 (M^-).

[00417] (2G): 2-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,3-dicarboxamide. Prepared according to the method of example 2 by using 3-(aminocarbonyl)- 2-methylbenzoic acid (synthesized according to reagent preparation 10) in step 4. ^{1}H-NMR(400 MHz, DMSO-d_6): 8.87 (t, 1H), 8.62 (d, 1H), 8.35 (d, 1H), 8.03 (dd, 1H), 7.76 (s, 1H0, 7.46 (s, 2H), 7.32-7.30 (m, 4H), 7.27 (s, 2H), 7.12 (s, 2H), 6.99 (d, 1H), 4.58 (s, 2H0, 4.46 (d, 2H), 3.87 (s, 1H), 2.32 (s, 3H), 2.23-2.20 (m, 2H), 2.11-1.99 (m, 4H), 1.97-1.86 (m, 2H). MS(EI) for $C_{29}H_{31}N_5O_3$: 498 (MH^+).

[00418] (2H): 6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyridin-3-ylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 3-(aminomethyl)pyridine in step 2 and 4-(hydroxymethyl)benzoic acid in step 4. ^{1}H-NMR (400 MHz, CD_3OD): 8.61(s, 1H), 8.58 (s, 1H), 8.47 (s, 1H), 8.21(d, 1H), 8.02 (d, 1H), 7.99 (d, 1H), 7.93-7.91 (m, 2H), 7.50-7.45 (m, 3H), 6.81 (d, 1H), 4.67 (s, 2H), 4.64 (s, 2H), 4.60 (s, 2H), 4.02 (s, 1H), 2.30-2.18 (m, 6H), 2.00-1.96 (m, 2H). MS(EI) for $C_{27}H_{29}N_5O_3$: 472 (MH^+).

[00419] (2I): N-[8-(5-{[(pyridin-3-ylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using 3-(aminomethyl)pyridine in step 2 and terephthalic acid monoamide in step 4. ^{1}H-NMR(400 MHz, CD_3OD): 8.53 (d, 1H), 8.46 (s, 1H), 8.35 (d, 1H), 8.27 (d, 1H), 7.91-7.86 (m, 3H), 7.77-7.75 (m, 2H), 7.32 (t, 1H), 6.71 (d, 1H), 4.54 (brs, 2H), 4.49 (s, 2H), 3.92 (br s, 1H), 2.19-2.2.10 (m, 6H), 1.89-1.83 (m, 2H). MS(EI) for $C_{27}H_{28}N_6O_3$: 485 (MH^+).

[00420] (2J): 6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(5-methylpyrazin-2-yl)methyl]pyridine-3-carboxamide. Prepared according the method of example 2 by using 2-(aminomethyl)-5-

methylpyrazine in step 2 and 4-(hydroxymethyl)benzoic acid in step 4. ^{1}H-NMR (400 MHz, CD_3OD): 8.55 (s, 1H), 8.40- 8. 39 (m, 2H), 7.91 (dd, 1H), 7.68-7.65 (m, 2H), 7.37 (d, 2H), 6.68 (d, 1H), 4.58 (s, 2H), 4.57 (s, 2H), 4.54(s, 2H), 3.92 (br s, 1H), 2.45 (s, 3H), 2.21-2.17 (m, 6H), 189-1.83 (m, 2H). MS (EI) for $C_{27}H_{30}N_6O_3$: 487 (MH^+).

[00421] (2K): N-{8-[5-({[(5-methylpyrazin-2-yl)methyl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according the method of example 2 by using 2-(aminomethyl)-5-methylpyrazine in step 2 and terephthalic acid monoamide in step 4. ^{1}H-NMR(400 MHz, CD_3OD): 8.51-8.45 (m, 4H), 8.25 (d, 1H), 7.98-7.96 (m, 2H), 7.88-7.85 (m, 2H), 7.18 (d, 1H), 4.72 (s, 2H), 4.68 (s, 2H), 4.10 (br s, 1H), 2.54 (s, 3H), 2.38-2.24 (m, 6H), 2.16-2.12 (m, 2H). MS(EI) for $C_{27}H_{29}N_7O_3$: 500 (MH^+).

[00422] (2L): 6-(3-endo-{[(5-methyl-2,3-dihydro-1,4-benzodioxin-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 5-methyl-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid (see: J. Med. Chem. 1997, 40, 18-23) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.82-8.77 (m, 1H), 8.65 (s, 1H), 8.08 (d, 1H), 7.98 (dd, 1H), 7.35-7.28 (m, 4H), 7.26-7.21 (m, 1H), 6.81-6.74 (m, 3H), 4.54 (br s, 2H), 4.45 (d, 2H), 4.30-4.22 (m, 4H), 3.84-3.78 (m, 1H), 3.34 (s, 3H), 2.22-1.94 (m, 9H), 1.87-1.80 (m, 2H). MS (EI) for $C_{30}H_{32}N_4O_4$: 513 (MH^+).

[00423] (2M): 6-(3-endo-{[(4-methyl-1,3-benzodioxol-5-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 4-methyl-1,3-benzodioxole-5-carboxylic acid (see: J. Med. Chem. 1997, 40, 18-23. Prepared using bromochloromethane in place of dibromoethane) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.82-8.77 (m, 1H), 8.65 (d, 1H), 8.12 (d, 1H), 7.98 (dd, 1H), 7.35-7.28 (m, 4H), 7.26-7.21 (m, 1H), 6.89 (d, 1H), 6.82 (d, 1H), 6.76 (d, 1H), 6.05 (s, 2H), 4.54 (br s, 2H), 4.45 (d, 2H), 3.84-3.78 (m, 1H), 3.34 (s, 3H), 2.24-2.17 (m, 5H), 2.11-1.95 (m, 4H), 1.88-1.81 (m, 2H). MS (EI) for $C_{29}H_{30}N_4O_4$: 499 (MH^+).

[00424] (2N): 6-(3-endo-{[(5-methyl-2,3-dihydro-1,4-benzodioxin-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide. Prepared as the acetate salt according to the method of example 2 by using 4-(4-methylpiperazin-1-yl)benzylamine in step 2 and 5-methyl-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid (J. Med. Chem. 1997,

40, pp18-23) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.72-8.66 (m, 1H), 8.63 (d, 1H), 8.09 (d, 1H), 7.96 (dd, 1H), 7.15 (d, 2H), 6.88 (d, 2H), 6.81-6.72 (m, 3H), 4.54 (br s, 2H), 4.37-4.21 (m, 6H), 3.84-3.78 (m, 1H), 3.10-3.06 (m, 4H), 2.45-2.41 (m, 4H), 2.23-2.13 (m, 8H), 2.10-1.94 (m, 4H), 1.90-1.80 (m, 7H). MS (EI) for $C_{35}H_{42}N_6O_4$: 611 (MH^+).

[00425] (2O): 6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 7-methyl-1-benzofuran-6-carboxylic acid (synthesized according to reagent preparation 15) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.82-8.78 (m, 1H), 8.66 (s, 1H), 8.26-8.24 (m, 1H), 8.10 (s, 1H), 8.00-7.97 (m, 1H), 7.56-7.53 (m, 1H), 7.35-7.22 (m, 5H), 7.00 (s, 1H), 6.79-6.75 (m, 1H), 4.57 (br s, 2H), 4.46 (d, 2H), 3.98 (m, 1H), 2.52 (s, 3H), 2.65-2.20 (m, 2H), 2.15-2.07 (m, 2H), 2.03-1.98 (m, 2H), 1.91-1.85 (m, 2H). MS (EI) for $C_{30}H_{30}N_4O_3$: 495 (MH^+).

[00426] (2P): 8-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]quinoline-7-carboxamide. Prepared according to the method of example 2 by using 8-methylquinoline-7-carboxylic acid (see: US2006069144) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.99 (dd, 1H), 8.85-8.80 (m, 1H), 8.66 (d, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.00 (dd, 1H), 7.88 (d, 1H), 7.61-7.57 (m, 1H), 7.47 (d, 1H), 7.35-7.30 (m, 4H), 7.26-7.21 (m, 1H), 6.82-6.77 (m, 1H), 4.59 (br s, 2H), 4.46 (d, 2H), 3.99-3.93 (m, 1H), 2.76 (s, 3H), 2.28-2.13 (m, 4H), 2.03-1.98 (m, 2H), 1.92-1.86 (m, 2H). MS (EI) for $C_{31}H_{31}N_5O_2$: 506 (MH^+).

[00427] (2Q): 3-methyl-4-({[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]amino}carbonyl)phenyl carbamate. Synthesized as the trifluoroacetate salt according to the method of example 2 using 4-[(aminocarbonyl)oxy]-2-methylbenzoic acid (synthesized according to reagent preparation 12) in step 4. ^{1}H NMR (400 MHz, DMSO): 9.00-8.93 (br s, 1H), 8.59-8.56 (s, 1H), 8.33-8.29 (s, 1H), 8.15-8.10 (d, 1H), 7.37-7.21 (m, 6H), 7.05-6.90 (m, 3H), 4.67-4.59 (br s, 2H), 4.50-4.45 (d, 2H), 4.40-4.00 (br s, 2H), 3.91-3.84 (br s, 2H), 2.36-2.32 (s, 3H), 2.31-2.23 (m, 2H), 2.18-2.08 (m, 2H), 2.05-1.99 (m, 2H), 1.97-1.89 (d, 2H). MS (EI) for $C_{29}H_{31}N_5O_4 \cdot C_2H_1O_2F_3$: 514 ($MH^+$).

[00428] (2R): 2-methyl-3-({[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]amino}carbonyl)phenyl carbamate. Synthesized as the trifluoroacetate salt according to the method of example 2 using 3-

[(aminocarbonyl)oxy]-2-methylbenzoic acid (synthesized according to reagent preparation 12) in step 4. ^{1}H NMR (400 MHz, CD_3OD): 8.51-8.48 (d, 1H), 8.48-8.46 (s, 1H), 8.28-8.23 (d, 1H), 7.38-7.12 (m, 8H), 4.72-4.67 (br s, 2H), 4.58-4.56 (s, 2H), 2.39-2.05 (m, 11H). MS (EI) for $C_{29}H_{31}N_5O_4 \cdot C_2H_1O_2F_3$: 514 ($MH^+$).

[00429] (2S): 6-[3-endo-({[4-(hydroxymethyl)-2-methylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide. Synthesized as the trifluoroacetate salt according to the method of example 2 using 4-(hydroxymethyl)-2-methylbenzoic acid (synthesized according to reagent preparation 13) in step 4. ^{1}H NMR (400 MHz, CD_3OD): 8.37-8.33 (d, 2H), 8.25-8.20 (d, 1H), 7.28-7.13 (m, 8H), 4.64-4.60 (br s, 2H), 4.52.4.50 (s, 2H), 4.49-4.47 (s, 2H), 4.03-3.97 (m, 1H), 2.33-2.30 (s, 3H), 2.29-2.00 (m, 8H). MS (EI) for $C_{29}H_{31}N_5O_4 \cdot C_2H_1O_2F_3$: 485 ($MH^+$).

[00430] (2T): 6-[3-endo-({[4-(hydroxymethyl)-2-methylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyridin-3-ylmethyl)pyridine-3-carboxamide. Synthesized as the trifluoroacetate salt according to the method of example 2 using (piperidin-3-yl)methylamine in step 2 and 4-(hydroxymethyl)-2-methylbenzoic acid (synthesized according to reagent preparation 13) in step 4. ^{1}H NMR (400 MHz, CD_3OD): 8.86-8.81 (d, 1H), 8.76-8.70 (d, 1H), 8.52-8.47 (m, 2H), 8.29-8.23 (d, 1H), 7.99-7.93 (m, 1H), 7.36-7.30 (d, 2H), 7.27-7.21 (m, 3H), 4.76-4.69 (br s, 4H), 4.62-4.59 (s, 2H), 4.49-4.47 (s, 2H), 4.12-4.04 (m, 1H), 2.83-2.80 (s, 3H), 2.45-2.07 (m, 8H). MS (EI) for $C_{28}H_{31}N_5O_3 \cdot C_2H_1O_2F_3$: 486 ($MH^+$).

[00431] (2U): 6-{3-endo-[({4-[amino(imino)methyl]phenyl}carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-N-(phenylmethyl)pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 2 by using 4-amidinobenzoic acid hydrochloride in step 4. ^{1}H NMR (400 MHz, methanol-d_4): 8.53 (d, 1H), 8.50 (d, 1H), 8.22 (dd, 1H), 8.00 (d, 2H), 7.90 (d, 2H), 7.33 (m, 5H), 7.26 (m, 1H), 7.13 (d, 1H), 4.71 (br s, 2H), 4.57 (s, 2H), 4.10 (m, 1H), 2.30 (m, 6H), 2.11 (d, 2H); MS (EI) for $C_{28}H_{30}N_6O_2$: 407 (MH^+).

[00432] (2V): 6-[3-endo-({[3-(methyloxy)-2-propylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 2 by using 3-methoxy-2-

propylbenzoic acid (synthesized according to reagent preparation 18) in step 4. ^{1}H NMR (400 MHz, methanol-d_4): 8.47 (d, 1H), 8.39 (d, 1H), 8.25 (dd, 1H), 7.33 (d, 1H), 7.27-7.16 (m, 3H), 7.02 (d, 1H), 6.90 (d, 1H), 4.68 (br s, 2H), 4.57 (s, 2H), 4.06 (m, 1H), 3.83 (s, 3H), 2.67 (m, 2H), 2.33 (m, 4H), 2.20 (m, 2H), 2.06 (d, 2H), 1.57 (m, 2H), 0.92 (t, 3H); MS (EI) for $C_{31}H_{36}N_4O_3$: 513 (MH^+).

[00433] (2W): 6-[3-endo-({[3-(methyloxy)-2-prop-2-en-1-ylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 3-(methyloxy)-2-prop-2-en-1-ylbenzoic acid (synthesized according to reagent preparation 19) in step 4. ^{1}H NMR (400 MHz, methanol-d_4): 8.46 (d, 1H), 8.31 (d, 1H), 8.26 (dd, 1H), 7.37-7.23 (m, 6H), 7.19 (d, 1H), 7.05 (d, 1H), 6.94 (d, 1H), 5.90 (m, 1H), 4.94 (m, 2H), 4.68 (br s, 2H), 4.57 (s, 2H), 4.05 (m, 1H), 3.84 (s, 3H), 3.51 (d, 2H), 2.31 (m, 4H), 2.18 (m, 2H), 2.07 (d, 2H); MS (EI) for $C_{31}H_{34}N_4O_3$: 511 (MH^+).

[00434] (2X): N4-(8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[2-(methylsulfonyl)ethyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using cyclopentylamine in step 2 and 4-(aminocarbonyl)-3-{[2-(methylsulfonyl)ethyl]amino}benzoic acid (synthesized according to reagent preparation 39) in step 4. ^{1}H NMR (400 MHz, methanol-d_4): 8.57 (d, 1H), 8.14 (d, 1H), 7.95 (dd, 1H), 7.67 (d, 1H), 7.13 (d, 1H), 7.01 (dd, 1H), 6.75 (d, 1H), 4.62 (br s, 2H), 4.30 (m, 1H), 4.00 (m, 1H), 3.81 (t, 2H), 3.47 (t, 2H), 3.01 (s, 3H), 2.24 (m, 6H), 1.97 (m, 4H), 1.78 (m, 2H), 1.60 (m, 4H); MS (EI) for $C_{29}H_{38}N_6O_5S$: 538 (MH^+).

[00435] (2Y): N4-(8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-[(4-trans-hydroxycyclohexyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using cyclopentylamine in step 2 and 4-(aminocarbonyl)-3-[(trans-4-hydroxycyclohexyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 4. ^{1}H NMR (400 MHz, methanol-d_4): 8.57 (d, 1H), 7.96 (dd, 1H), 7.62 (d, 1H), 7.07 (d, 1H), 6.89 (dd, 1H), 6.75 (d, 1H), 4.63 (br s, 2H), 4.30 (m, 1H), 4.00 (m, 1H), 3.63 (m, 1H), 3.41 (m, 1H), 2.20 (m, 8H), 1.99 (m, 6H), 1.78 (m, 2H), 1.60 (m, 4H), 1.38 (m, 4H); MS (EI) for $C_{32}H_{42}N_6O_4$: 575 (MH^+).

[00436] (2Z): N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-indole-6-carboxamide. Prepared according to the method of example 2 by using 1H-indole-6-carboxylic acid in step 4. ^{1}H NMR (400 MHz, DMSO-d_6): 11.39 (s, 1H), 8.81 (t, 1H), 8.67 (d, 1H), 8.12 (d, 1H), 7.99 (dd, 1H), 7.88 (s, 1H), 7.59 (d, 1H), 7.50 (dd, 1H), 7.45 (dd, 1H), 7.32 (m, 4.5H), 7.24 (m, 0.5H), 6.78 (d, 1H), 6.49 (m, 1H), 4.60 (bs, 2H), 4.46 (d, 2H), 3. 84 (m, 1H), 2.30 (m, 2H), 2.06 (m, 4H), 1.94 (d, 2H). MS (EI) for $C_{29}H_{29}N_5O_2$: 480 (MH^+).

[00437] (2AA): 1-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-indole-4-carboxamide. Prepared according to the method of example 2 by using 1-methyl-1H-indole-4-carboxylic acid in step 4. ^{1}H NMR (400 MHz, DMSO-d_6): 8.81 (t, 1H), 8.66 (d, 1H), 8.10 (d, 1H), 7.99 (dd, 1H), 7.61 (d, 1H) 7.42 (d, 1H), 7.38 (d, 1H), 7.32 (m, 4H), 7.24 (m, 2H), 6.78 (m, 2H), 4.60 (bs, 2H), 4.46 (d, 2H), 3. 86 (m, 1H), 3.81 (s, 3H), 2.28 (m, 2H), 2.06 (m, 4H), 1.94 (d, 2H). MS (EI) for $C_{30}H_{31}N_5O_2$: 494 (MH^+).

[00438] (2AB): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide. Isolated in trifluoroacetate salt form according to the method of example 2 by using 7-methyl-2,3-dihydro-1-benzofuran-6-carboxylic acid (synthesized according to reagent preparation 16) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 9.02 (m, 1H), 8.55 (d, 1H), 8.18 (m, 2H), 7.32 (m, 4H), 7.25 (m, 1H), 7.10 (m, 2H), 6.81 (d, 1H), 4.65 (broad s, 2H), 4.53 (t, 2H), 4.47 (d, 2H), 3.87 (m, 1H), 3.20 (t, 2H), 2.27 (m, 2H), 2.14 (s, 3H), 2.11 (m, 2H), 2.02 (m, 2H), 1.97 (d, 2H). MS (EI) for $C_{30}H_{32}N_4O_3$: 497 (MH^+).

[00439] (2AC): 6-(3-endo-{[(8-methyl-3,4-dihydro-2H-chromen-7-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 8-methyl-3,4-dihydro-2*H*-chromene-7-carboxylic acid (Sawada, Y. et al, *Pest Management Science*, **2003**, 59(*1*), 36-48.) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.79 (t, 1H), 8.63 (d, 1H), 8.10 (d, 1H), 7.91 (dd, 1H), 7.28 (m, 4H), 7.21 (m, 1H), 6.92 (d, 1H), 6.72 (t, 2H), 4.52 (broad s, 2H), 4.44 (d, 2H), 4.16 (t, 2H), 3.81 (m, 1H), 2.72 (t, 2H), 2.18 (m, 2H), 2.07 (s, 3H), 2.04 (m, 2H), 1.96 (m, 2H), 1.92 (m, 2H), 1.84 (d, 2H). MS (EI) for $C_{31}H_{34}N_4O_3$: 511 (MH^+).

[00440] (2AD): 4-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-benzimidazole-5-carboxamide. Prepared according to the method of example 2 by using 7-methyl-1H-benzimidazole-6-carboxylic acid (synthesized according to reagent preparation 23) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.81 (m, 1H), 8.66 (dd, 1H), 8.23 (m, 1H), 8.14 (broad s, 1H), 7.98 (m, 1H), 7.31 (m, 4H), 7.23 (m, 1H), 6.76 (dd, 1H), 4.57 (broad s, 2H), 4.46 (t, 2H), 3.88 (m, 1H), 2.62 (m, 2H), 2.27 (m, 1H), 2.14 (m, 2H), 2.07 (m, 2H), 1.90 (m, 2H), 1.64 (d, 2H). MS (EI) for $C_{29}H_{30}N_6O_2$: 495 (MH^+).

[00441] (2AE): N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-benzimidazole-5-carboxamide. Isolated as the trifluoroacetate salt according to the method of example 2 by using 1*H*-benzimidazole-5-carboxylic acid in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 9.07 (m, 1H), 8.60 (m, 1H), 8.21 (m, 2H), 7.96 (m, 2H), 7.34 (m, 4H), 7.26 (m, 1H), 7.15 (m, 1H), 4.71 (broad s, 2H), 4.49 (d, 2H), 3.95 (m, 1H), 2.79 (m, 2H), 2.35 (m, 1H), 2.15 (m, 1H), 2.08 (m, 4H). MS (EI) for $C_{28}H_{28}N_6O_2$: 481 (MH^+).

[00442] (2AF): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using (R)-1-isopropylpyrrolidin-3-amine (synthesized according to reagent preparation 9) in step 2 and 4-(aminocarbonyl)-3-[(cyclopropylmethy)amino]benzoic acid (synthesized according to reagent preparation 39) in step 4. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.32-8.24 (m, 2H), 8.17 (d, 1H), 7.96 (dd, 1H), 7.93 (br s, 1H), 7.67 (d, 1H), 7.30 (br s, 1H), 6.98 (d, 1H), 6.89 (dd, 1H), 6.78 (d, 1H), 4.58 (br s, 2H), 4.48-4.35 (m, 1H), 3.85-3.78 (m, 1H), 3.65-2.55 (m, 7H), 3.03 (dd, 2H), 2.25-2.12 (m, 2H), 2.12-1.97 (m, 4H), 1.95-1.86 (m, 2H), 1.29-1.04 (m, 7H), 0.54-0.49 (m, 2H), 0.27-0.22 (m, 2H); MS (EI) for $C_{32}H_{43}F_3N_7O_3$: 574 (MH^+).

[00443] (2AG): 5-[(1-ethylpropyl)amino]-N-{8-[5-({[(1-ethylpyrrolidin-2-yl)methyl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using 1-(ethylpyrrolidin-2-yl)methanamine in step 2 and 4-(aminocarbonyl)-2-methyl-5-[(1-ethylpropyl)amino]benzoic acid (synthesized according to reagent preparation 42) in step 4. ^{1}H NMR (400 MHz, d_6-DMSO): 8.58 (d, 1H), 8.28 (d, 1H), 8.16 (t, 1H), 8.04 (d, 1H), 7.92 (dd, 1H), 7.84 (br s, 1H), 7.48 (s, 1H), 7.16 (br s,

1H), 6.74 (d, 1H), 6.56 (s, 1H), 4.54 (br s, 2H), 3.82 (br s, 1H), 3.28-3.18 (m, 1H), 3.06-2.96 (m, 2H), 2.88-2.77 (m, 1H), 2.58-2.50 (m, 1H), 2.30-2.20 (m, 3H), 2.18 (s, 3H), 2.16-1.94 (m, 5H), 1.92-1.83 (m, 3H), 1.82-1.72 (m, 1H), 1.68-1.42 (m, 7H), 1.04 (t, 3H), 0.88 (t, 6H); MS (EI) for $C_{34}H_{49}N_7O_3$: 604 (MH^+).

[00444] (2AH): N4-(8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using cyclopentylamine in step 2 and 4-(aminocarbonyl)-3-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}benzoic acid (prepared according to the methods in reagent preparation 40) in step 4. ^{1}H NMR (400 MHz, CD_3OD): 8.56 (d, 1H), 7.94 (dd, 1H), 7.72 (d, 1H), 7.43 (d, 1H), 7.05-7.02 (m, 2H), 6.98-6.93 (m, 2H), 6.72 (d, 1H), 4.57 (br s, 2H), 4.36 (m, 3H), 3.93 (m, 1H), 3.86 (s, 3H), 3.42 (m, 2H), 2.89 (s, 6H), 2.21 (m, 2H), 2.09 (br s, 2H), 2.00 (m, 2H), 1.94 (s, 3H), 1.88 (d, 2H), 1.77 (m, 2H), 1.67-1.52 (m, 4H); MS (EI) for $C_{37}H_{47}N_7O_5$: 670 (MH^+).

[00445] (2AI): 6-[3-endo-({[2-iodo-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 2-iodo-3-methoxybenzoic acid (synthesized according to reagent preparation 21) in step 4. ^{1}H NMR (400 MHz, d6-DMSO): 8.95 (br. s,1H), 8.57 (s, 1H), 8.38-8.34 (d, 1H), 8.16-8.09 (d, 1H), 7.42-7.22 (m, 4H), 7.05-6.97 (m, 2H), 6.88-6.84 (d, 2H), 4.66-4.59 (m, 2H), 4.50-4.45 (d, 2H), 3.92-3.83 (m, 4H), 2.36-2.28 (m, 2H), 2.19-2.10 (m, 2H), 2.02-1.89 (m, 4H). MS (EI) for $C_{28}H_{29}IN_4O_3$: 597 (MH^+).

[00446] (2AJ): 2,6-dimethyl-N1-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using 4-(aminocarbonyl)-2,6-dimethylbenzoic acid in step 4. ^{1}H NMR (400 MHz, d6-DMSO): 8.83-8.77 (m,1H), 8.66 (s, 1H), 8.41-8.37 (d, 1H), 8.01-7.96 (d, 1H), 7.92 (s, 1H), 7.56 (s, 2H), 7.36-7.21 (m, 6H), 6.78-6.74 (d, 1H), 4.59-4.53 (m, 2H), 4.48-4.44 (d, 2H), 3.96-3.91 (m, 1H), 2.26 (s, 6H), 2.21-2.11 (m, 4H), 2.00-1.91 (m, 2H), 1.83-1.75 (m, 2H). MS (EI) for $C_{30}H_{33}N_5O_3$: 512 (MH^+).

[00447] (2AK): 2-[(4-trans-hydroxycyclohexyl)amino]-N4-{8-[5-({[1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-

endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using (3R)-1-(1-methylethyl)pyrrolidin-3-amine in step 2 (synthesized according to reagent preparation 9) and 4-(aminocarbonyl)-3-[(trans-4-hydroxycyclohexyl)amino]-benzoic acid (synthesized according to reagent preparation 39) in step 4. ^{1}H NMR (400 MHz, d6-DMSO): 8.63-8.60 (d,1H), 8.24-8.16 (m, 3H), 8.00-7.87 (m, 2H), 7.68-7.63 (d, 1H), 7.31-7.25 (br. s, 1H), 6.96 (s, 1H), 6.85-6.80 (d, 1H), 6.78-6.73 (d, 1H), 4.64-4.51 (m, 3H), 4.39-4.29 (m, 2H), 3.86-3.80 (m, 1H), 2.84-2.87 (m, 2H), 2.70-2.61 (m, 2H), 2.47-2.40 (m, 2H), 2.38-2.30 (m, 2H), 2.28-2.20 (m, 2H), 2.12-1.92 (m, 4H), 1.79-1.69 (m, 2H), 1.37-1.17 (m, 6H), 1.06-0.99 (m, 6H), 0.97-0.93 (m, 2H). MS (EI) for $C_{34}H_{47}N_7O_4$: 618 (MH^+).

[00448] (2AL): 6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 4-(hydroxymethyl)benzoic acid in step 4. ^{1}H NMR (400 MHz, Methanol-d_4): 8.62 (d, 1H), 7.99 (dd, 1H), 7.79-7.74 (m, 2H), 7.48-7.44 (m, 2H), 7.37-7.28 (m, 4H), 7.27-7.20 (m, 1H), 6.77 (d, 1H), 4.67 (s, 2H), 4.62 (br s, 2H), 4.55 (s, 2H), 4.05-3.97 (m, 1H), 2.35-2.09 (m, 6H), 1.96 (d, 2H); MS (EI) for $C_{28}H_{30}N_4O_3$: 471 (MH^+).

[00449] (2AO): 6-(3-endo-{[(2-amino-6-chloro-9H-purin-9-yl)acetyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 2 by using 2-amino-6-chloro-9H-purine-9-acetic acid in step 4. ^{1}H NMR (400 MHz, Metahnol-d_4): 8.45 (d, 1H), 8.39 (d, 1H), 8.25 (dd, 1H), 8.07 (s, 1H), 7.18 (d, 1H), 4.67 (br s, 2H), 3.99-3.91 (m, 1H), 3.33-3.28 (s, 2H), 2.38-2.16 (m, 6H), 1.99 (d, 2H); MS (EI) for $C_{27}H_{28}ClN_9O_2$: 456 (MH^+).

[00450] (2AP): 6-[3-endo-({[2-methyl-3,4-bis(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 2 by using 3,4-dimethoxy-2-methylbenzoic acid (synthesized according to reagent preparation 17) in step 4. ^{1}H NMR (400 MHz, Methanol-d_4): 8.42 (d, 1H), 8.36-8.29 (m, 2H), 7.38-7.23 (m, 5H), 6.94 (s, 1H), 6.84 (s, 1H), 4.72 (br s, 2H), 4.57 (s, 2H), 4.12-4.05 (m, 1H), 3.85-3.83 (m, 6H), 2.45-2.20 (m, 9H), 2.14 (d, 2H); MS (EI) for $C_{30}H_{34}N_4O_4$: 515 (MH^+).

[00451] (2AQ): 6-[3-endo-({[2-bromo-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 2-bromo-3-methoxybenzoic acid (synthesized according to reagent preparation 20) in step 4. ^{1}H NMR (400 MHz, DMSO-d_6): 8.80 (t, 1H), 8.65 (d, 1H), 8.38 (d, 1H), 7.98 (dd, 1H), 7.39 (t, 1H), 7.36-7.28 (m, 4H), 7.27-7.20 (m, 1H), 7.14 (dd, 1H), 6.91 (dd, 1H), 6.76 (d, 1H), 4.54 (br s, 2H), 4.46 (d, 2H), 3.90-3.80 (m, 4H), 2.30-2.20 (m, 2H), 2.15-2.04 (m, 2H), 2.00-1.89 (m, 2H), 1.83 (d, 2H); MS (EI) for $C_{28}H_{29}BrN_4O_3$: 547 (M-H).

[00452] (2AR): 4-methyl-N-(8-{5-[({[4-(4-methylpiperazin-1-yl)phenyl]methyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1H-benzimidazole-5-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 2 by using 7-methyl-1H-benzimidazole-6-carboxylic acid (synthesized according to reagent preparation 23) in step 4. ^{1}H NMR (400 MHz, Methanol-d_4): 9.38 (s, 1H), 8.58 (d, 1H), 8.49 (d, 1H), 8.22 (dd, 1H), 7.72 (d, 1H), 7.59 (d, 1H), 7.32-7.28 (m, 2H), 7.16 (d, 1H), 7.02-6.98 (m, 2H), 4.71 (br s, 2H), 4.49 (s, 2H), 4.20-4.09 (m, 1H), 3.87-3.78 (m, 2H), 3.64-3.55 (m, 2H), 3.29-3.20 (m, 2H), 3.07-2.94 (m, 5H), 2.69 (s, 3H), 2.43-2.16 (m, 6H), 2.09 (d, 2H); MS (EI) for $C_{34}H_{40}N_8O_2$: 593 (MH^+).

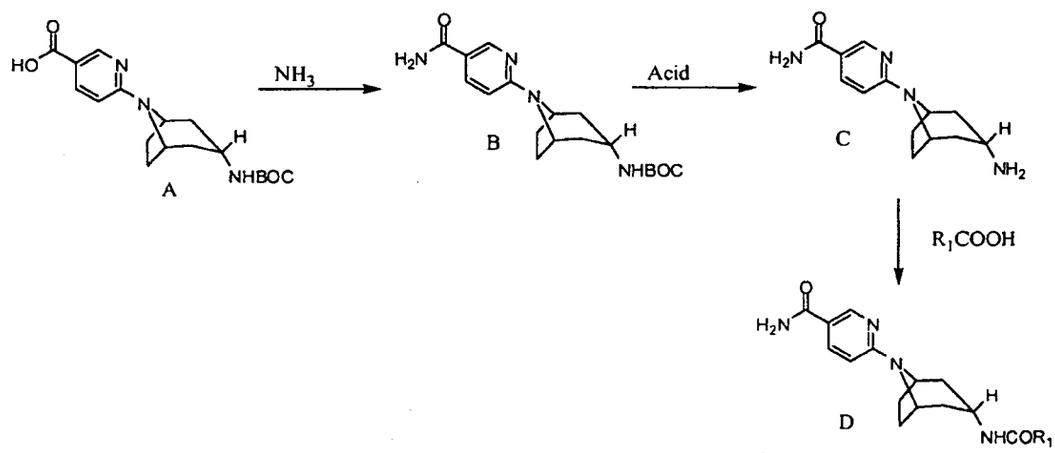
[00453] (2AS): N4-(8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using 4-aminocarbonyl-3-(cyclopropylmethyl)benzoic acid (synthesized according to reagent preparation 39) in step 4. ^{1}H NMR (400 MHz, DMSO-d_6): 8.59 (d, 1H), 8.25 (t, 1H), 8.15 (d, 1H), 8.01 (d, 1H), 7.96-7.90 (m, 2H), 7.67 (d, 1H), 7.28 (br s, 1H), 6.98 (s, 1H), 6.88 (dd, 1H), 6.75 (d, 1H), 4.55 (br s, 2H), 4.23-4.16 (m, 1H), 3.85-3.78 (m, 1H), 3.04 (t, 2H), 2.25-1.79 (m, 10H), 1.76-1.43 (m, 6H), 1.17-1.05 (m, 1H), 0.54-0.48 (m, 2H), 0.27-0.22 (m, 2H); MS (EI) for $C_{30}H_{38}N_6O_3$: 531 (MH^+).

[00454] 2(AT): 6-(3-endo-{[(2,3-dimethylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide. Prepared according to the method of example 2 by using 2,3-dimethylbenzoic acid in step 4. ^{1}H NMR (400 MHz, DMSO-d_6): 8.81-8.79 (m, 1H), 8.65 (d, 1H), 8.23 (d, 1H), 7.97 (dd, 1H), 7.33-7.24 (m, 3H), 7.23-7.07 (m, 3H), 6.76 (d, 1H), 4.55 (br s, 2H), 4.47 (s,

2H), 3.85 (br s, 1H), 2.22 (s, 3H), 2.20 (s, 2H), 2.11 (s, 3H), 2.09-2.08 (m, 2H), 1.98-1.97 (m, 2H), 1.87-1.84 (m, 2H). MS(EI) for $C_{29}H_{32}N_4O_2$: 469 (MH^+).

[00455] 2(AU): 2-[(cyclopropylmethyl)amino]-N4-[8-(5-{[methyl(methyloxy)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide. Prepared according to the method of example 2 by using N,O-dimethylhydroxylamine hydrochloride in step 2 and 4-(aminocarbonyl)-3-[(cyclopropylmethyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 4. ^{1}H NMR (400 MHz, methanol-d_4): 8.55 (d, 1H), 7.93 (dd, 1H), 7.63 (d, 1H), 7.05 (d, 1H), 6.91 (dd, 1H), 6.75 (d, 1H), 4.63 (br s, 2H), 4.00 (m, 1H), 3.64 (s, 3H), 3.35 (s, 3H), 3.08 (d, 2H), 2.24 (m, 6H), 1.97 (d, 2H), 1.15 (m, 1H), 0.58 (m, 2H), 0.29 (m, 2H); MS (EI) for $C_{27}H_{34}N_6O_4$: 507 (MH^+).

SYNTHETIC SCHEME 3:



[00456] Scheme 3 generally describes the synthesis of all of the compound(s) listed in Example 3, wherein R_1 is as defined in the specification.

[00457] In Scheme 3, ammonia is added to compound (A) under suitable reaction conditions to form compound (B). Compound B is then deprotected under acidic conditions, such as with the use of HCl, to remove BOC and form compound (C). To compound (C) is added R_1COOH under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (D).

[00458] EXAMPLE 3: 6-[3-endo-({[2-fluoro-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide.

[00459] STEP 1: To 6-(3-endo-(tert-butoxycarbonylamino)-8-azabicyclo[3.2.1]octan-8-yl)nicotinic acid (prepared in example 2) (4.43 g, 12.8 mmol) in THF (100 ml) was added triethylamine (2.69 ml, 19.2 mmol) and isobutyl chlororoformate (1.67 ml, 13.4 mmol). The mixture was stirred at 0°C for 1 hour, at which time a 28% solution of concentrated aqueous ammonia (20 ml) was added. The reaction mixture was stirred for 3 hours then the volume was reduced *in vacuo*. The resultant mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* to afford (1.85 g, 42% yield) of tert-butyl 8-(5-carbamoylpyridin-2-yl)-8-azabicyclo[3.2.1]octan-3-endo-ylcarbamate, which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (s, 1H), 7.94-7.88 (d, 1H), 7.71 (s, 1H), 7.09 (s, 1H), 6.86 (s, 1H), 6.72-6.67 (d, 1H), 4.52-4.40 (m, 2H), 3.45-3.39 (m, 1H), 2.15-2.07 (m, 2H), 2.02-1.87 (m, 2H), 1.86-1.87 (m, 2H), 1.75-1.66 (m, 2H), 1.39 (s, 9H). MS (EI) for $C_{18}H_{26}N_4O_3$: 347 (MH^+).

[00460] STEP 2: To tert-butyl 8-(5-carbamoylpyridin-2-yl)-8-azabicyclo[3.2.1]octan-3-endo-ylcarbamate (1.85 g, 5.3 mmol) in methanol (20 ml) was added a solution of 4N hydrogen chloride in dioxane (2.65 ml) and the reaction mixture refluxed for five minutes. After cooling to room temperature, the reaction mixture was concentrated and dried to afford 6-(3-endo-amino-8-azabicyclo[3.2.1]octan-8-yl)nicotinamide as the hydrochloride salt (1.31 g, 100% yield). MS (EI) for $C_{13}H_{18}N_4O$: 247 (MH^+).

[00461] STEP 3: A mixture of tert-butyl 8-(5-carbamoylpyridin-2-yl)-8-azabicyclo[3.2.1]octan-3-endo-ylcarbamate hydrochloride salt (0.050 g, 0.157 mmol), 2-fluoro-3-methoxybenzoic acid (0.027 g, 0.157 mmol), HOAt (0.314 ml, 0.5 M solution in dimethylformamide, 0.157 mmol), HATU (0.060 g, 0.157 mmol), and N-methylmorpholine (0.069 ml, 0.628 mmol) in dimethylformamide (0.5 mL) was stirred at room temperature for 16 h. The reaction mixture was poured into water (2 ml) and the resulting precipitate was collected by filtration. The filter cake was washed with water (2 x 1 mL), and dried to give 6-[3-endo-({[2-fluoro-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-

carboxamide (0.038 g, 61% yield). ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.41 (d, 1H), 7.94 (dd, 1H), 7.74 (br s, 1H), 7.36 (t, 1H), 7.20 (dd, 1H), 7.12 (br s, 1H), 6.95 (dd, 1H), 6.73 (d, 1H), 4.54 (br s, 2H), 3.90-3.82 (m, 4H), 2.28-2.18 (m, 2H), 2.14-2.03 (m, 2H), 2.00-1.88 (m, 2H), 1.83 (d, 2H); MS (EI) for $C_{21}H_{23}ClN_4O_3$: 415 (MH^+).

[00462] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [(3B)-(3Q)] were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00463] (3B): 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 3 by using 2-methyl-3-methoxybenzoic acid in step 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.62 (d, 1H), 8.22 (d, 1H), 7.94 (dd, 1H), 7.74 (br s, 1H), 7.23 (t, 1H), 7.12 (br s, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.73 (d, 1H), 4.54 (br s, 2H), 3.84 (m, 1H), 3.80 (s, 3H), 2.20 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H); MS (EI) for $C_{22}H_{26}N_4O_3$: 395 (MH^+).

[00464] (3C): 6-[3-endo-({[2-chloro-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 3 by using 2-chloro-3-methoxybenzoic acid in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.38-8.34 (m, 1H), 7.94 (dd, 1H), 7.74 (br s, 1H), 7.31-7.25 (m, 1H), 7.23-7.16 (m, 1H), 7.12 (br s, 1H), 7.09-7.03 (m, 1H), 6.73 (d, 1H), 4.55 (br s, 2H), 3.87 (s, 3H), 2.28-2.17 (m, 2H), 2.12-1.90 (m, 4H), 1.84 (d, 2H); MS (EI) for $C_{21}H_{23}FN_4O_3$: 399 (MH^+).

[00465] (3D): 6-(3-endo-{[(4-amino-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Prepared as the acetate salt according to the method of example 3 by using 4-amino-2-methylbenzoic acid in step 3. ^{1}H NMR (400 MHz, CD_3OD): 8.62 (s, 1H), 8.01-7.96 (d, 1H), 7.18-7.14 (d, 1H), 6.77-6.73 (d, 1H), 6.55-6.50 (m, 2H), 4.64-4.58 (br. s, 2H), 4.00-3.93 (m, 1H), 2.32 (s, 3H), 2.31-2.11 (m, 6H), 1.91 (s, 3H), 1.90-1.88 (m, 2H). MS (EI) for $C_{21}H_{25}N_5O_2$: 380 (MH^+).

[00466] (3E): 6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide . Prepared according to the method of example 3 by using 4-(hydroxymethyl)benzoic acid in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.15 (d, 1H), 7.95 (dd, 1H), 7.79-7.70 (m, 3H), 7.41 (d, 2H),

7.12 (br s, 1H), 6.75 (d, 1H), 5.32 (t, 1H), 4.62-4.52 (m, 4H), 3.88-3.82 (m, 1H), 2.26-2.16 (m, 2H), 2.13-1.86 (m, 6H); MS (EI) for $C_{21}H_{24}N_4O_3$: 379 (M-H).

[00467] (3F): N-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide . Prepared according to the method of example 3 by using terephthalic acid monoamide in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.54 (br s, 1H), 8.16 (d, 1H), 8.12-8.04 (m, 1H), 7.90 (br s, 1H), 7.47 (d, 2H), 7.41 (d, 2H), 7.38-7.26 (m, 2H), 6.99 (br s, 1H), 4.64 (br s, 2H), 4.53 (s, 2H), 3.92-3.85 (m, 1H), 3.83 (s, 3H), 2.30-2.20 (m, 2H), 2.18-1.92 (m, 6H); MS (EI) for $C_{22}H_{26}N_4O_4$: 409 (M-H).

[00468] (3G): 6-[3-endo-({[4-(hydroxymethyl)-3-(methyloxy)phenyl]carbonyl}-amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared as the trifluoroacetate salt according to the method of example 3 by using 4-(hydroxymethyl)-3-methoxybenzoic acid (synthesized according to reagent preparation 24) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.32 (d, 1H), 8.10 (br s, 1H), 7.98-7.92 (m, 3H), 7.86-7.80 (m, 2H), 7.75 (br s, 1H), 7.53 (br s, 1H), 7.13 (br s, 1H), 6.75 (d, 1H), 4.57 (br s, 2H), 3.91-3.83 (m, 1H), 2.28-2.17 (m, 2H), 2.14-1.96 (m, 4H), 1.91 (d, 2H); MS (EI) for $C_{22}H_{23}N_5O_3$: 392 (M-H).

[00469] (3J): 6-[3-endo-({[2-(4-hydroxybut-1-yn-1-yl)-3-(methyloxy)phenyl]-carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 3 by using 2-(4-hydroxybut-1-ynyl)-3-methoxybenzoic acid (synthesized according to reagent preparation 28) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO: 8.61 (d, 1H), 8.21 (d, 1H), 7.95 (dd, 1H), 7.74 (br s, 1H), 7.33 (t, 1H), 7.15-7.06 (m, 2H), 6.94 (d, 1H), 6.73 (d, 1H), 4.83 (br s, 1H), 4.55 (br s, 2H), 3.89-3.84 (m, 1H), 3.82 (s, 3H), 3.58-3.52 (m, 2H), 2.55 (t, 2H), 2.26-2.20 (m, 2H), 2.15-2.05 (m, 2H), 1.97-1.92 (m, 2H), 1.83 (d, 2H); MS (EI) for $C_{25}H_{28}N_4O_4$: 449 (MH+).

[00470] (3K): N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[2-(methyloxy)ethyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 3 by using 4-aminocarbonyl-3-(2-methoxyethylamino)benzoic acid (synthesized according to reagent preparation 39) in step 3 . ^{1}H NMR (400 MHz, d_4-MeOH): 8.53 (d, 1H), 7.89 (dd, 1H), 7.54 (d, 1H), 7.80 (d, 1H), 6.84 (dd, 1H), 6.66 (d, 1H), 4.54 (br, 2H), 3.91 (tr, 1H), 2.55 (tr, 2H),

3.30 (tr, 2H), 3.29 (s, 3H), 2.20-2.09 (m, 7H), 1.89 (m, 2H); MS (EI) for $C_{24}H_{30}N_6O_4$: 467 (MH^+).

[00471] (3L): N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(2-morpholin-4-ylethyl)oxybenzene-1,4-dicarboxylate. Prepared according to the method of example 3 by using 4-aminocarbonyl-3-(2-morpholinoethoxy)benzoic acid (synthesized according to reagent preparation 27) in step 3. ^{1}HNMR (400 MHz, d_4-MeOH): 8.50(d, 1H), 8.40(d, 1H), 8.23(dd, 1H), 7.68(d, 1H), 7.62(s, 1H), 7.55(d, 1H), 7.15(d, 1H), 4.72(s, 2H), 4.61(s, 2H), 4.09-3.99(m, 4H), 3.62-3.60(m, 4H), 2.37-2.26(m, 6H), 2.15(d, 2H). MS(EI) for $C_{27}H_{34}N_6O_5$: 523(MH^+).

[00472] (3M): N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(4-hydroxycyclohexyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 3 by using 4-(aminocarbonyl)-3-[(trans-4-hydroxycyclohexyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.62 (d, 1H), 8.20 (m, 2H), 7.95 (dd, 1H), 7.91 (br s, 1H), 7.75 (br s, 1H), 7.66 (d, 1H), 7.27 (br s, 1H), 7.12 (br s, 1H), 7.06 (br s, 1H), 6.96 (s, 1H), 6.83 (d, 1H), 6.75 (d, 1H), 4.60 (d, 1H), 4.57 (br s, 2H), 3.83 (m, 1H), 3.48 (m, 1H), 2.24 (m, 2H), 2.10-1.81 (m, 10H), 1.25 (m, 4H); MS (EI) for $C_{27}H_{34}N_6O_4$: 507 (MH^+).

[00473] (3N): 2-(acetylamino)-N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 3 by using 3-(acetylamino)-4-(aminocarbonyl)benzoic acid (synthesized according to reagent preparation 29) in step 3. ^{1}H NMR (400 MHz, d_4-MeOH): 8.68 (d, 1H), 8.53 (d, 1H), 7.89 (dd, 1H), 7.73 (d, 1H), 7.42 (dd, 1H) 6.67 (d, 1H),4.54 (br, 2H), 3.93 (tr, 1H), 2.18 (m, 5H), 2.10 (s, 3H), 2.08 (m, 3H), 1.86 (m, 2H);MS (EI) for $C_{23}H_{26}N_6O_4$: 451 (MH^+).

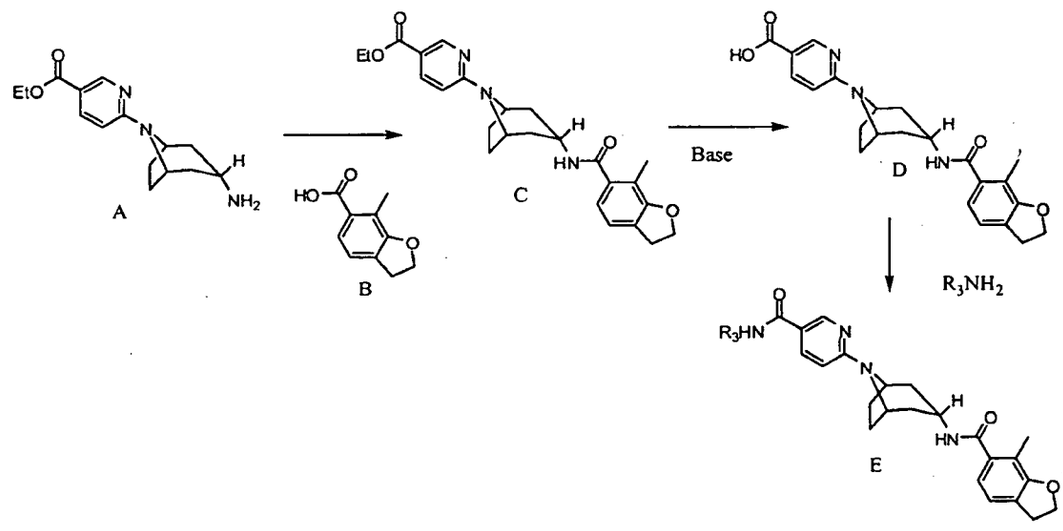
[00474] (3O): N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-1H-indole-4,7-dicarboxamide. Prepared according to the method of example 3 by using 7-carbamoyl-1H-indole-4-carboxylic acid (synthesized according to reagent preparation 30) in step 3. ^{1}H NMR (400 MHz, DMSO- d_6): 11.28 (s, 1H), 8.64 (s, 1H), 8.59 (d, 1H), 8.22 (d, 1H), 8.18 (bs, 1H), 8.00 (dd, 1H), 7.74 (d, 1H), 7.52 (bs, 1H), 7.42 (s, 1H), 7.32 (m, 2H), 6.78 (bs, 1H), 6.76 (d, 1H), 4.54 (bs, 2H),

3.84 (m, 1H), 2.28 (m, 2H), 2.08 (m, 4H), 1.96 (m, 2H). MS (EI) for $C_{23}H_{24}N_6O_3$: 432 (MH^+).

[00475] (3P): N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[2-(methylsulfonyl)ethyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 3 by using 4-(aminocarbonyl)-3-{[2-(methylsulfonyl)ethyl]amino}benzoic acid (synthesized according to reagent preparation 39) in step 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.64 (d, 1H), 8.32 (t, 1H), 8.19 (d, 1H), 7.95 (m, 2H), 7.75 (br s, 1H), 7.69 (d, 1H), 7.36 (br s, 1H), 7.12 (br s, 1H), 7.01 (s, 1H), 7.01 (s, 1H), 6.95 (d, 1H), 6.75 (d, 1H), 4.57 (br s, 2H), 3.84 (m, 1H), 3.66 (m, 2H), 3.46 (t, 2H), 3.03 (s, 3H), 2.21 (m, 2H), 2.08 (m, 2H), 2.00 (m, 2H), 1.90 (d, 2H); MS (EI) for $C_{24}H_{30}N_6O_5S$: 515 (MH^+).

[00476] (3Q): N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(cyclobutylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 3 by using 4-(aminocarbonyl)-3-[(cyclobutyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO: 8.62 (d, 1H), 8.31 (d, 1H), 8.18 (d, 1H), 7.98-7.92 (m, 2H), 7.74 (br s, 1H), 7.67 (d, 1H), 7.32 (br s, 1H), 7.12 (br s, 1H), 6.89 (d, 1H), 6.85 (s, 1H), 6.75 (d, 1H), 4.57 (br s, 2H), 4.01-3.91 (m, 1H), 3.86-3.79 (m, 1H), 2.44-2.33 (m, 2H), 2.26-2.16 (m, 2H), 2.13-1.70 (m, 10H); MS (EI) for $C_{25}H_{30}N_6O_3$: 463 (MH+).

SYNTHETIC SCHEME 4:



[00477] Scheme 4 generally describes the synthesis of all of the compound(s) listed in Example 4, wherein R_3 is as defined in the specification.

[00478] In Scheme 4, compound (B) is added to compound (A) under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (C). The carboxylate of compound C is hydrolyzed with a base, such as LiOH, to form compound (D). To compound (D) is added R_3NH_2 under appropriate reaction conditions and with a suitable coupling reagent, such as HOBT and EDCI, to condense and form the amide bond in compound (E).

[00479] EXAMPLE 4: N-(1-ethylazetidin-3-yl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide.

[00480] STEP 1: To a solution of 7-methyl-2,3-dihydro-1-benzofuran-6-carboxylic acid (synthesized in reagent preparation 16) (1.72 g, 9.63 mmol), HATU (3.66 g, 9.63 mmol), and DIEA (6.70 ml, 38.5 mmol) in DMF (25 mL) was added ethyl 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylate (synthesized in example 1) (2.68 g, 9.63 mmol). The mixture was stirred at 30°C for 22 hours, at which time it was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was separated and washed with lithium chloride and then brine. The organic layer was dried over anhydrous sodium sulfate, filtered then concentrated *in vacuo* to afford (5.39 g, 129%) of ethyl 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylate which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): 8.67-8.64 (s, 1H), 8.18-8.13 (s, 1H), 7.98-7.89 (d, 1H), 7.13-7.07 (d, 1H), 6.83-6.73 (m, 2H), 4.64-4.50 (m, 4H), 4.29-4.21 (m, 2H), 3.88-3.81 (m, 1H), 3.25-3.15 (m, 2H), 2.26-2.18 (d, 2H), 2.16-2.12 (s, 3H), 2.10-1.85 (m, 6H), 1.32-1.26 (m, 3H). MS (EI) for $C_{25}H_{29}N_3O_4$: 436 (MH^+).

[00481] STEP 2: To a solution of ethyl 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylate (4.19 g, 9.63 mmol) in methanol (100 ml) was added 2M lithium hydroxide (24.0 ml, 48.0 mmol). The mixture was stirred at 50°C for 24 hours, at which time the volume was reduced *in vacuo*, the pH adjusted to 5 with 1 N hydrochloric acid, and extracted

with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* to afford (3.27 g, 83%) of 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylic acid, which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): 12.65-12.34 (br. s, 1H), 8.64-8.61 (s, 1H), 8.16-8.12 (d, 1H), 7.93-7.89 (d, 1H), 7.13-7.07 (d, 1H), 6.82-6.79 (d, 1H), 6.76-6.72 (d, 1H), 4.62-4.50 (m, 4H), 3.88-3.81 (m, 1H), 3.25-3.15 (m, 2H), 2.26-2.18 (d, 2H), 2.15-2.12 (s, 3H), 2.10-1.85 (m, 6H). MS (EI) for $C_{23}H_{25}N_3O_4$: 408 (MH^+).

[00482] STEP 3: To a solution of 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylic acid (236 mg, 0.580 mmol), HOBT (94 mg, 0.696 mmol), N-methylmorpholine (127 μL, 1.16 mmol) and EDCI (133 mg, 0.696 mmol) in DMF (3 mL) was added tert-butyl 3-aminoazetidine-1-carboxylate (120 mg, 0.696 mmol). The reaction mixture was stirred at room temperature for 5 h, at which time it was concentrated *in vacuo* then purified by flash chromatography (5% methanol in dichloromethane eluent) to afford 1,1-dimethylethyl 3-({[6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridin-3-yl]carbonyl}amino)azetidine-1-carboxylate (270 mg, 83%) as a white powder. MS (EI) for $C_{31}H_{39}N_5O_5$: 560 (M-H).

[00483] STEP 4: To a solution of 1,1-dimethylethyl 3-({[6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridin-3-yl]carbonyl}amino)azetidine-1-carboxylate (270 mg, 0.480 mmol) in acetonitrile (5 mL) was added a solution of hydrogen chloride (4.0M in dioxane, 500 μL) at room temperature and stirred for 15 h. The white suspension was filtered and the product washed with diethyl ether to give N-azetidin-3-yl-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide hydrochloride salt (233 mg, 97%). MS (EI) for $C_{26}H_{31}N_5O_3$: 462 (MH^+).

[00484] STEP 5: To a solution of N-azetidin-3-yl-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide hydrochloride salt (50 mg, 0.100 mmol) in methanol (1 mL) and tetrahydrofuran (1 mL) at 0°C was added acetaldehyde (11 μL, 0.200 mmol). The reaction mixture was stirred at 0°C for 20 min, at which time sodium

cyanoborohydride (13 mg, 0.200 mmol) was added then stirred at room temperature for 5 h. The reaction mixture was quenched with 1N aqueous hydrochloric acid then diluted with water. The solution was purified by preparatory HPLC (0.1% aqueous ammonium acetate-acetonitrile) to afford the title compound (11.7 mg) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): 8.59 (d, 1H), 8.47 (d, 1H), 8.12 (d, 1H), 7.94 (dd, 1H), 7.10 (d, 1H), 6.80 (d, 1H), 6.74 (d, 1H), 4.55-4.51 (m, 4H), 4.45-4.40 (m, 1H), 3.85-3.79 (br m, 1H), 3.51 (t, 2H), 3.20 (t, 2H), 2.87 (t, 2H), 2.42-2.37 (m, 2H), 2.22-2.17 (m, 2H), 2.13 (s, 3H), 2.10-2.04 (m, 2H), 1.99-1.96 (m, 2H), 1.86-1.83 (m, 2H), 0.87 (t, 3H). MS (EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00485] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [(4A)-(4AC)] were prepared. Alternative starting reagents were obtained commercially unless otherwise indicated.

[00486] (4B): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[3-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide. Prepared according to the method of example 4 by using (S)-1-(3-methoxyphenyl)ethanamine in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.72 (m, 1H), 8.60 (d, 1H), 8.18 (d, 1H), 8.13 (m, 1H), 7.22 (t, 1H), 7.11 (d, 1H), 6.98 (m, 1H), 6.94 (m, 2H), 6.80 (m, 2H), 5.12 (m, 1H), 4.66 (bs, 2H), 4.52 (m, 2H), 3.86 (m, 1H), 3.74 (s, 3H), 3.20 (m, 2H), 2.24 (m, 2H), 2.16 (s, 3H), 2.09 (m, 2H), 2.02 (m, 2H), 1.94 (m, 2H), 1.46 (d, 3H). MS (EI) for $C_{32}H_{36}N_4O_4$: 541 (MH^+).

[00487] (4C): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide. Prepared according to the method of example 4 by using (4-(4-methylpiperazin-1-yl)phenyl)methanamine in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.70 (t, 1H), 8.63 (d, 1H), 8.13 (d, 1H), 7.96 (dd, 1H), 7.15 (d, 2H), 7.11 (d, 1H), 6.88 (m, 2H), 6.80 (d, 1H), 6.74 (d, 1H), 4.58 (m, 4H), 4.34 (d, 2H), 3.82 (m, 1H), 3.20 (m, 2H), 3.08 (m, 4H), 2.43 (m, 4H), 2.21 (s, 3H), 2.20 (m, 2H), 2.13 (s, 3H), 2.07 (m, 2H), 1.97 (m, 2H), 1.84 (d, 2H). MS (EI) for $C_{35}H_{42}N_6O_3$: 595 (MH^+).

[00488] (4D): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Isolated as hydrochloride salt. Prepared according to the method of example 4 by using ammonia

in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, CD_3OD): 8.44 (d, 1H), 8.36 (d, 1H), 8.32 (dd, 1H), 7.29 (d, 1H), 7.10 (d, 1H), 6.85 (d, 1H), 4.71 (br s, 2H), 4.56 (t, 2H), 4.07 (m, 1H), 3.23 (t, 2H), 2.34 (m, 4H), 2.23 (m, 2H), 2.21 (s, 3H), 2.13 (d, 2H); MS (EI) for $C_{23}H_{26}N_4O_3$: 407 (MH^+).

[00489] (4E): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide. Prepared according to the method of example 4 by using (S)-1-(4-(4-methylpiperazin-1-yl)phenyl)ethanamine (synthesized according to reagent preparation 3) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, $CDCl_3$ w/ 10% CD_3OD): 8.59 (d, 1H), 7.88 (dd, 1H), 7.27 (d, 1H), 7.06 (d, 1H), 6.83 (dd, 4H),6.57 (d, 1H), 5.18 (m, 1H), 4.57 (t, 3H), 4.06 (m, 1H), 3.26 (t, 2H), 3.12 (dd, 4H), 2.70 (s, 4H), 2.55 (dd, 4H), 2.35-2.20 (br m, 8H), 2.19-2.04 (br m, 4H), 1.83 (br d, 2H), 1.51 (d, 3H), 1.41 (s, 2H). MS (EI) for $C_{36}H_{44}N_6O_3$: 609 (MH^+).

[00490] (4F): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{4-(4-methylpiperazin-1-yl)phenylmethyl}pyridine-3-carboxamide. Prepared according to the method of example 4 by using 4-(1-methylpiperidin-4-yl)benzylamine (synthesized according to reagent preparation 2) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, CD_3OD): 8.41 (d, 1H), 8.37 (dd, 1H), 7.38 (d, 1H), 7.31 (dd, 4H), 7.10 (d, 1H), 6.85 (d, 1H), 4.75 (br s, 2H), 4.57 (t, 2H), 4.55 (s, 2H), 4.09 (t, 1H), 3.60 (br d, 2H),3.21 (br m, 6H), 2.91 (s, 4H), 2.88 (s, 2H), 2.40-1.85 (br m, 11H).). MS (EI) for $C_{36}H_{43}N_5O_3$: 593 (MH^+).

[00491] (4G): N-[(4-{[2-(diethylamino)ethyl]oxy}phenyl)methyl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Prepared according to the method of example 4 by using 2-[4-(aminomethyl)phenoxy]-N,N-diethylethylamine (synthesized according to reagent preparation 4) in step 4, then omission of steps 5 and 6. ^{1}H NMR(400 MHz, CD_3OD): 8.40 (d, 1H), 8.39 (dd, 1H), 7.39- 7.33 (m, 3H), 7.11 (d, 1H), 7.01- 6.99 (m, 2H), 6.86 (d, 1H), 4.59 (s, 2H), 4.56- 4.36 (m, 4H), 4.34- 4.33 (m, 2H), 4.09 (t, 1H), 3.60 (q, 2H), 3.32-3.31(m, 3H), 3.23 (t, 2H), 2.38-2.33 (m, 4H), 2.32- 2.24 (m, 8H), 1.38(s, 2H), 1.37(s, 2H), 1.35 (s, 2H); MS(EI) for $C_{36}H_{45}N_5O_4$: 612 (MH^+).

[00492] (4H): N-(cyclopropylmethyl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide hydrochloride. Prepared according to the method of example 4 by using cyclopropylmethanamine in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.70-8.60 (br. s, 1H), 8.52-8.47 (s, 1H), 8.27-8.16 (d, 2H), 7.22-7.09 (m, 2H), 6.84-6.79 (d, 1H), 4.78-4.65 (br. s, 2H), 4.59-4.49 (m, 2H), 3.93-3.88 (m, 1H), 3.25-3.10 (m, 4H), 2.32-2.24 (d, 2H), 2.18-1.97 (m, 9H), 1.07-0.97 (m, 1H), 0.47-0.40 (m, 2H), 0.26-0.19 (m, 2H). MS (EI) for $C_{27}H_{32}N_4O_3$: 461 (MH^+).

[00493] (4I): N-[2-(diethylamino)ethyl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Isolated as hydrochloride salt. Prepared according to the method of example 4 by using N,N-diethylethane-1,2-diamine in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 9.08 (br s, 1H), 8.60 (s, 1H), 8.30-8.20 (m, 2H), 7.25-7.10 (m, 2H), 6.81 (d, 1H), 4.77 (br s, 2H), 4.54 (t, 2H), 3.87 (br s, 1H), 3.66-3.61 (m, 2H), 3.25-3.15 (m, 8H), 2.30-1.95 (m, 11H), 1.25-1.21 (t, 6H). MS (EI) for $C_{29}H_{39}N_5O_3$: 506 (MH^+).

[00494] (4J): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 4 by using (*R*)-1-methylpyrrolidin-3-amine in step 4, then omission of steps 5 and 6. ^{1}H NMR(400 MHz, CD_3OD): 8.50 (s, 1H), 8.40(s, 1H), 7.38 (d, 1H), 7.11 (d, 1H), 6.08 (d, 1H), 4.80(s, 2H), 4.65 (s, 1H), 4.55(t, 2H), 4.08-4.03 (m, 2H), 3.98-3.88(m, 1H), 3.77-3.75(m, 2H), 3.49-3.41(m, 2H), 3.34(t, 4H), 3.05(s, 1H), 2.98(s, 2H), 2.72-2.61 (m, 1H), 2.38- 2.19(m, 8H), 2.18 (s, 3H); MS(EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00495] (4K): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 4 by using (*S*)-1-methylpyrrolidin-3-amine in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, CD_3OD): 8.50(s, 1H), 8.40(s, 1H), 7.38 (d, 1H), 7.10 (d, 1H), 6.85 (d, 1H), 4.76 (s, 2H), 4.66-4.60(m, 1H), 4.57(t, 3H), 4.10-4.08(m, 2H), 3.80-3.77 (m, 2H), 3.46-3.40 (m, 1H), 3.23(t, 3H), 3.18 (s, 2H), 3.05 (s, 2H), 2.70-2.60(m, 1H), 2.38-2.19(m, 8H), 2.26 (s, 3H); MS(EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00496] (4L): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(1-methylpiperidin-4-yl)pyridine-3-carboxamide. Prepared according to the method of example 4 by using 1-methylpiperidin-4-amine in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.62-8.58 (s, 1H), 8.15-8.11 (d, 1H), 8.05-8.00 (d, 1H), 7.95-7.90 (d, 1H), 7.13-7.09 (d, 1H), 6.82-6.78 (d, 1H), 6.76-6.72 (d, 1H), 4.58-4.48 (m, 4H), 3.87-3.78 (m, 1H), 3.24-3.15 (m, 2H), 3.00-2.91 (m, 1H), 2.39-2.30 (br. s, 4H), 2.25-2.17 (d, 2H), 2.15-2.12 (s, 3H), 2.11-2.03 (m, 2H), 2.01-1.95 (m, 2H), 1.93-1.90 (s, 3H), 1.87-1.77 (m, 4H), 1.68-1.55 (m, 2H). MS (EI) for $C_{27}H_{37}N_5O_3$: 504 (MH^+).

[00497] (4M): N-[(1S)-1-(4-{[2-(diethylamino)ethyl]oxy}phenyl)ethyl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Prepared according to the method of example 4 by using (S)-2-[4-(1-aminoethyl)phenoxy]-N,N-diethylethylamine (synthesized according to reagent preparation 4) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, CD_3OD): 8.59 (d, 1H), 7.97 (dd, 1H), 7.35 (d, 2H), 7.09 (d, 1H), 6.97 (d, 2H), 6.84 (d, 1H), 6.75 (d, 1H), 5.22-5.14 (m, 1H), 4.64-4.52 (m, 4H), 4.30-4.26 (m, 2H), 4.01-3.94 (m, 1H), 3.51-3.43 (m, 2H), 3.27-3.15 (m, 6H), 2.33-2.09 (m, 9H), 1.89 (d, 2H), 1.53 (d, 3H), 1.31 (t, 6H); MS (EI) for $C_{37}H_{47}N_5O_4$: 626 (MH^+).

[00498] (4N): 7-methyl-N-(8-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2,3-dihydro-1-benzofuran-6-carboxamide. Prepared according to the method of example 4 by using 1-methylpiperazine in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.29 (d, 1H), 7.61 (dd, 1H), 7.05 (d, 1H), 6.81 (d, 1H), 6.54 (d, 1H), 6.22 (d, 1H), 4.60 (m, 4H), 4.24 (q, 1H), 3.39 (br s, 3H), 3.24 (t, 2H), 2.45 (br s, 3H), 2.37-2.12 (br m, 7H), 2.05-1.95 (br m, 3H), 1.81 (br d, 2H), 1.25 (s, 3H). MS (EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00499] (4O): N-(1-ethylpiperidin-3-yl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Prepared according to the method of example 4 by using 1-ethylpiperidin-3-amine in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.64 (br s, 1H), 7.96 (br s, 1H), 7.05 (d, 1H) 6.87 (d, 1H), 6.54 (d, 1H), 6.23 (d, 1H), 4.58 (m, 2H), 4.36-4.22 (br m, 2H), 3.24 (t, 2H), 2.75-2.15 (br m, 11H), 2.07-

1.95 (br m, 2H), 1.80 (br d, 4H), 1.60 (br s, 2H), 1.25 (s, 1H), 1.09 (br s, 2H)). MS (EI) for $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00500] (4P): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 4 by using (R)-1-isopropylpyrrolidin-3-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. ^1H NMR (400 MHz, DMSO-d_6): 8.61 (d, 1H), 8.27 (br s, 1H), 8.13 (d, 1H), 7.95 (dd, 1H), 7.11 (d, 1H), 6.80 (d, 1H), 6.76 (d, 1H), 4.56-4.51 (m, 4H), 4.41 (br m, 1H), 3.82 (br m, 1H), 3.20 (t, 2H), 2.23-2.17 (m, 2H), 2.13 (s, 3H), 2.11-2.04 (m, 2H), 2.01-1.96 (m, 2H), 1.87-1.82 (m, 2H), 1.13 (br m, 6H). MS (EI) for $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00501] (4Q): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-methylpiperidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 4 by using (S)-1-methylpiperidin-3-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. ^1H NMR (400 MHz, DMSO-d_6): 8.60 (s, 1H), 8.13 (d, 1H), 7.93 (dd, 1H), 7.11 (d, 1H), 6.80 (d, 1H), 6.76 (d, 1H), 4.56-4.51 (m, 4H), 3.84-3.79 (br m, 2H), 3.20 (t, 4H), 2.22-2.17 (m, 2H), 2.13 (s, 3H), 2.10-2.04 (m, 2H), 2.01-1.96 (m, 2H), 1.87-1.81 (m, 4H). MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00502] (4R): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-(1-methylethyl)pyrrolidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 4 by using (S)-1-isopropylpyrrolidin-3-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. ^1H NMR (400 MHz, $CDCl_3$): 8.64 (d, 1H), 7.95 (dd, 1H), 7.05 (d, 1H), 6.80 (d, 1H), 6.52 (d, 1H), 6.23 (d, 1H), 4.74 (br s, 1H), 4.60 (br s, 1H), 4.59 (t, 3H), 4.23 (q, 1H), 3.24 (t, 2H), 3.18 (br s, 1H), 2.98 (br d, 1H), 2.73 (dd, 1H), 2.59 m, 1H), 2.47-2.32 (br m, 3H), 2.24 (s, 3H), 2.25-2.19 (br m, 2H), 2.01 (q, 2H), 1.82 (d, 3H), 1.19 (t, 6H). MS (EI) for $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00503] (4S): N-[(3S)-1-ethylpyrrolidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Prepared according to the method of example 4 by using (S)-1-ethylpyrrolidin-3-amine (synthesized according to reagent preparation 9) in step 4,

then omission of steps 5 and 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.60 (d, 1H), 7.92 (d, 1H), 7.08 (d, 1H), 6.87 (d, 1H), 6.53 (d, 1H), 6.40 (d, 1H), 6.24 (d, 1H), 4.62 (m, 4H), 4.23 (q, 1H), 3.24 (t, 2H), 2.97 (m, 1H), 2.76 (br m, 1H), 2.55-2.45 (br m, 3H), 2.43-2.26 (br m, 6H), 2.25-2.18 (br m, 2H), 2.02 (m, 3H), 1.82 br d, 2H), 1.72 (m, 1H), 1.12 (t, 3H). MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00504] (4T): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]-amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[1-(1-methylethyl)piperidin-4-yl]pyridine-3-carboxamide. Prepared according to the method of example 4 by using 1-(1-methylethyl)piperidin-4-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (d, 1H), 7.91 (d, 1H), 7.05 (d, 1H), 6.87 (d, 1H), 6.53 (d, 1H), 6.21 (d, 1H), 5.77 (d, d, 1H), 4.60 (m, 4H), 4.22 (q, 1H), 3.98(m, 1H), 3.24 (t, 2H), 2.81 (d, 2H), 2.74 (m, 1H), 2.32 (m, 8H), 2.22 (m, 2H), 2.11-1.98 (br m, 4H), 1.82 (br m, 4H), 1.67 (br s, 2H), 1.52 (m, 2H), 1.05 (d, 6H). MS (EI) for $C_{31}H_{41}N_5O_3$: 532 (MH^+).

[00505] (4U): N-[1-ethylpiperidin-4-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Prepared according to the method of example 4 by using 1-ethylpiperidin-4-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.56 (d, 1H), 7.91 (d, 1H), 7.04 (d, 1H), 6.86 (d, 1H), 6.53 (d, 1H), 6.22 (d, 1H), 5.86 (d, 1H), 4.60 (m, 4H), 4.22 (q, 1H), 4.01 (m, 1H), 3.24 (t, 2H), 2.93 (br d, 2H), 2.47 (q, 2H), 2.37-2.28 (br m, 5H), 2.27-1.96 (br m, 6H), 1.81 (br d, 2H), 1.61 (m, 2H), 1.11 (t, 3H). MS (EI) for $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00506] (4V): N-[(3R)-1-ethylpiperidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Prepared according to the method of example 4 by using (R)-1-methylpiperidin-3-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (s, 1H), 8.13 (d, 1H), 7.93 (dd, 1H), 7.11 (d, 1H), 6.80 (d, 1H), 6.75 (d, 1H), 4.56-4.51 (m, 4H), 3.82 (br m, 1H), 3.20 (t, 2H), 2.22-2.17 (m, 2H), 2.14 (s, 3H), 2.10-2.04 (m, 2H), 2.00-1.96 (m, 2H), 1.87-1.81 (m, 4H), 1.07 (br m, 3H). MS (EI) for $C_{30}H_{39}N_5O_3$: 516 (M-H).

[00507] (4W): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[1-(1-methylethyl)azetidin-3-

yl]pyridine-3-carboxamide. Prepared according to the method of example 4 by using acetone in step 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (d, 1H), 8.50 (br s, 1H), 8.13 (d, 1H), 7.94 (dd, 1H), 7.11 (d, 1H), 6.80 (d, 1H), 6.75 (d, 1H), 4.56-4.51 (m, 4H), 4.40 (br m, 1H), 3.82 (br m, 1H), 3.61 (br s, 1H), 3.22-3.18 (m, 2H), 2.21-2.19 (m, 2H), 2.14 (s, 3H), 2.11-2.04 (m, 2H), 2.00-1.96 (m, 2H), 1.87-1.82 (m, 2H), 0.91 (d, 6H). MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00508] (4X): N-(1-methylazetidin-3-yl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Prepared according to the method of example 4 by using 1-methylazetidin-3-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (d, 1H), 8.48 (d, 1H), 8.13 (d, 1H), 7.94 (dd, 1H), 7.11 (d, 1H), 6.80 (d, 1H), 6.74 (d, 1H), 4.56-4.51 (m, 4H), 4.43-4.38 (m, 1H), 3.82 (br m, 1H), 3.56-3.52 (m, 2H), 3.22-3.18 (m, 4H), 2.94-2.91 (m, 2H), 2.34-2.32 (m, 1H), 2.24 (s, 3H), 2.14 (s, 3H), 2.10-2.05 (m, 2H), 1.99-1.95 (m, 2H). MS (EI) for $C_{27}H_{33}N_5O_3$: 476 (MH^+).

[00509] (4Y): N-[(3R)-1-ethylpyrrolidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Prepared according to the method of example 4 by using (R)-1-ethylpyrrolidin-3-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

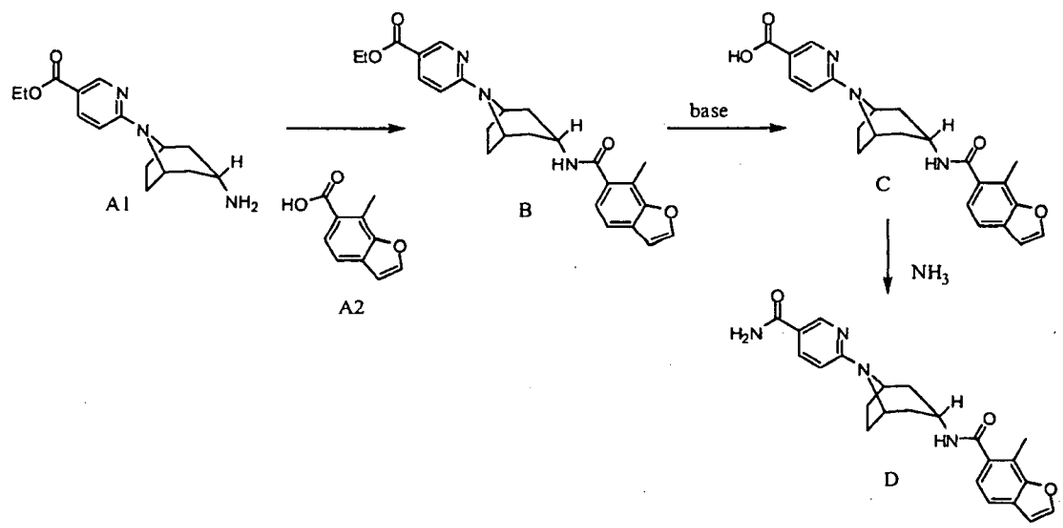
[00510] (4Z): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-(1-methylethyl)piperidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 4 by using (R)-1-isopropylpiperidin-3-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (s, 1H), 7.93 (d, 1H), 7.04 (d, 1H), 6.86 (d, 1H), 6.54 (d, 1H), 6.31 (d, 1H), 4.59 (m, 4H), 4.21 (m, 2H), 3.23 (t, 2H), 2.75 (m, 1H), 2.70-2.50 (br m, 3H), 2.40-1.45 (br m, 8H), 1.01 (dd, 6H). MS (EI) for $C_{31}H_{41}N_5O_3$: 532 (MH^+).

[00511] (4AA): N-[(3S)-1-ethylpiperidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide. Prepared according to the method of example 4 by using (S)-1-ethylpiperidin-3-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. MS (EI) for $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00512] (4AB): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-(1-methylethyl)piperidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 4 by using (S)-1-isopropylpiperidin-3-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.60 (d, 1H), 7.93 (d, 1H), 7.04 (d, 1H), 6.88 (d, 1H), 6.54 (d, 1H), 6.30 (d, 1H), 4.59 (m, 4H), 4.21 (m, 2H), 3.23 (t, 2H), 2.79-2.42 (br m, 4H), 2.39-2.30 (br m, 6H), 2.28-2.11 (br m, 2H), 2.03 (m, 2H), 1.92-1.44 (br m, 6H), 1.01 (dd, 6H). MS (EI) for $C_{31}H_{41}N_5O_3$: 532 (MH^+).

[00513] (4AC): 6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]-amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-methylpiperidin-3-yl]pyridine-3-carboxamide. Prepared according to the method of example 4 by using (R)-1-methylpiperidin-3-amine (synthesized according to reagent preparation 9) in step 4, then omission of steps 5 and 6. MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

SYNTHETIC SCHEME 5:



[00514] Scheme 5 generally describes the synthesis of all of the compound(s) listed in Example 5.

[00515] In Scheme 5, compound (A2) is added to compound (A1) under appropriate reaction conditions and with a suitable coupling reagent, such as HATU,

to condense and form the amide bond in compound (B). The carboxylate of compound B is hydrolyzed with a base, such as KOH, to form compound (C). To compound (C) is added NH_3 under appropriate reaction conditions to form compound (D).

[00516] EXAMPLE 5: 6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide.

[00517] STEP 1: A solution of ethyl 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylate (191 mg, 0.69 mmol, synthesized in example 1, step 2, 7-methyl-1-benzofuran-6-carboxylic acid (synthesized in reagent preparation 15) (122 mg, 0.69 mmol), HATU (262 mg, 0.69 mmol), and diisopropylethylamine (267 mg, 2.07 mmol) in DMF (5 mL) was stirred at room temperature for 23 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with saturated sodium bicarbonate (50 mL), 5% aqueous lithium chloride (2 x 20 mL), and brine (20 mL), dried over sodium sulfate, filtered and dried to give ethyl 6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylate (329 mg). ^{1}H NMR (400 MHz, DMSO-d_6): 8.66 (d, 1H), 8.26 (d, 1H), 8.09 (d, 1H), 7.93 (dd, 1H), 7.54 (d, 1H), 7.25 (d, 1H), 6.99 (d, 1H), 6.78 (d, 1H), 4.61 (br s, 2H), 4.25 (q, 2H), 3.91 (m, 1H), 2.53 (s, 3H), 2.26 (m, 2H), 2.10 (m, 2H), 2.01 (m, 2H), 1.91 (d, 2H), 1.29 (t, 3H); MS (EI) for $C_{25}H_{27}N_3O_4$: 434 (MH^+).

[00518] STEP 2: A suspension of ethyl 6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylate (324 mg, 0.75 mmol) and potassium hydroxide (84 mg, 1.50 mmol) in methanol (9 mL) and water (3 mL) was stirred at 60 °C for 3 h. After cooling to room temperature some of the methanol was evaporated, water was added to the resulting mixture, and the pH adjusted to 5 with 1N aqueous hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried to afford 6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylic acid (204 mg, 67% yield). ^{1}H NMR (400 MHz, DMSO-d_6): 12.47 (br s, 1H), 8.64 (d, 1H), 8.26 (d, 1H), 8.09 (d, 1H), 7.92 (dd, 1H), 7.55 (d, 1H), 7.25 (d, 1H), 7.00 (d, 1H), 6.77 (d, 1H), 4.60 (br s, 2H), 3.91 (m, 1H), 2.25 (m, 2H), 2.10 (m, 2H), 2.01 (m, 2H), 1.90 (d, 2H); MS (EI) for $C_{23}H_{23}N_3O_4$: 406 (MH^+).

[00519] STEP 3: Ammonia was bubbled through a solution of 6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-

carboxylic acid (70 mg, 0.17 mmol) and HATU (66 mg, 0.17 mmol) in DMF (3 mL) for 15 min, and the reaction mixture was stirred for 80 min at room temperature. Ammonia introduction was then repeated for another 15 min, and stirring at room temperature was continued for 22 h. The mixture was poured into water, the precipitated product was collected by filtration then further purified by preparatory reverse phase HPLC (0.1% aqueous trifluoroacetic acid-acetonitrile eluent). Pure fractions were concentrated and the residue lyophilized from 1N aqueous hydrochloric acid to provide 6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]-amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide hydrochloride (28 mg, 37% yield). ^{1}H NMR (400 MHz, methanol-d_4): 8.47 (d, 1H), 8.44 (d, 1H), 8.35 (dd, 1H), 7.86 (d, 1H), 7.53 (d, 1H), 7.35 (d, 1H), 7.27 (d, 1H), 6.87 (d, 1H), 4.75 (br s, 2H), 4.15 (m, 1H), 2.59 (s, 3H), 2.38 (m, 4H), 2.26 (m, 2H), 2.19 (d, 2H); MS (EI) for $C_{23}H_{24}N_4O_3$: 405 (MH^+).

[00520] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [(5B)-(5D)] were prepared. Alternative starting reagents were obtained commercially unless otherwise indicated.

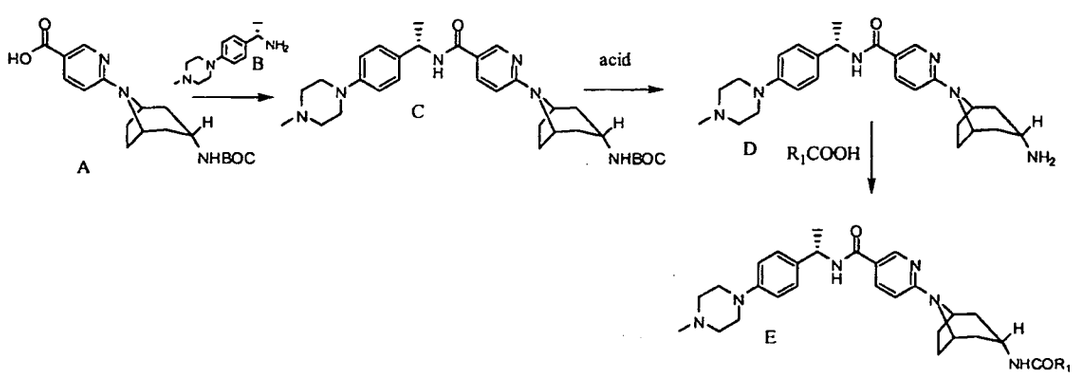
[00521] (5B): 6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide. Prepared according to the method of example 5 by using (1S)-1-[4-(4-methylpiperizin-1-yl)phenyl]ethanamine (synthesized according to reagent preparation 3) in step 3. ^{1}H NMR (400 MHz, $CDCl_3$): 8.56 (d, 1H), 7.86 (d, 1H), 7.71 (d, 1H), 7.45 (d,1H), 7.27 (m, 1H), 6.90 (d, 2H), 6.78 (d, 1H), 6.51 (d, 1HH), 6.32 (d, 1H), 6.14 (1H), 5.25 (m, 1H), 4.61 (br s, 2H), 4.25 (q, 1H), 3.47 (s, 2H), 3.21 (m, 4H), 2.41-2.29 (br m, 5H), 2.27-2.18 (br m, 2H), 2.09-1.98 (br m, 2H), 1.56 (d, 3H). MS (EI) for $C_{36}H_{42}N_6O_3$: 606 (MH^+).

[00522] (5C): 6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(1-methylpiperidin-4-yl)phenyl]methyl}pyridine-3-carboxamide. Prepared according to the method of example 5 by using 4-(1-methylpiperidin-4-yl)benzylamine (synthesized according to reagent preparation 2) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 10.25 (d, 1H), 8.82 (t, 1H), 8.65 (d, 1H), 8.25 (d, 1H), 8.09 (d, 1H), 7.98 (d, 1H), 7.54 (m, 1H), 7.54 (d, 1H), 7.38-7.17 (br m, 5H), 7.00 (d, 1H), 6.76 (d, 1H), 4.56 (s, 2H), 4.42 (d, 2H), 4.11 (br s, 1H), 3.88 (br s,

1H), 3.47 (d, 2H), 3.17 (s, 3H), 3.04 (br s, 2H), 2.52 (s, 3H), 2.25 (d, 1H), 2.16-1.81 (br m, 6H). MS (EI) for $C_{36}H_{41}N_5O_3$: 592 (MH^+).

[00523] (5D): 6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide. Prepared as the hydrochloride salt according to the method of example 5 by using 4-(4-methylpiperazin-1-yl)benzylamine in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 10.95 (br s, 1H), 9.32 (br s, 1H), 8.53 (s, 1H), 8.38-8.32 (m, 2H), 8.10 (s, 1H), 7.55 (d, 2H), 7.36 (d, 1H), 7.27-7.21 (m, 3H), 7.00-6.95 (m, 3H), 4.56 (br s, 2H), 3.96 (br s, 1H), 3.77 (d, 2H), 3.45 (d, 2H), 3.17-3.02 (m, 4H), 2.79 (s, 3H), 2.53 (2, 3H), 2.36-2.32 (m, 2H), 2.24-2.01 (m, 6H). MS (EI) for $C_{35}H_{40}N_6O_3$: 593 (MH^+).

SYNTHETIC SCHEME 6:



[00524] Scheme 6 generally describes the synthesis of all of the compound(s) listed in Example 6, wherein R_1 is as defined in the specification.

[00525] To compound (A) is added compound (B) under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (C). Compound (C) is deprotected to form compound (D) under acidic conditions, such as with the use of HCl. To compound (D) is added R_1COOH under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (E).

[00526] EXAMPLE 6: 6-(3-endo-{[(3-hydroxy-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide.

[00527] STEP 1: A solution of 6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}-amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (prepared in example 2) (164 mg, 0.47 mmol), (1*S*)-1-[4-(4-methylpiperazine-1-yl)phenyl]ethanamine dihydrochloride (synthesized according to reagent preparation 3) (140 mg, 0.47 mmol), HATU (180 mg, 0.47 mmol) and *N*-methylmorpholine (516 µl, 4.7 mmol) in dimethylformamide (3 mL) was heated at 40°C for 15 hours. On cooling to room temperature the solution was diluted with ethyl acetate, then washed with 5% aqueous lithium chloride, 0.5N aqueous sodium hydroxide, brine, and then dried over anhydrous sodium sulfate. Filtration and concentration afforded an orange residue which was purified by silica gel column chromatography eluting with 5-10% methanol in dichloromethane. Pure fractions were pooled and concentrated to afford 192 mg, 0.35 mmol (74%) of 1,1-dimethylethyl (8-{5-[({(1*S*)-1-[4-(4-methylpiperazine-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)carbamate as a yellow foam. MS (EI) for $C_{31}H_{44}N_6O_3$: 549 (MH^+).

[00528] STEP 2: To a solution of 1,1-dimethylethyl (8-{5-[({(1S)-1-[4-(4-methylpiperazine-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)carbamate (192 mg, 0.35 mmol) in methanol (5 mL) was added a solution of 4N hydrogen chloride in dioxane (2 mL), and the reaction mixture was refluxed for 2 min. After cooling to room temperature the mixture was diluted with ethyl acetate and basified using 1N aqueous sodium hydroxide until the pH reached 10. The layers were separated, and the aqueous layer was further extracted using ethyl acetate. The combined organic layers were washed with brine then dried over anhydrous sodium sulfate. Filtration and concentration afforded a colorless residue which was purified by silica gel column chromatography eluting with 5-10% of a (10% concentrated aqueous ammonia solution in methanol) in chloroform. Pure fractions were pooled and concentrated to give 6-(3-endo-[amino]-8-azabicyclo[3.2.1]oct-8-yl)-*N*-{(1*S*)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (d, 1H), 7.84 (dd, 1H), 7.29 (s, 1H), 6.90 (d, 2H), 6.47 (d, 1H), 6.01 (d, 1H), 5.28-5.21 (m, 1H), 4.51 (br s, 2H), 3.26-3.18 (m, 5H), 2.58-2.55 (m, 4H), 2.35 (s, 3H), 2.33-2.28 (m, 2H), 2.19-2.13 (m, 2H), 2.09-2.04 (m, 2H), 1.56 (d, 3H), 1.48-1.44 (m, 2H). MS (EI) for $C_{26}H_{36}N_6O_1$: 449 (MH^+).

[00529] STEP 3: A solution of 6-(3-endo-[amino]-8-azabicyclo[3.2.1]oct-8-yl)-*N*-{(1*S*)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide, 3-Hydroxy-2-methylbenzoic acid (8.5 mg, 0.06 mmol), HATU (22 mg, 0.06 mmol), and *N*-methylmorpholine (18 µl, 0.17 mmol) in dimethylformamide (1 mL) was stirred at 40°C for 15 hours. The reaction mixture was purified by preparative reverse phase HPLC (ammonium acetate buffered aqueous acetonile eluent) to afford 17 mg, 0.03 mmol (50%) of 6-(3-endo-{[(3-hydroxy-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide acetate salt. ^{1}H NMR (400 MHz, d_6-DMSO): 9.48 (s, 1H), 8.62 (s, 1H), 8.43 (d, 1H), 8.16 (d, 1H), 7.96 (dd 1H), 7.22 (d, 2H), 7.06-7.02 (m, 1H), 6.91-6.83 (m, 3H), 6.75-6.70 (m, 2H), 5.11-5.04 (m, 1H), 4.53 (br s, 2H), 4.53 (d, 2H), 3.81 (br s, 1H), 3.71-3.10 (m, 4H), 2.67-2.56 (m, 2H), 2.37-2.31 (m, 2H), 2.25-2.17 (m, 2H), 2.11-1.82 (m, 12H), 1.42 (d, 3H). MS (EI) for $C_{34}H_{42}N_6O_3$: 583 (MH^+).

[00530] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [(6B-6U)] were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00531] (6B): N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)- carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1,3-benzothiazole-5-carboxamide. Prepared as the acetate salt according to the method of example 6 by using benzothiazole-5-carboxylic acid in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 9.51 (s, 1H), 8.64 (d, 1H), 8.52 (d, 1H), 8.44 (d, 1H), 8.41 (d, 1H), 8.28 (d, 1H), 7.99 (dd, 1H), 7.91 (dd, 1H), 7.22 (d, 2H), 6.88 (d, 2H), 6.77 (d, 1H), 5.05-5.12 (m, 1H), 4.59 (br s, 2H), 3.90 (br s, 1H), 3.08 (t, 4H), 2.43 (t, 4H), 2.24-2.29 (m, 2H), 2.21 (s, 3H), 2.10-2.15 (m, 2H), 2.03-2.05 (m, 2H), 1.98 (s, 1H), 1.94 (s, 1H), 1.43 (d, 3H). MS (EI) for $C_{34}H_{39}N_7O_2S$: 610 (MH^+).

[00532] (6C): 6-(3-endo-{[(8-methyl-3,4-dihydro-2H-chromen-7-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide. Prepared as the acetate salt according to the method of example 6 by using 8-methyl-3,4-dihydro-2H-chromene-7-carboxylic acid (Sawada, Y. et al, *Pest Management Science*, **2003**, 59(*1*), 36-48.) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.42 (d, 1H), 8.11 (d, 1H), 7.96 (dd, 1H), 7.20 (d, 2H), 6.94-6.86 (m, 1H), 6.73 (d, 2H), 5.10-5.04 (m, 1H), 4.53 (br s, 2H), 4.20-4.16

(m, 2H), 3.80 (br s, 1H), 3.10-3.06 (m, 4H), 2.76-2.73 (m, 2H), 2.44-2.41 (m, 4H), 2.20-2.02 (m, 10H), 2.00-1.81 (m, 9H), 1.41 (d, 3H). MS (EI) for $C_{37}H_{46}N_6O_3$: 623 (MH^+).

[00533] (6D): 6-[3-endo-({[2-methyl-3-(methylthio)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide. Prepared as the trifluoracetate salt according to the method of example 6 by using 2-methyl-3-(methylthio)benzoic acid (synthesized according to reagent preparation 33) in step 3. ^{1}H NMR (400 MHz, $CDCl_3$): 8.56 (d, 1H), 7.87 (dd, 1H), 7.32-7.27 (m, 3H), 7.22-7.18 (m, 1H), 7.13-7.11 (m, 1H), 6.93 (d, 2H), 6.52 (d, 1H), 6.18 (d, 1H), 6.06 (d, 1H), 5.30-5.22 (m, 1H), 4.60 (br s, 2H), 4.27-4.22 (m, 1H), 3.22-2.96 (m, 4H), 2.66 (s, 3H), 2.60-2.55 (m, 4H), 2.42 (s, 3H), 2.35-2.30 (m, 5H), 2.24-2.18 (m, 2H), 2.02-1.94 (m, 2H), 1.84-1.78 (m, 2H), 1.56 (d, 3H). MS (EI) for $C_{35}H_{44}N_6O_2S$: 613 (MH^+).

[00534] (6E): 2-methyl-3-(methyloxy)-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared as the trifluoroacetate salt according to the method of example 6 by using 4-(aminocarbonyl)-2-methyl-3-(methyloxy)benzoic acid (synthesized according to reagent preparation 34) in step 3. ^{1}H NMR (400 MHz, CD_3OD): 8.71 (d, 1H), 8.56-8.48 (m, 2H), 8.17 (d, 1H), 7.69 (d, 1H), 7.33 (d, 2H), 7.19 (d, 1H), 7.08-7.00 (m, 3H), 5.19-5.13 (m, 1H), 4.66 (br s, 2H), 4.10-4.03 (m, 1H), 3.87-3.78 (m, 4H), 3.63-3.55 (m, 2H), 3.04-2.94 (m, 4H), 2.38-2.15 (m, 8H), 2.06-1.99 (m, 2H), 1.54 (d, 3H), 1.34-1.26 (m, 2H). MS (EI) for $C_{36}H_{45}N_7O_4$: 640 (MH^+).

[00535] (6F): 6-{3-endo-[({3-[(4-hydroxycyclohexyl)amino]phenyl}-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide. Prepared according to the method of example 6 by using 3-[(trans-4-hydroxycyclohexyl)amino]benzoic acid (synthesized according to reagent preparation 37) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (d, 1H), 8.43 (d, 1H), 8.02 (d, 1H), 7.97 (dd, 1H), 7.21 (d, 2H), 7.13 (t, 1H), 6.84-6.89 (m, 4H), 6.75 (d, 1H), 6.67-6.70 (m, 1H), 5.64 (d, 1H), 5.04-5.11 (m, 1H), 4.56 (br s, 2H), 3.81 (br s, 1H), 3.34 (s, 5H), 3.08 (t, 4H), 2.49-2.51 (m, 6H), 2.21 (s, 5H), 1.82-2.02 (m, 6H), 1.62 (s, 1H), 1.42 (d, 3H), 1.12-1.31 (m, 3H). MS (EI) for $C_{39}H_{51}N_7O_3$: 666 (MH^+).

[00536] (6G): N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-(phenylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 6 by using 4-(aminocarbonyl)-3-(phenylamino)benzoic acid (synthesized according to reagent preparation 39) in step 3. MS (EI) for $C_{14}H_{12}N_2O_3$: 257 (MH^+); ^{1}HNMR (400MHz, d_4-methanol): 8.49, (d, 1H), 7.85 (dd, 1H), 7.63 (dd, 1H), 7.55 (d, 1H), 7.25-7.15 (m, 6H), 6.97 (m, 2H), 6.86 (d, 2H), 6.61 (d, 1H), 5.06 (q, 1H), 4.47 (br, 2H), 3.85 (tr, 1H), 3.14 (br, 4H), 2.73 (br, 4H), 2.41 (s, 3H), 2.13-1.97 (m, 6H), 1.81 (d, 2H), 1.42 (d, 3H); MS (EI) for $C_{40}H_{46}N_8O_3$: 689 (MH^+).

[00537] (6H): 1,4-dimethyl-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole-5-carboxamide. Prepared as the acetate salt according to the method of example 6 by using 1,4-dimethyl-1H-benzimidazole-5-carboxylic acid (synthesized according to reagent preparation 35) in step 3. ^{1}HNMR (400MHz, d_4-methanol): 8.60 (d, 1H), 8.18 (s, 1H), 7.96 (dd, 1H), 7.45 (d, 1H), 7.35 (d, 1H), 7.29 (d, 2H), 6.95 (d, 2H), 6.74 (d, 1H), 5.17 (q, 1H), 4.61 (br, 2H), 4.04 (tr, 1H), 3.90 (s, 3H), 3.22 (br, 4H), 2.78 (br, 4H), 2.68 (s, 3H), 2.47 (s, 3H), 2.35-2.10 (m, 5H), 1.95 (br, 1H), 1.93 (s, 3H), 1.92 (br, 1H), 1.52 (d, 3H); MS (EI) for $C_{36}H_{44}N_8O_2$: 621 (MH^+).

[00538] (6I): 4-methyl-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1H-1,2,3-benzotriazole-5-carboxamide. Prepared according to the method of example 6 by using 4-methyl-1H-benzotriazole-5-carboxylic acid (synthesized according to reagent preparation 22) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (d, 1H), 8.43 (d, 1H), 8.26 (d, 1H), 7.97 (dd, 1H), 7.71 (d, 1H), 7.31 (d, 1H), 7.21 (d, 2H), 6.88 (d, 2H), 6.75 (d, 1H), 5.08 (m, 1H), 4.56 (broad s, 2H), 3.90 (m, 1H), 3.08 (m, 4H), 2.69 (s, 3H), 2.43 (m, 4H), 2.24 (d, 2H), 2.21 (s, 3H), 2.13 (m, 2H), 2.01 (m, 2H), 1.84 (m, 6H), 1.42 (d, 3H). MS (EI) for $C_{34}H_{41}N_9O_2$: 608 (MH^+).

[00539] (6J): 2-(methyloxy)-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared according to the method of example 6 by using 4-(aminocarbonyl)-3-(methyloxy)benzoic acid (synthesized according to reagent preparation 26) in step 3. ^{1}H NMR (CD_3OD): 8.60 (s, 1H), 8.46 (d, 1H), 8.03-7.96 (m, 2H), 7.52 (s, 1H), 7.44 (d, 1H), 7.40 (d, 1H), 6.99-6.97 (m, 2H), 6.78

(d, 1H), 5.18-5.16 (m, 1H), 4.04 (s, 2H), 4.03-4.00 (m,4 H), 3.05 (s, 3H), 2.31-2.16 (m, 6H), 1.97-1.93 (m, 2H), 1.53 (d, 3H). MS (EI) for $C_{35}H_{43}N_7O_4$: 626 (MH^+).

[00540] (6K): 2-(cyclobutyloxy)-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared as the trifluoroacetate salt according to the method of example 6 by using 4-(aminocarbonyl)-3-(cyclobutyloxy)benzoic acid (synthesized according to reagent preparation 25) in step 3. ^{1}H NMR (CD_3OD): 8.46 (d, 1H), 8.23 (d, 1H), 8.28 (d, 1H), 8.04 (d, 1H), 7.43 (d, 1H), 7.34-7.32 (m, 3H), 7.23 (d, 1H), 7.01-6.99 (m, 1H), 5.18-5.17 (m, 1H), 4.73 (s, 2H), 4.08 (s, 1H), 3.84 (d, 2H), 3.58 (d, 2H), 3.29-3.25 (m, 4H), 3.06-2.98 (m, 4H), 2.58-2.54 (m, 2H), 2.37-2.26 (m, 4H), 2.17 (d, 2H), 1.95-1.93 (m, 1H), 1.92-1.81 (m, 1H), 1.78-1.53 (m, 3H). MS (EI) for $C_{38}H_{47}N_7O_4$: 666(MH^+).

[00541] (6L): 6-[3-endo-({[2-methyl-3-(methylamino)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide. Prepared as the acetate salt according to the method of example 6 by using 2-methyl-3-(methylamino)benzoic acid (synthesized according to reagent preparation 31) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (s, 1H), 8.44-8.40 (d, 1H), 8.10 (s, 1H), 7.99-7.94 (d, 1H), 7.24-7.18 (d, 2H), 7.09-7.04 (m, 1H), 6.91-6.85 (d, 2H), 6.76-6.71 (d, 1H), 6.55-6.49 (m, 2H), 5.19-5.16 (br. s, 1H), 5.11-5.02 (m, 1H), 4.58-4.50 (br. s, 2H), 3.85-3.77 (m, 1H), 3.16 (s, 3H), 3.11-3.05 (m, 4H), 2.75-2.71 (m, 2H), 2.46-2.40 (m, 2H), 2.23-2.16 (m, 5H), 2.12-2.00 (m, 5H), 1.99-1.94 (m, 2H), 1.89-1.81 (m, 5H), 1.44-1.39 (d, 3H). MS (EI) for $C_{35}H_{45}N_7O_2$: 596 (MH^+).

[00542] (6M): 6-[3-endo-({[3-(dimethylamino)-2-methylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide. Prepared as the acetate salt according to the method of example 6 by using 3-(dimethylamino)-2-methylbenzoic acid (synthesized according to reagent preparation 32) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (s, 1H), 8.44-8.40 (d, 1H), 8.21 (s, 1H), 7.99-7.94 (d, 1H), 7.25-7.17 (m, 3H), 7.13-7.09 (d, 1H), 6.95-6.91 (d, 1H), 6.91-6.85 (d, 2H), 6.76-6.71 (d, 1H), 5.11-5.02 (m, 1H), 4.58-4.50 (br. s, 2H), 3.87-3.80 (m, 1H), 3.16 (s, 3H), 3.11-3.05 (m, 4H), 2.63 (s, 6H), 2.46-2.40 (m, 4H), 2.26-2.18 (m, 5H), 2.15-

2.05 (m, 2H), 2.02-1.93 (m, 2H), 1.89-1.81 (m, 5H), 1.44-1.39 (d, 3H). MS (EI) for $C_{36}H_{47}N_7O_2$: 610 (MH^+).

[00543] (6N): N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}-amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-(pyridin-4-ylamino)benzene-1,4-dicarboxylate. Prepared as the trifluoroacetate salt according to the method of example 6 by using 4-aminocarbonyl-3-(pyridine-4-ylamino)benzoic acid (synthesized according to reagent preparation 39) in step 3. ^{1}H NMR (400 MHz, d_4-methanol): 8.42 (d, 1H), 8.38 (d, 1H), 8.18-8.10 (m, 3H), 7.81-7.71 (m, 3H), 7.26-7.22 (m, 2H), 7.11-7.06 (m, 3H), 6.94-6.88 (m, 2H), 5.11-5.04 (m, 1H), 4.64 (br s, 2H), 4.00 (br s, 2H), 3.77-3.68 (m, 2H), 3.55-3.46 (m, 2H), 3.21-3.12 (m, 2H), 2.99-2.85 (m, 5H), 2.31-1.98 (m, 8H), 1.45 (d, 3H); MS (EI) for $C_{39}H_{45}N_9O_3$: 688 (MH^+).

[00544] (6O): N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}-amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[1-(methylsulfonyl)piperidin-4-yl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 6 by using 4-aminocarbonyl-3-(1-methylsulfonyl)piperidin-4-ylamino)benzoic acid (synthesized according to reagent preparation 39) in step 3. ^{1}H NMR (400 MHz, d_4-methanol): 8.50 (d, 1H), 7.88 (dd, 1H), 7.57 (d, 1H), 7.22-7.17 (m, 2H), 7.02 (br s, 1H), 6.89-6.82 (m, 3H), 6.66 (d, 1H), 5.11-5.04 (m, 1H), 4.53 (br s, 2H), 3.93-3.86 (m, 1H), 3.61-3.47 (m, 2H), 3.16-3.09 (m, 4H), 3.02-2.92 (m, 2H), 2.76 (s, 3H), 2.70-2.63 (m, 4H), 2.36 (s, 3H), 2.25-1.99 (m, 8H), 1.91-1.79 (m, 3H), 1.63-1.46 (m, 2H), 1.43 (d, 3H); MS (EI) for $C_{40}H_{53}N_9O_5S$: 772 (MH^+).

[00545] (6P): 2-(cyclobutylamino)-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared as the trifluoroacetate salt according to the method of example 6 by using 4-aminocarbonyl-3-(cyclobutylamino)benzoic acid (synthesized according to reagent preparation 39) in step 3. ^{1}H NMR (400 MHz, d_4-methanol): 8.45 (d, 1H), 8.34-8.28 (m, 2H), 7.64 (d, 1H), 7.35-7.31 (m, 2H), 7.28-7.23 (m, 1H), 7.03-6.98 (m, 2H), 6.96-6.93 (m, 1H), 6.92-6.90 (m, 1H), 5.20-5.14 (m, 1H), 4.73 (br s, 2H), 4.11-3.98 (m, 2H), 3.86-3.78 (m, 2H), 3.64-3.54 (m, 2H), 3.29-3.21 (m, 2H), 3.07-2.94 (m, 5H), 2.54-2.11 (m, 8H), 2.00-1.80 (m, 4H), 1.54 (d, 3H); MS (EI) for $C_{38}H_{48}N_8O_3$: 665 (MH^+).

[00546] (6Q): N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[3,4,5-tris(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 6 by using 4-aminocarbonyl-3-(3,4,5-trimethoxyphenylamino)benzoic acid (synthesized according to reagent preparation 39) in step 3. ^{1}H NMR (400 MHz, d_4-methanol): 8.58 (d, 1H), 7.95 (dd, 2H), 7.72 (d, 1H), 7.54 (d, 2H), 7.31-7.27 (m, 1H), 7.08 (dd, 2H), 6.98-6.93 (m, 2H), 6.72 (d, 1H), 6.55 (s, 2H), 5.19-5.12 (m, 1H), 4.57 (br s, 2H), 3.97-3.90 (m, 1H), 3.81 (s, 6H), 3.74 (s, 3H), 3.27-3.21 (m, 4H), 2.89-2.82 (m, 4H), 2.52 (s, 3H), 2.26-2.16 (m, 2H), 2.09 (br s, 4H), 1.96 (s, 3H), 1.89 (d, 2H), 1.52 (d, 3H); MS (EI) for $C_{43}H_{52}N_8O_6$: 777 (MH^+).

[00547] (6R): 3-(ethylamino)-2,5-dimethyl-N1-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 6 by using 4-(aminocarbonyl)-3-(ethylamino)-2,5-dimethylbenzoic acid (synthesized according to reagent preparation 36) in step 3. ^{1}H NMR (400 MHz, CD_3OD): 8.59 (d, 1H), 7.97 (dd, 1H), 7.29 (d, 2H), 6.96 (d, 2H), 6.76 (s, 1H), 6.75 (d, 1H), 5.17 (q, 1H), 4.60 (br, 2H), 3.99 (t, 1H), 3.28-3.19 (m, 4H), 3.11 (q, 2H), 2.79-2.74 (m, 4H), 2.45 (s, 3H), 2.34-2.26 (m, 2H), 2.32 (s, 3H), 2.23-2.09 (m, 4H), 2.22 (s, 3H), 1.93-1.86 (m, 2H), 1.52 (d, 3H), 1.17 (t, 3H); MS (EI) for $C_{38}H_{50}N_8O_3$: 667 (MH^+).

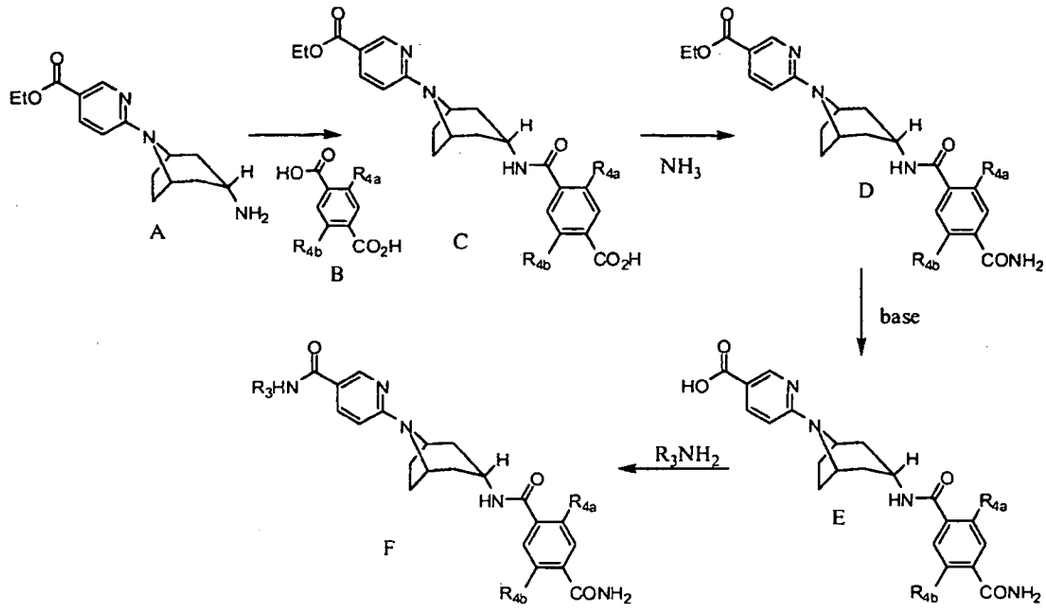
[00548] (6S): 2-[(4-hydroxycyclohexyl)amino]-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared according to the method of example 6 by using 4-(aminocarbonyl)-3-[(trans-4-hydroxycyclohexyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 3. ^{1}H NMR (400 MHz, d_4-methanol): 8.60 (d, 1H), 7.97 (dd, 1H), 7.62 (d, 1H), 7.31 (d, 2H), 7.07 (s, 1H), 6.98 (d, 2H), 6.89 (dd, 2H), 6.75 (d, 1H), 5.16 (m, 1H), 4.63 (br s, 2H), 3.99 (m, 1H), 3.63 (m, 1H), 3.41 (m, 1H), 3.03 (m, 4H), 2.70 (s, 3H), 2.30-2.12 (m, 8H), 1.98 (m, 4H), 1.53 (d, 3H), 1.50-1.26 (m, 4H); MS (EI) for $C_{40}H_{52}N_8O_4$: 709 (MH^+).

[00549] (6T): N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}-amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[2-

(methylsulfonyl)ethyl]amino}benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 6 by using 4-(aminocarbonyl)-3-{[2-(methylsulfonyl)ethyl]amino}benzoic acid (synthesized according to reagent preparation 39) in step 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (d, 1H), 8.43 (d, 1H), 8.32 (m, 1H), 8.19 (d, 1H), 7.98 (m, 2H), 7.69 (d, 1H), 7.36 (br s, 1H), 7.21 (d, 2H), 7.01 (s, 1H), 6.95 (d, 1H), 6.88 (d, 2H), 6.76 (d, 1H), 5.08 (m, 1H), 4.57 (br s, 2H), 3.83 (br s, 1H), 3.66 (m, 2H), 3.46 (t, 2H), 3.07 (m, 4H), 3.03 (s, 3H), 2.43 (m, 4H), 2.22 (m, 2H), 2.20 (s, 3H), 2.08 (m, 2H), 2.01 (m, 2H), 1.91 (s, 3H), 1.87 (m, 2H), 1.42 (d, 3H); MS (EI) for $C_{37}H_{48}N_8O_5S$: 717 (MH^+).

[00550] (6U): 2-[(cyclopropylmethyl)amino]-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 6 by using 4-(aminocarbonyl)-3-[(cyclopropylmethyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 3. ^{1}HNMR (400MHz, d_4-methanol): 8.59, (d, 1H), 7.96 (dd, 1H), 7.62 (dd, 1H), 7.29 (d, 2H), 7.05 (br s, 1H), 6.98-6.89 (m, 3H), 6.75 (d, 1H), 5.20-5.14 (m, 1H),4.62 (br s, 2H), 4.01-3.95 (m, 1H), 3.28-3.22 (m, 4H), 3.08 (d, 2H), 2.92-2.87 (m, 4H), 2.56 (s, 3H), 2.30-2.14 (m, 6H), 1.98-1.92 (m, 3H), 1.52 (d, 3H), 1.20-1.11(m, 1H), 0.60-.055 (m, 2H), 0.31-0.26 (m, 2H); MS (EI) for $C_{38}H_{48}N_8O_3$: 665 (MH^+).

SYNTHETIC SCHEME 7:



[00551] Scheme 7 generally describes the synthesis of all of the compound(s) listed in Example 7, wherein R_3, R_{4a}, and R_{4b} are as defined in the specification. This scheme is applicable when R_{4a} and R_{4b} are the same.

[00552] In Scheme 7, to compound (A) is added compound (B) under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (C). To compound (C) is added NH_3 under appropriate reaction conditions to form compound (D). The carboxylate of compound (D) is then hydrolyzed with a base, such as LiOH, to form compound (E). To compound (E) is added R_3NH_2 and a suitable coupling agent, such as HOBT and EDCI, under appropriate reaction conditions to form compound (F).

[00553] EXAMPLE 7: 2,5-dimethyl-N-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide

[00554] STEP 1: A solution of 2,5-Dimethylbenzene-1,4-dicarboxylic acid (1.14 g, 5.86 mmol), 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (2.23 g, 5.86 mmol) and N,N-diisopropylethylamine (4.7 mL, 27 mmol) in N,N-dimethylformamide (20 mL) was stirred at room temperature for 30 minutes. Then ethyl 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-

carboxylate hydrochloride (prepared in example 1) (1.66 g, 5.32 mmol) was added and the resultant solution was stirred at 50°C for 12 hours. On cooling to room temperature, the solution was concentrated *in vacuo*. The residue was split into two portions and both portions were taken up in 10 mL N,N-dimethylformamide, and 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (1.11 g, 2.93 mmol) and N,N-diisopropylethylamine (2.3 mL, 13 mmol) were added to each. The solutions were warmed to 50°C and ammonia (gas) was bubbled through the solutions for 20 minutes. The solutions were combined, then the solvent was removed *in vacuo*. The crude material was partitioned between water and 10% methanol in dichloromethane. The layers were separated and the aqueous layer was extracted (2 x 100 mL dichloromethane). The combined organic layers were dried (magnesium sulfate), filtered and concentrated. The crude solid was triturated with methanol/hexanes/ethyl acetate and the solid collected by filtration to give ethyl 6-[3-endo-({[4-(aminocarbonyl)-2,5-dimethylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (1.79 g, 75% yield). ^{1}H NMR (400 MHz, d_6-DMSO): 8.58 (d, 1H), 8.28 (d, 1H), 8.01 (dd, 1H), 7.70 (br s, 1H), 7.40 (br s, 1H), 7.24 (s, 1H), 7.13 (s, 1H), 6.93 (d, 1H), 4.64 (broad s, 2H), 4.27 (q, 2H), 3.88 (m, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 2.24 (m, 2H), 2.13 (m, 2H), 2.01 (m, 2H), 1.93 (d, 2H), 1.30 (t, 3H). MS (EI) for $C_{25}H_{38}N_4O_4$: 451 (MH^+).

[00555] STEP 2: To a solution of ethyl 6-[3-endo-({[4-(aminocarbonyl)-2,5-dimethylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (1.00 g, 2.21 mmol) in methanol (6.0 mL) and tetrahydrofuran (6.0 mL) was added 3.0 mL of 2.0 M lithium hydroxide (aqueous) and the resultant solution was warmed to 50°C for one hour. The organic solvents were removed *in vacuo*, and the remaining aqueous solution was brought to pH 2 using concentrated aqueous hydrochloric acid. The solid thus formed was collected by filtration and dried *in vacuo* to give 1.18 g (70% yield) of the desired 6-[3-endo-({[4-(aminocarbonyl)-2,5-dimethylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid, which was used without further purification in step 3.

[00556] STEP 3: A solution of 6-[3-endo-({[4-(aminocarbonyl)-2,5-dimethylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (0.050 g, 0.12 mmol), (3*R*)-1-(1-methylethyl)pyrrolidin-3-amine hydrochloride (synthesized in reagent preparation 9) (0.14 mmol), 1-hydroxybenzotriazole (0.019 g,

0.14 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.027 g, 0.14 mmol), and 4-methylmorpholine (0.05 mL, 0.5 mmol) in N,N-dimethylformamide (2.0 mL) was stirred at room temperature for 12 hours. The solution was then diluted with water and purified by HPLC (reverse-phase, acetonitrile/water with 0.1% ammonium acetate). Concentration *in vacuo* and lyophilization from water gave 0.034 g (54% yield) of the desired 2,5-dimethyl-N-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide as the acetate salt. ^{1}H NMR (400 MHz, d_6-DMSO): 8.61 (d, 1H), 8.22 (dd, 1H), 7.98 (dd, 1H), 7.70 (broad s, 1H), 7.40 (broad s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (broad s, 2H), 4.35 (m, 1H), 3.84 (m, 1H), 2.81 (t, 1H), 2.67 (t, 1H), 2.44 (m, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 2.19 (m, 2H), 2.10 (m, 4H), 1.98 (m, 2H), 1.91 (s, 3H), 1.83 (m, 2H), 1.73 (m, 2H), 1.02 (t, 6H). MS (EI) for $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00557] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [(7B)-(7S)] were prepared. Alternative starting reagents were obtained commercially unless otherwise indicated.

[00558] (7B): 2,5-dimethyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide. Prepared according to the method of example 7 by using 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide (synthesized in example 2) in step 1 and omitting steps 2 and 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (s, 1H), 8.71 (s, 1H), 8.31 (d, 1H), 8.07 (d, 1H), 7.76 (s, 1H), 7.46 (s, 1H), 7.41-7.28 (m, 6H), 7.19 (s, 1H), 6.86 (d, 1H), 4.64 (br s, 2H), 4.53 (d, 2H), 3.92 (br s, 1H), 2.41 (s, 3H), 2.36 (s, 3H), 2.30-1.90 (m, 8H). MS (EI) for $C_{30}H_{33}N_5O_3$: 512 (MH^+).

[00559] (7C): 2,5-dichloro-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide. Prepared according to the method of example 7 as an acetate salt by using 2,5-dichloroterephthalic acid and 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide (synthesized in example 2) in step 1 and omitting steps 2 and 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.83-8.78 (m, 1H), 8.67-8.64 (d, 1H), 8.57-8.54 (d, 1H), 8.03-7.96 (m, 2H), 7.80-7.77 (s, 1H), 7.59 (s, 1H), 7.53 (s, 1H), 7.36-7.29 (m, 4H), 7.26-7.21 (m, 1H), 6.26-6.21 (m, 1H), 4.59-4.53 (br. s, 2H), 4.48-4.44 (d, 2H), 3.92-

3.84 (m, 1H), 2.26-2.18 (m, 2H), 2.15-2.07 (m, 2H), 2.01-1.93 (m, 2H), 1.86-1.78 (d, 2H) . MS (EI) for $C_{28}H_{27}Cl_2N_5O_3$: 553 (MH^+).

[00560] (7D): 2,5-dimethyl-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared according to the method of example 7 as an acetate salt by using 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)-*N*-{(1*S*)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide (synthesized in example 6) in step 1 and omitting steps 2 and 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.66-8.61 (s, 1H), 8.47-8.41 (d, 1H), 8.25 (s, 1H), 8.01-7.94 (d, 1H), 7.70 (s, 1H), 7.40 (s, 1H), 7.27-7.21 (m, 3H), 7.12 (s, 1H), 6.95-6.88 (d, 2H), 6.79-6.71 (d, 1H), 5.13-5.03 (m, 1H), 4.59-4.53 (br. s, 2H), 3.86-3.79 (m, 1H), 3.27-3.15 (br. s, 4H), 2.93-2.81 (br. s, 4H), 2.52 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 2.24-2.16-(d, 2H), 2.15-2.07 (m, 2H), 2.02-1.95 (m, 2H), 1.87-1.80 (d, 2H), 1.46-1.39 (d, 3H). MS (EI) for $C_{36}H_{45}N_7O_3$: 624 (MH^+).

[00561] (7E): N-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide. Prepared according to the method of example 7 as an acetate salt by using 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide (synthesized in example 3) in step 1 and omitting steps 2 and 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.51 (s, 1H), 8.26 (s, 1H), 8.06 (d, 1H), 7.90-7.83 (br. s, 1H), 7.68 (s, 1H), 7.38 (s, 1H), 7.33-7.26 (br. s, 1H), 7.25-7.17 (d, 1H), 7.13-7.04 (d, 1H), 6.93 (s, 1H), 4.66-4.55 (br. s, 2H), 3.89-3.82 (m, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 2.26-2.19 (m, 2H), 2.15-2.07 (m, 2H), 2.03-1.96 (m, 2H), 1.93-1.86 (d, 2H). MS (EI) for $C_{28}H_{27}N_5O_3$: 422 (MH^+).

[00562] (7F): 2,5-dimethyl-N-{8-[5-({[(3S)-1-methylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 7 by using (3*S*)-1-methylpiperidin-3-amine hydrochloride (synthesized according to reagent preparation 9) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.93 (m, 2H), 7.70 (broad s, 1H), 7.40 (broad s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (broad s, 2H), 3.90 (m, 2H), 2.82 (m, 1H), 2.68 (m, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 2.19 (m, 4H), 2.12 (m, 2H), 1.99 (m, 2H), 1.91 (s, 3H), 1.83 (m, 4H), 1.78 (m, 2H), 1.71 (m, 2H), 1.53 (m, 1H), 1.27 (m, 2H). MS (EI) for $C_{30}H_{40}N_6O_3$: 519 (MH^+).

[00563] (7G): N-{8-[5-({[(3R)-1-ethylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 7 by using (3*R*)-1-ethylpiperidin-3-amine hydrochloride (synthesized according to reagent preparation 9) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.60 (d, 1H), 8.23 (d, 1H), 7.92 (m, 2H), 7.70 (broad s, 1H), 7.40 (broad s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (broad s, 2H), 3.88 (m, 3H), 2.88 (m, 1H), 2.76 (m, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.19 (m, 2H), 2.10 (m, 2H), 1.99 (m, 1H), 1.91 (s, 3H), 1.80 (m, 4H), 1.68 (m, 2H), 1.49 (m, 2H), 1.32 (m, 2H), 1.01 (t, 3H). MS (EI) for $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00564] (7H): 2,5-dimethyl-N-{8-[5-({[(3R)-1-methylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 7 by using (3*R*)-1-methylpiperidin-3-amine hydrochloride (synthesized according to reagent preparation 9) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.93 (m, 2H), 7.70 (broad s, 1H), 7.40 (broad s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (broad s, 2H), 3.89 (m, 3H), 2.79 (m, 1H), 2.64 (m, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.18 (m, 2H), 2.10 (m, 2H), 1.99 (m, 2H), 1.91 (s, 3H), 1.80 (m, 4H), 1.68 (m, 2H), 1.50 (m, 2H), 1.27 (m, 2H). MS (EI) for $C_{29}H_{38}N_6O_3$: 519 (MH^+).

[00565] (7I): 2,5-dimethyl-N-{8-[5-({[(3R)-1-methylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 7 by using (3*R*)-1-methylpyrrolidin-3-amine in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.60 (d, 1H), 8.23 (dd, 1H), 7.96 (d, 1H), 7.70 (broad s, 1H), 7.40 (broad s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.73 (d, 1H), 4.54 (broad s, 2H), 4.37 (m, 1H), 3.83 (m, 1H), 2.68 (m, 1H), 2.57 (m, 1H), 2.39 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.25 (s, 3H), 2.21 (m, 2H), 2.12 (m, 4H), 1.98 (m, 2H), 1.91 (s, 3H), 1.83 (m, 2H), 1.72 (m, 1H). MS (EI) for $C_{28}H_{36}N_6O_3$: 505 (MH^+).

[00566] (7J): 2,5-dimethyl-N-[8-(5-{[(1-methylpiperidin-4-yl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 7 by using 1-methylpiperidin-4-amine in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.94 (m, 2H), 7.69 (broad s, 1H), 7.39 (broad s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (broad s, 2H), 3.85 (m, 1H), 3.70 (m, 1H), 2.76 (m,

2H), 2.35 (s, 3H), 2.29 (s, 3H), 2.19 (m, 2H), 2.10 (m, 2H), 2.00 (m, 2H), 1.92 (m, 4H), 1.91 (s, 3H), 1.72 (m, 2H), 1.54 (m, 2H). MS (EI) for $C_{29}H_{38}N_6O_3$: 519 (MH^+).

[00567] (7K): N-[8-(5-{[(1-ethylpiperidin-4-yl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2,5-dimethylbenzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 7 by using 1-ethylpiperidin-4-amine (synthesized according to reagent preparation 9) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.94 (m, 2H), 7.70 (broad s, 1H), 7.40 (broad s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (broad s, 2H), 3.83 (m, 1H), 3.71 (m, 1H), 2.86 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.19 (m, 2H), 2.10 (m, 2H), 1.99 (m, 2H), 1.91 (s, 3H), 1.90 (m, 4H), 1.75 (m, 2H), 1.52 (m, 2H), 1.00 (t, 3H). MS (EI) for $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00568] (7L): 2,5-dimethyl-N-{8-[5-({[1-(1-methylethyl)piperidin-4-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 7 by using 1-(1-methylethyl)piperidin-4-amine hydrochloride (synthesized according to reagent preparation 9) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.93 (m, 2H), 7.70 (broad s, 1H), 7.40 (broad s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.54 (broad s, 2H), 3.84 (m, 1H), 3.67 (m, 1H), 2.79 (m, 2H), 2.69 (m, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 2.13 (m, 6H), 2.00 (m, 2H), 1.91 (s, 3H), 1.82 (m, 2H), 1.49 (m, 2H), 0.96 (d, 6H). MS (EI) for $C_{31}H_{42}N_6O_3$: 547 (MH^+).

[00569] (7M): N-{8-[5-({[(3S)-1-ethylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide. Prepared according to the method of example 7 as hydrochloride salt by using (3S)-1-ethylpyrrolidin-3-amine hydrochloride (synthesized according to reagent preparation 9) in step 3. ^{1}H NMR (400 MHz, $CDCl_3$ w/10% CD_3OD): 8.68 (d, 1H), 8.00 (dd, 1H), 7.28 (s, 1H), 7.16 (s, 1H), 6.58 (d, 1H), 4.84 (br s, 1H), 4.61 (br s, 1H), 3.66 (br s, 1H), 3.51 d, 1H), 3.12-2.94 (m, 3H), 2.85 (q, 1H), 2.53-2.42 (m, 1H), 2.43 (s, 3H), 2.43 (s, 3H), 2.35-2.24 (m, 2H), 2.22-2.07 (m, 4H), 1.91 (br d, 2H), 1.33 (t, 3H). MS (EI) for $C_{29}H_{38}N_6O_4$: 519 (MH^+).

[00570] (7N): 2,5-dimethyl-N-{8-[5-({[(3R)-1-(1-methylethyl)piperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 7 as an acetate salt by using (3R)-1-(1-methylethyl)piperidin-3-amine hydrochloride (synthesized according

to reagent preparation 9) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.94 (dd, 1H), 7.89 (d, 1H), 7.70 (s, 1H), 7.40 (s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (br s, 2H), 3.84 (br s, 2H), 2.81 (dd, 1H), 2.65-2.75 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.17-2.22 (m, 2H), 1.97-2.13 (m, 7H), 1.76-1.82 (m, 2H), 1.66-1.69 (m, 1H), 1.41-1.51 (m, 1H), 1.24-1.34 (m, 1H), 0.96 (d, 6H). MS (EI) for $C_{31}H_{42}N_6O_3$: 547 (MH^+).

[00571] (7O): N-{8-[5-({[(3S)-1-ethylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide. Prepared according to the method of example 7 as an acetate salt by using (3S)-1-ethylpiperidine-3-amine hydrochloride (synthesized according to reagent preparation 9) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.90-7.95 (m, 2H), 7.70 (s, 1H), 7.40 (s, 1H), 7.24 (s, 1H), 7.12 (S, 1H), 6.74 (d, 1H), 4.55 (br s, 2H), 3.83-3.92 (m, 2H), 2.87 (dd, 1H), 2.75 (dd, 1H), 2.35 (s, 4H), 2.32 (d, 1H), 2.30 (s, 4H), 2.17-2.22 (m, 2H), 2.08-2.13 (m, 2H), 1.98-2.00 (m, 2H), 1.76-1.82 (m, 5H), 1.66-1.70 (m, 1H), 1.44-1.53 (m, 1H), 1.25-1.35 (m, 1H), 0.99 (t, 3H). MS (EI) for $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00572] (7P): 2,5-dimethyl-N-{8-[5-({[(3S)-1-(1-methylethyl)piperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 7 as an acetate salt by using (3S)-1-(1-methylethyl)piperidin-3-amine hydrochloride (synthesized according to reagent preparation 9) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.94 (dd, 1H), 7.89 (d, 1H), 7.70 (s, 1H), 7.40 (s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (br s, 2H), 3.84 (br s, 2H), 2.81 (d, 1H), 2.65-2.75 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.17-2.22 (m, 2H), 2.07-2.13 (m, 3H), 1.97-2.04 (m, 3H), 1.76-1.82 (m, 2H), 1.66-1.70 (m, 1H), 1.41-1.50 (m, 1H), 1.24-1.34 (m, 1H), 0.96 (d, 6H). MS (EI) for $C_{31}H_{42}N_6O_3$: 547 (MH^+).

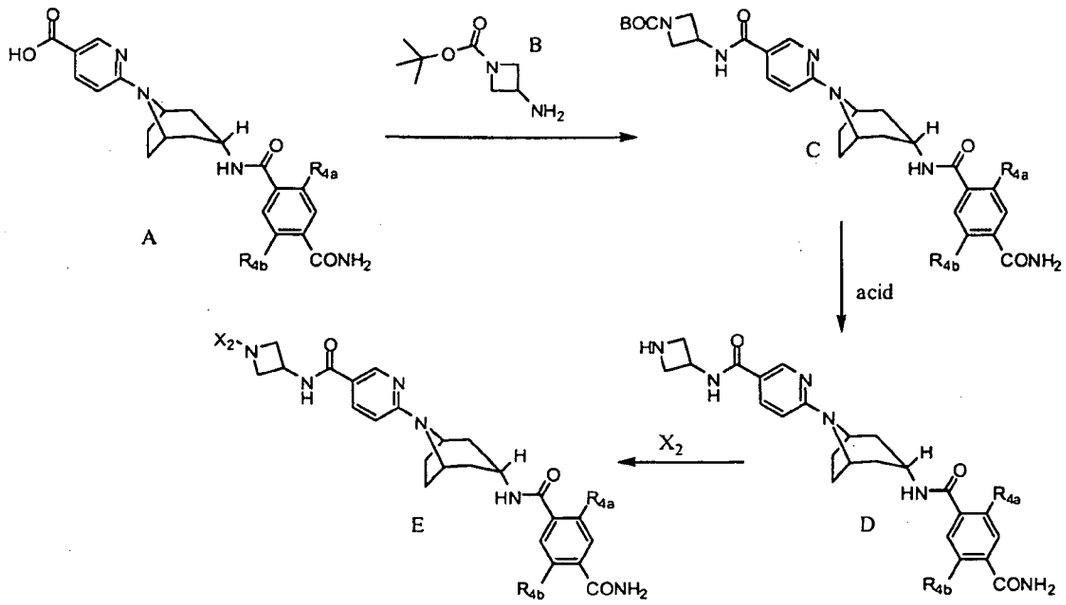
[00573] (7Q): 2,5-dimethyl-N-{8-[5-({[(3S)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 7 as a hydrochloride salt by using (S)-1-isopropylpyrrolidin-3-amine (synthesized according to reagent preparation 9) in step 3. ^{1}H NMR (400 MHz, $CDCl_3$ w/ 10% CD_3OD): 8.64 (d, 1H), 7.97 (d, 1H), 7.29 (s, 1H), 7.17 (s, 1H), 6.61 (d, 1H), 4.69-6.60 (br m, 3H), 4.13 (m,

1H), 3.13 (d, 1H), 3.15 (m, 2H), 2.92 (d, 1H0; 2.68 (t, 2H), 2.58-2.03 (br m, 10H), 1.92 (d, 2H), 1.09 (dd, 6H). MS (EI) for $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00574] (7R): 2,5-dimethyl-N-{8-[5-({[(3S)-1-methylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 7 as a hydrochloride salt by using (3S)-1-methylpyrrolidin-3-amine in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (s, 1H), 7.95 (dd, 1H), 7.46 (d, 1H), 9.29 (s, 1H), 7.17 (s, 1H), 6.60 (d, 1H), 4.75 (m, 1H), 3.36 (m, 3H), 3.15 (q, 1H), 2.85 (br d, 1H), 2.66 (m, 1H), 2.49-2.27 (br m, 12H), 2.25-2.05 (br m, 3H), 1.93-1.75 (br m, 3H), 1.72 (m,1H), 1.11 (t, 1H). MS (EI) for $C_{28}H_{36}N_6O_3$: 505 (MH^+).

[00575] (7S): N-{8-[5-({[(3R)-1-ethylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide. Prepared according to the method of example 7 as a hydrochloride salt by using (3R)-1-ethylpyrrolidin-3-amine hydrochloride (synthesized according to reagent preparation 9) in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 11.60 (br d, 1H), 8.63 (dd, 1H), 8.32 (d, 1H), 7.70 (s, 1H), 7.40 (s, 1H), 7.25 (s, 1H), 7.13 (s, 1H), 4.78 (br s, 1H), 4.65 (br s, 1H), 3.95-3.05 (br m, 9H), 2.45-1.90 (br m, 14H), 1.25 (dt, 3H). MS (EI) for $C_{29}H_{38}N_6O_3$: 519 (MH^+).

SYNTHETIC SCHEME 9:



[00576] Scheme 9 generally describes the synthesis of all of the compound(s) listed in Example 9, wherein X_2 , R_{4a}, and R_{4b} are as defined in the specification.

[00577] In Scheme 9, compound (B) is added to compound (A) under appropriate reaction conditions and suitable solvents to condense and form the amide bond in compound (C). Compound (C) is then deprotected with an acid, such as HCl, to remove BOC and form compound (D). Compound (D) is then converted to (E) by treatment with X_2 under reductive alkylation conditions, wherein X_2 is either an aldehyde or ketone reagent allowed to react with (D) in the presence of a suitable reducing agent such as sodium cyanoborohydride, and wherein X_2 becomes either a methyl group, or is otherwise an alkyl group attached to the azetidinyl group by way of a methylene linker.

EXAMPLE 10: N-{(1S)-2-amino-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide.

[00578] STEP 1: A solution of (S)-methyl 2-amino-2-(4-methoxyphenyl)acetate trifluoroacetate salt (synthesized according to reagent preparation 38) (0.30 g, 1.00 mmol), 6-[3-endo-({[2-methyl-3-methyloxy)phenyl]carbonyl}amino)-8-azabicyclo-[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (prepared in example 1, STEP 4) (0.43 g,

1.00 mmol), HOBt (0.16 g, 1.20 mmol), EDCI (0.23 g, 1.20 mmol) and 4-methylmorpholine (0.88 mL, 8.00 mmol) in dimethylformamide (5 mL) was stirred at room temperature for 18 hours. The reaction mixture was partitioned between ethyl acetate (100 mL) and brine (50 mL). The organic layer was separated and washed with brine (50 mL), dried over sodium sulfate, filtered and the solvent was concentrated. The residue was subjected to column chromatography (hexane:ethyl acetate 4:1 to 3:2) to give methyl (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoate, (0.51 g, 89% yield). MS (EI) for $C_{32}H_{36}N_4O_6$: 573 (MH^+).

[00579] STEP 2: A solution of methyl (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoate (0.48 g, 0.84 mmol) and an aqueous solution of 4M potassium hydroxide (0.42 mL, 1.68 mmol) in methanol (10 mL), tetrahydrofuran (5 mL) and water (5 mL) was stirred at 50 °C for 30 minutes. After cooling to room temperature the solvent was evaporated and the pH was adjusted to 2 with concentrated aqueous hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried to afford (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoic acid (0.42 g, 89%). MS (EI) for $C_{31}H_{34}N_4O_6$: 557 (M-H).

[00580] STEP 3: A solution of (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoic acid (0.10 g, 0.18 mmol), a 2M soltion of ammonia in methanol (0.18 mL, 0.36 mmol), HOBt (0.027 g, 0.20 mmol), EDCI (0.042 g, 0.22 mmol) and 4-methylmorpholine (0.10 mL, 0.90 mmol) in dimethylformamide (3 mL) was stirred at room temperature for 18 hours. The solvent was concentrated *in vacuo* and the residue was purified by preparatory reverse phase HPLC (0.1% ammonium acetate in aqueous acetonitrile mobile phase) to give N-{(1S)-2-amino-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide (17 mg, 11% yield). MS (EI) for $C_{31}H_{35}N_5O_5$: 558 (MH^+).

[00581] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [(9B)-(9E)] were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

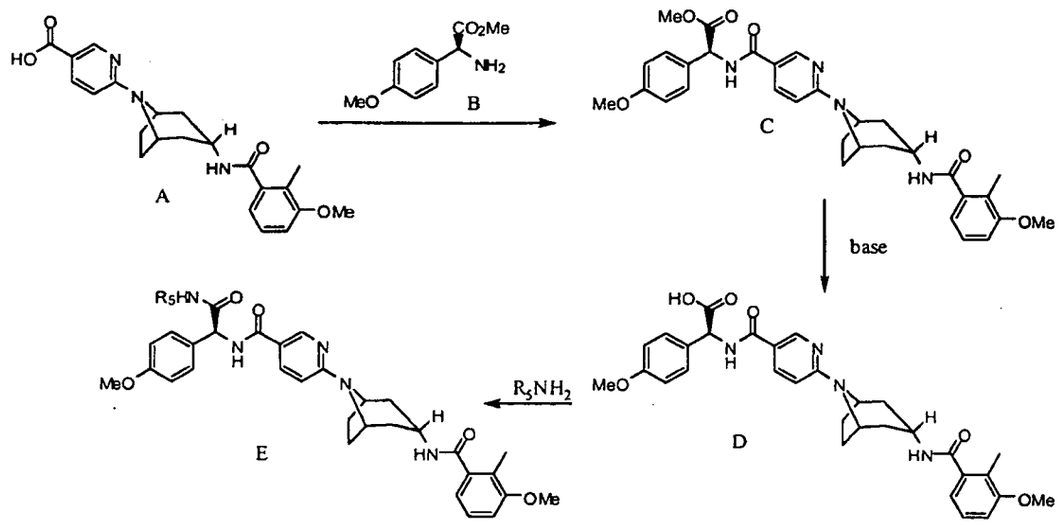
[00582] (9B): methyl (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}-amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]-ethanoate. Prepared in example 10 step 1. MS (EI) for $C_{32}H_{36}N_4O_6$: 573 (MH^+).

[00583] (9C): (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}-amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]-ethanoic acid. Prepared in example 10 step 2. MS (EI) for $C_{31}H_{34}N_4O_6$: 557 (M-H).

[00584] (9D): N-{(1S)-2-(methylamino)-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 10 by using methylamine in step 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.65 (d, 1H), 8.51 (d, 1H), 8.22 (d, 1H), 8.11 (m, 1H), 8.01 (dd, 1H), 7.38 (m, 2H), 7.22 (t, 1H), 7.01 (d, 1H), 6.90 (m, 2H), 6.86 (d, 1H), 6.73 (d, 1H), 5.54 (d, 1H), 4.54 (bs, 2H), 3.82 (m, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 2.60 (d, 3H), 2.20 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H). MS (EI) for $C_{32}H_{37}N_5O_5$: 572 (MH^+).

[00585] (9E): N-{(1S)-2-(ethylamino)-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 10 by using ethylamine in step 3. MS (EI) for $C_{33}H_{39}N_5O_5$: 586 (MH^+).

SYNTHETIC SCHEME 10:



[00586] Scheme 10 generally describes the synthesis of all of the compounds listed in Example 10, wherein R_5 is as defined in the specification.

[00587] In Scheme 10, compound (B) is added to compound (A) under appropriate reaction conditions and with a suitable coupling reagent, such as EDCI and HOBT, to condense and form the amide bond in compound (C). The ester in compound (C) is then hydrolyzed with a base, such as KOH, to form compound (D). To compound (D) is added R_5NH_2 under appropriate reaction conditions and with a suitable coupling reagent, such as EDCI and HOBT, to condense and form the amide bond in compound (E).

[00588] EXAMPLE 10: N-{(1S)-2-amino-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide.

[00589] STEP 1: A solution of (S)-methyl 2-amino-2-(4-methoxyphenyl)acetate trifluoroacetate salt (synthesized according to reagent preparation 38) (0.30 g, 1.00 mmol), 6-[3-endo-({[2-methyl-3-methyloxy)phenyl]carbonyl}amino)-8-azabicyclo-[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (prepared in example 1, STEP 4) (0.43 g, 1.00 mmol), HOBt (0.16 g, 1.20 mmol), EDCI (0.23 g, 1.20 mmol) and 4-methylmorpholine (0.88 mL, 8.00 mmol) in dimethylformamide (5 mL) was stirred at room temperature for 18 hours. The reaction mixture was partitioned between ethyl

acetate (100 mL) and brine (50 mL). The organic layer was separated and washed with brine (50 mL), dried over sodium sulfate, filtered and the solvent was concentrated. The residue was subjected to column chromatography (hexane:ethyl acetate 4:1 to 3:2) to give methyl (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoate, (0.51 g, 89% yield). MS (EI) for $C_{32}H_{36}N_4O_6$: 573 (MH^+).

[00590] STEP 2: A solution of methyl (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoate (0.48 g, 0.84 mmol) and an aqueous solution of 4M potassium hydroxide (0.42 mL, 1.68 mmol) in methanol (10 mL), tetrahydrofuran (5 mL) and water (5 mL) was stirred at 50 °C for 30 minutes. After cooling to room temperature, the solvent was evaporated and the pH was adjusted to 2 with concentrated aqueous hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried to afford (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoic acid (0.42 g, 89%). MS (EI) for $C_{31}H_{34}N_4O_6$: 557 (M-H).

[00591] STEP 3: A solution of (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoic acid (0.10 g, 0.18 mmol), a 2M soltion of ammonia in methanol (0.18 mL, 0.36 mmol), HOBt (0.027 g, 0.20 mmol), EDCI (0.042 g, 0.22 mmol) and 4-methylmorpholine (0.10 mL, 0.90 mmol) in dimethylformamide (3 mL) was stirred at room temperature for 18 hours. The solvent was concentrated *in vacuo* and the residue was purified by preparatory reverse phase HPLC (0.1% ammonium acetate in aqueous acetonitrile mobile phase) to give N-{(1S)-2-amino-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide (17 mg, 11% yield). MS (EI) for $C_{31}H_{35}N_5O_5$: 558 (MH^+).

[00592] Using analogous synthetic techniques and substituting with alternative starting reagents the following compounds [(10B)-(10E)] were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

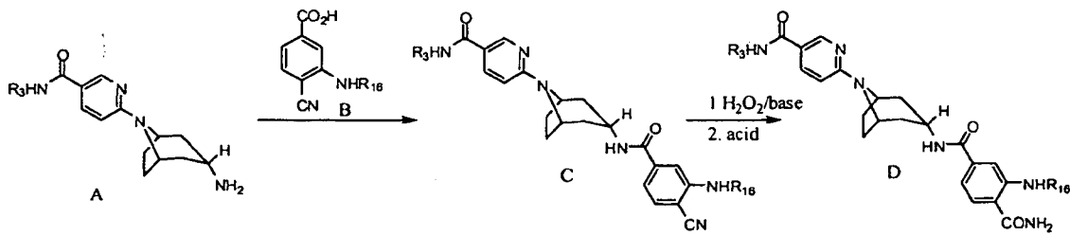
[00593] (10B): methyl (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoate. Prepared in example 10 step 1. MS (EI) for $C_{32}H_{36}N_4O_6$: 573 (MH^+).

[00594] (10C): (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoic acid. Prepared in example 10 step 2. MS (EI) for $C_{31}H_{34}N_4O_6$: 557 (M-H).

[00595] (10D): N-{(1S)-2-(methylamino)-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 10 by using methylamine in step 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.65 (d, 1H), 8.51 (d, 1H), 8.22 (d, 1H), 8.11 (m, 1H), 8.01 (dd, 1H), 7.38 (m, 2H), 7.22 (t, 1H), 7.01 (d, 1H), 6.90 (m, 2H), 6.86 (d, 1H), 6.73 (d, 1H), 5.54 (d, 1H), 4.54 (bs, 2H), 3.82 (m, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 2.60 (d, 3H), 2.20 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H). MS (EI) for $C_{32}H_{37}N_5O_5$: 572 (MH^+).

[00596] (10E): N-{(1S)-2-(ethylamino)-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 10 by using ethylamine in step 3. MS (EI) for $C_{33}H_{39}N_5O_5$: 586 (MH^+).

SYNTHETIC SCHEME 11:



[00597] Scheme 11 generally describes the synthesis of all of the compound(s) listed in Example 11, wherein R_3 and R_{16} are as defined in the specification.

[00598] In Scheme 11, compound (B) is added to compound (A) under appropriate reaction conditions and with a suitable coupling reagent, such as HOBT, to condense and form the amide bond in compound (C). Compound (C) is then converted to compound (D) by hydrolysis of the aromatic nitrile by treatment with a base, such as potassium carbonate, in the presence of a suitable oxidant, such as hydrogen peroxide, to arrive at the aromatic carboxamide (D).

EXAMPLE 11: N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(trans-4-aminocyclohexyl)amino]benzene-1,4-dicarboxamide

[00599] STEP 1: To a solution of methyl 3-bromo-4-cyanobenzoate (200 mg, 0.83 mmol) in dichloromethane (1.5 mL) and methanol (1.5) was added 1.0 N aqueous sodium hydroxide (1.7 mL, 1.7 mmol). The mixture was stirred vigorously for 2 h at room temperature. The volatile solvents were then removed *in vacuo*. The aqueous residue was acidified with 1 N aqueous hydrochloric acid and was then extracted with ethyl acetate. The organic layer was dried over magnessium sulfate, filtered, and concentrated to provide 3-bromo-4-cyanobenzoic acid (190 mg, 0.83 mmol, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.42 (d, 1H), 8.15 (dd, 1H), 7.80 (d, 1H).

[00600] STEP 2: To a solution of 3-bromo-4-cyanobenzoic acid (1.51 g, 6.69 mmol) in acetone (30 mL) was added cesium carbonate (4.4 g, 13.4 mmol) and benzyl bromide (790 uL, 6.69 mmol). The mixture was stirred at reflux for 15 hours at which point additional benzyl bromide was added (200 uL, 1.68 mmol). The mixture was stirred at reflux for a further 2 h and was then cooled to room temperature. Water and ethyl acetate were added and the layers were separated. The aqueous phase was then saturated with lithium chloride and extracted with ethyl acetate. The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (4:1 hexanes:ethyl acetate) to provide phenylmethyl 3-bromo-4-cyanobenzoate (957 mg, 3.03 mmol, 45% yield) as a yellow orange oil that slowly solidified. ^{1}H NMR (400 MHz, $CDCl_3$): 8.35 (d, 1H), 8.09 (dd, 1H), 7.73 (d, 1H), 7.46-7.35 (m, 5H), 5.35 (s, 2H).

[00601] STEP 3: A pressure vessel containing a magnetic stirbar was charged with phenylmethyl 3-bromo-4-cyanobenzoate (100 mg, 0.32 mmol), 1,1-dimethylethyl (*trans*-4-aminocyclohexyl)carbamate (69 mg, 0.32 mmol), cesium carbonate (125 mg, 0.38 mmol), XANTPHOS (19 mg, 0.032 mmol),

tris(dibenzylideneacetone)dipalladium(0) (15 mg, 0.016 mmol) and dioxane (1.5 mL). The vessel was then sealed and heated to 95 °C. The suspension was stirred for approximately 24 h at that temperature and was then allowed to cool to room temperature. The suspension was poured into water, and the resulting aqueous mixture was extracted twice with ethyl acetate. The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography (4:1 hexanes:ethyl acetate) to provide impure phenylmethyl 4-cyano-3-{[*trans*-4-({[(1,1-dimethylethyl)oxy]carbonyl}-amino)cyclohexyl]amino}benzoate (71.8 mg, 0.16 mmol) as a yellow powder. This material was carried into the subsequent step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 7.45-7.28 (m, 8H), 5.37 (s, 2H), 4.47 (m, 1H), 3.40 (m, 1H), 2.12 (m, 4H), 1.46 (s, 9H), 1.31 (m, 4H).

[00602] STEP 4: Palladium on carbon 10% by weight Degussa type (50 mg) was added to a solution of phenylmethyl 4-cyano-3-{[*trans*-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]amino}benzoate (71.8 mg, 0.16 mmol) in ethyl acetate (3 mL) and methanol (400 uL). The mixture was subjected to 1 atm of hydrogen for 70 min. The catalyst was then removed by filtration through celite. The resulting filtrate was concentrated to provide 4-cyano-3-{[*trans*-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]amino}benzoic acid (55.8 mg, 0.16 mmol) which was carried into the subsequent step without further purification. ^{1}H NMR (400 MHz, CD_3OD): 7.47 (d, 1H), 7.37 (s, 1H), 7.24 (d, 1H), 3.47-3.21 (m, 2H), 2.09 (m, 2H), 1.98 (m, 2H), 1.88 (m, 2H), 1.43 (s, 9H), 1.24 (m, 2H); MS (EI) for $C_{19}H_{25}N_3O_4$: 304 (MH^+-*tert*-butyl).

[00603] STEP 5: To a solution of 4-cyano-3-{[*trans*-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]amino}benzoic acid (55.8 mg, 0.16 mmol) was added HATU (59 mg, 0.16 mmol). The resulting mixture was stirred at room temperature for 2.5 h. More HATU (60 mg, 0.16 mmol) was then added, and the mixture was stirred for a further 40 min at room temperature. At that point 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide (synthesized in example 3) (45 mg, 0.16 mmol) was added followed by diisopropylethylamine (167 uL, 0.96 mmol). The solution was stirred 45 min at room temperature after which water was added. The aqueous mixture was then extracted twice with ethyl acetate. The organic extracts were combined, washed with 10% aqueous lithium chloride

solution, dried over magnesium sulfate, filtered, and concentrated. The residue was subject to column chromatography (5% methanol in dichloromethane) to provide 1,1-dimethylethyl [*trans*-4-({5-[({8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}amino)carbonyl]-2-cyanophenyl}amino)cyclohexyl]carbamate (50.8 mg, 0.061 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): 8.62 (d, 1H), 7.94 (dd, 1H), 7.44 (d, 1H), 7.15 (s, 1H), 6.80 (d, 1H), 6.62 (d, 1H), 6.56 (d, 1H), 4.65 (br s, 2H), 4.53 (d, 1H), 4.47 (br d, 1H), 4.22 (m, 1H), 3.55-3.36 (m, 2H), 2.39-2.25 (m, 4H), 2.18-2.02 (m, 6H), 1.86 (d, 2H), 1.45 (s, 9H), 1.37-1.22 (m, 4H); MS (EI) for $C_{32}H_{41}N_7O_4$: 588 (MH^+).

[00604] STEP 6: To a solution of 1,1-dimethylethyl [*trans*-4-({5-[({8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}amino)carbonyl]-2-cyanophenyl}amino)cyclohexyl]carbamate (40.7 mg, 0.069 mmol) in DMSO (1 mL) was added potassium carbonate (19 mg, 0.138 mmol) followed by aqueous hydrogen peroxide (30%, 2 drops). The mixture was stirred at room temperature for 1 h. Additional hydrogen peroxide (4 drops) was then added, and the mixture was stirred a further 35 min at 45 °C. After cooling to room temperature, the solution was diluted to 2 mL total volume with acetonitrile:water (2.5:1), and the mixture was purified by preparative reverse phase HPLC to provide 1,1-dimethylethyl [*trans*-4-({2-(aminocarbonyl)-5-[({8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}amino)carbonyl]phenyl}amino)cyclohexyl]carbamate (17.6 mg, 0.029 mmol, 42% yield). ^{1}H NMR (400 MHz, CD_3OD): 8.64 (d, 1H), 7.99 (dd, 1H), 7.63 (d, 1H), 7.06 (s, 1H), 6.88 (dd, 1H), 6.76 (d, 1H), 4.64 (br s, 2H), 4.00 (m, 1H), 3.37 (m, 2H), 2.30-2.12 (m, 8H), 2.02-1.93 (m, 4H), 1.43 (s, 9H), 1.35 (m, 4H).

[00605] STEP 7: To a flask containing 1,1-dimethylethyl [*trans*-4-({2-(aminocarbonyl)-5-[({8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}amino)carbonyl]phenyl}amino)cyclohexyl]carbamate (17.6 mg, 0.029 mmol) was added 2.0 M aqueous hydrochloric acid (2 mL, 4 mmol). The mixture was stirred for 1 h at room temperature then the resulting solution was lyophilized to give N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(*trans*-4-aminocyclohexyl)amino]benzene-1,4-dicarboxamide as the hydrochloride salt. ^{1}H NMR (400 MHz, CD_3OD): 8.45 (d, 1H), 8.38 (dd, 1H), 8.13 (d, 1H), 8.03 (d, 1H), 7.96 (dd, 1H), 7.40 (d, 1H), 4.82 (br s, 2H), 4.15 (br s, 1H), 3.77 (m, 1H), 3.20 (m,

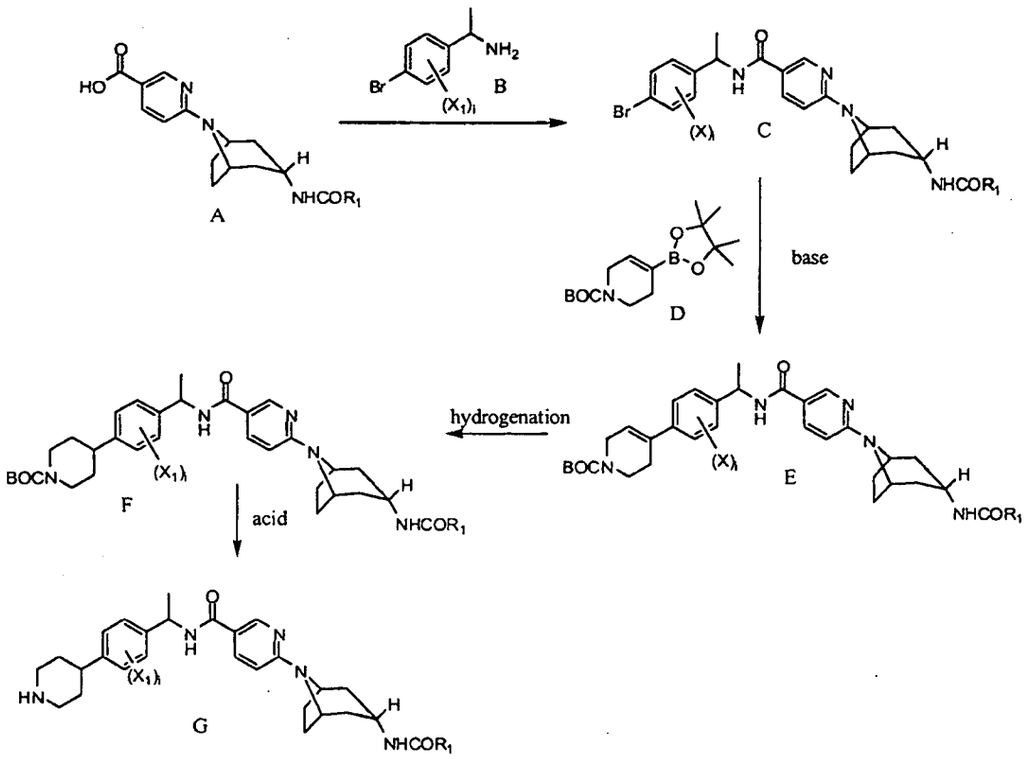
1H), 2.49 (m, 2H), 2.43-2.24 (m, 6H), 2.17 (m, 4H), 1.71 (m, 2H), 1.56 (m, 2H); MS (EI) for $C_{27}H_{35}N_7O_3$: 506 (MH^+).

[00606] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [(11B)-(11C)] were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00607] (11B): N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 11 by using 3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)aniline (Gaster et al. *J. Med Chem.* **1998**, *41*, 1218-1235) in step 3 then omission of step 7. ^{1}H NMR (400 MHz, CD_3OD): 8.42 (d, 1H), 8.37 (dd, 1H), 7.74 (d, 1H), 7.48 (d, 1H), 7.36 (d, 1H), 7.08-6.99 (m, 3H), 6.95 (d, 1H), 4.75 (br s, 2H), 4.34 (m, 2H), 4.06 (m, 1H), 3.88 (s, 3H), 3.58 (m, 2H), 3.02 (s, 6H), 2.33-2.15 (m, 8H); MS (EI) for $C_{32}H_{39}N_7O_5$: 602 (MH^+).

[00608] (11C): N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-[(2-morpholin-4-ylethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 11 by proceeding directly to step 5 using 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide (synthesized in example 6) and 3-bromo-4-cyanobenzoic acid (synthesized in step 1 above) then conducting step 3 using 2-morpholin-4-ylethanamine and step 6. ^{1}H NMR (400 MHz, CD_3OD): 8.60 (d, 1H), 7.97 (dd, 1H), 7.63 (d, 1H), 7.29 (d, 2H), 7.08 (s, 1H), 6.96 (d, 2H), 6.93 (d, 1H), 6.75 (d, 1H), 5.17 (q, 1H), 4.62 (br s, 2H), 3.98 (m, 1H), 3.73 (m, 4H), 3.35 (t, 2H), 3.24 (m, 4H), 2.84 (m, 4H), 2.68 (t, 2H), 2.54 (m, 4H), 2.51 (s, 3H), 2.30-2.12 (m, 6H), 1.97 (m, 2H), 1.94 (s, 6H), 1.52 (d, 3H); (EI) for $C_{40}H_{53}N_9O_4$: 724.6 (MH^+).

SYNTHETIC SCHEME 12:



[00609] Scheme 12 generally describes the synthesis of all of the compound(s) listed in Example 12, wherein X_1, R_1 and (i) are as defined in the specification.

[00610] In Scheme 12, compound (B) is added to compound (A) under appropriate reaction conditions and with a suitable coupling reagent, such as EDCI and HOBT, to condense and form the amide bond in compound (C). Aryl bromide (C) is then treated with a boronate ester (D) under suitable reaction conditions in the presence of an appropriate palladium catalyst to arrive at compound (E). Compound (E) is reduced with a reducing agent, such as 10% palladium on charcoal, to arrive at compound (F). Compound (F) is then deprotected in the presence of an acid, such as HCl, to remove BOC and arrive at compound (G).

[00611] EXAMPLE 12: N-[1-(2,6-difluoro-4-piperidin-4-ylphenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide.

[00612] STEP 1: To a mixture of 1-(4-bromo-2,6-difluorophenyl)ethanone (450 mg, 0.91 mmol), titanium isopropoxide (1.14 mL, 4.61 mmol) in ethanol (10 mL) was added a solution of 2M ammonia in ethanol (4.8 mL, 9.6 mmol), and the resulting

mixture was stirred at room temperature. After 18 hours, sodium borohydride (115 mg, 3.48 mmol) was added and stirring was continued at room temperature for three hours. The reaction mixture was poured into a 2M aqueous ammonium hydroxide solution (100 mL) then filtered. The filtrate was extracted with ethyl acetate (3 x 50 mL), and the combined extract was washed with water (100 mL), then brine (100 mL), dried over sodium sulfate, filtered and concentrated to give 1-(4-bromo-2,6-difluorophenyl)ethanamine (236 mg, 62% yield), MS (EI) for $C_8H_8BrF_2N$: 237 (MH^+).

[00613] STEP 2: A mixture of 6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]-carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (synthesized in example 1)(276 mg, 0.70 mmol), EDCI (95 mg, 0.70 mmol), 1-hydroxybenzotriazole (95 mg, 0.70 mmol), and N,N-diisopropylethylamine (0.37 mL, 2.1 mmol) in N,N-dimethylformamide (3 mL) was stirred at room temperature for 15 minutes. To this mixture was added a solution of 1-(4-bromo-2,6-difluorophenyl)ethanamine (165 mg, 0.70 mmol) in N,N-dimethylformamide (0.5 mL) and stirring was continued for 18 hours. The reaction mixture was diluted with ethyl acetate (30 mL), washed with 5% aqueous lithium chloride solution (2x10 mL), saturated sodium bicarbonate solution (10 mL), dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (65-95% ethyl acetate-hexanes) to give the N-[1-(4-bromo-2,6-difluorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide (348 mg, 81% yield). ^{1}HNMR (400MHz, $CDCl_3$): 8.58 (d, 1H), 7.86 (dd, 1H), 7.20-7.17 (dd, 1H), 7.08 (s, 1H), 7.06 (s, 1H), 6.95 (dd, 2H), 6.70 (br, 1H), 6.36-6.35(br, 1H), 6.69-6.67 (m, 1H), 4.50 (br, 2H), 4.22-4.20 (m, 1H), 3.86 (s, 3H), 2.29-2.27 (m, 2H), 2.28 (s, 3H), 2.20-2.17 (m, 2H), 2.00 (d, 2H), 1.85-1.81 (d, 2H), 1.58-1.57 (d, 3H); MS (EI) for $C_{30}H_{31}BrF_2N_4O_3$: 614 (MH^+).

[00614] STEP 3: A mixture of N-[1-(4-bromo-2,6-difluorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide (348 mg, 0.57 mmol), 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid pinacol ester (228 mg, 0.74 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (28 mg, 5 mol %), potassium carbonate (234 mg, 1.7 mmol), and N,N-dimethylformamide (4.5 mL) was first degassed with nitrogen for 10 minutes

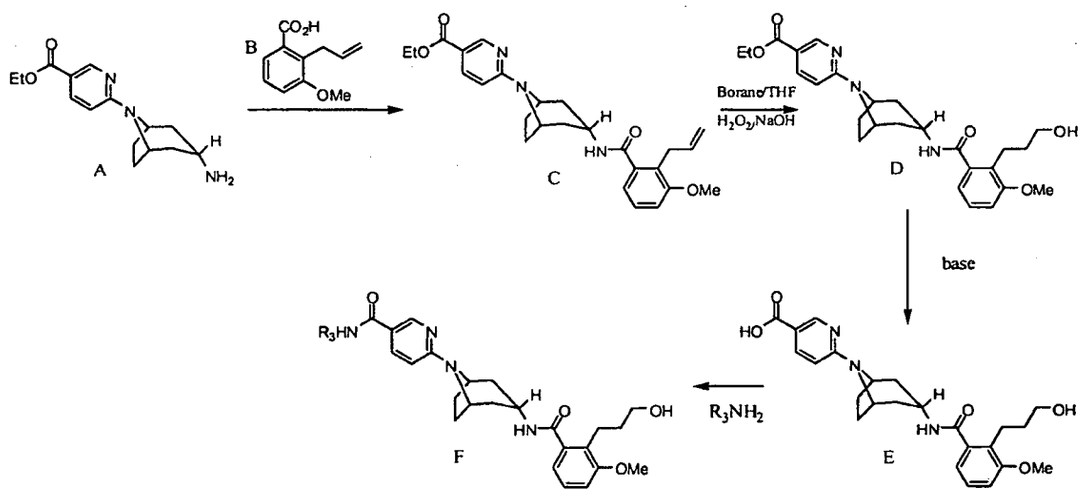
then stirred at 80°C for 18 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (45 mL), washed with 5% aqueous lithium chloride solution (2x 20 mL), dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (65-95% ethyl acetate in hexanes) to give 1,1-dimethylethyl 4-(3,5-difluoro-4-{1-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino]ethyl}phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (290 mg, 71% yield). ^{1}HNMR (400MHz, $CDCl_3$): 8.59 (d, 1H), 7.90 (dd, 1H), 7.21 (dd, 1H), 6.94-6.88 (m, 4H), 6.60 (d, 1H), 6.53 (d, 1H), 6.20 (d, 1H), 6.06 (br, 1H), 5.78-5.74 (m, 1H), 4.61 (br, 2H), 4.27 (q, 1H), 4.07 (br, 2H), 3.85 (s, 3H), 3.62 (tr, 2H), 2.42 (br, 2H), 2.36-2.31 (m, 2H), 2.29 (s, 3H), 2.22-2.20 (m, 2H), 2.03-1.97 (m, 2H), 1.85 (br, 1H), 1.81 (br, 1H), 1.62 (d, 3H), 1.49 (s 9H); MS (EI) for $C_{40}H_{47}F_2N_5O_5$: 716 (MH^+).

[00615] STEP 4: A mixture of 1,1-dimethylethyl 4-(3,5-difluoro-4-{1-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino]ethyl}phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (133 mg, 0.19 mmol), 10% palladium on charcoal (Degussa type, 100 mg), acetic acid (100 uL, 1.0 mmol), and methanol (20 mL) was shaken in a Parr hydrogenation apparatus at 30 psi for 6 hours. The reaction mixture was filtered, concentrated, re-dissolved in a 1:1 mixture (6 mL) of methanol and 4M hydrogen chloride in dioxane, and stirred at room temperature overnight. The reaction mixture was basified with 2M ammonia in methanol, concentrated, and purified by preparatory reverse phase HPLC (ammonium acetate buffered aqueous acetonitrile eluent). The product containing fractions were combined, and lyophillized to give a solid (58 mg, 0.094 mmol) which dissolved in methanol (4 mL) containing and 4M hydrogen chloride in dioxane (49 uL, 0.20 mmol), then evaporated to dryness which gave N-[1-(2,6-difluoro-4-piperidin-4-ylphenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide hydrochloride. (65 mg, 51% yield). ^{1}HNMR (400MHz, d_4-methanol): 8.40 (d, 1H), 8.34 (dd, 1H), 7.37(d, 1H), 7.23 (dd, H), 7.01 (d, 1H), 6.94-6.90 (m, 3H), 5.48 (q, 1H), 4.80 (br, 2H), (4.10 (tr, 1H), 3.84 (s, 3H), 3.47 (br, 2H), 3.16 (m, 2H), 3.93 (m, 2H), 2.37-2.33 (m, 4H), 2.24-2.15 (m, 2H), 2.20 (s, 3H), 2.06 (d, 2H), 1.94-1.89 (m, 2H), 1.65 (d, 2H); MS (EI) for $C_{35}H_{41}F_2N_5O_3$: 618 (MH^+).

[00616] Using analogous synthetic techniques and substituting with alternative starting reagents, compound (12B) was prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00617] (12B): N-[1-(2-fluoro-4-piperidin-4-ylphenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared as the hydrochloride salt according to the method of example 12 by starting with 4-bromo-2-fluoroacetophenone in step 1. ^{1}H-NMR (400MHz, d_4-methanol): 8.44 (s, 1H), 8.38 (d, 1H), 7.40 (m, 2H), 7.24 (dd, 1H), 7.19 (d, 1H), 7.02 (dd, 2H), 6.91 (d, 1H), 5.41 (q, 1H), 4.79 (br, 2H), 4.11 (tr, 1H), 3.84 (s, 3H), 3.48 (d, 2H) 3.14 (m, 2H), 2.90 (m, 2H), 2.38-2.35 (m, 4H), 2.24-2.15 (m, 4H), 2.21 (s, 3H), 2.10-2.20 (m, 2H), 1.92-1.87 (m, 2H), 1.57 (d, 3H); MS (EI) for $C_{35}H_{42}FN_5O_3$: 600 (MH^+).

SYNTHETIC SCHEME 13:



[00618] Scheme 13 generally describes the synthesis of all of the compound(s) listed in Example 13, wherein R_3 is as defined in the specification.

[00619] In Scheme 13, compound (B) is added to compound (A) under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (C). Compound (C) is then converted to intermediate (D) by hydroboration. Thus, (C) is first treated with borane in THF followed by reaction with hydrogen peroxide in the presence of a suitable base such

as sodium hydroxide. The carboxylate of compound (D) is then hydrolyzed by a base, such as KOH, to arrive at compound (E). R_3NH_2 is then added to compound (E) under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (F).

[00620] EXAMPLE 13: 6-[3-endo-({[2-(3-hydroxypropyl)-3-(methyloxy)phenyl]-carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide.

[00621] STEP 1: A solution of ethyl 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxylate hydrochloride (synthesized in example 1) (2.60 g, 6.69 mmol), 3-(methyloxy)-2- prop-2-en-1-ylbenzoic acid (synthesized in reagent preparation 19) (1.28 g, 6.69 mmol), HATU (2.54 g, 6.69 mmol), and diisopropylethylamine (3.46 g, 26.76 mmol) in DMF (10 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (250 mL), washed with saturated sodium bicarbonate (100 mL), 5% lithium chloride (2 x 100 mL), and brine (100 mL), dried over sodium sulfate, filtered and concentrated to give crude ethyl 6-[3-endo-({[3-(methyloxy)-2-prop-2-en-1-ylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (3.52 g) as a brown oil. MS (EI) for $C_{26}H_{31}N_3O_4$: 450 (MH^+).

[00622] STEP 2: To a solution of ethyl 6-[3-endo-({[3-(methyloxy)-2-prop-2-en-1-ylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (213 mg, 0.40 mmol) in THF (5 mL) was added a 1.0 M solution of borane THF complex in THF (0.40 mL, 0.40 mmol) at 0 °C. After removing the ice bath, the mixture was stirred at room temperature for 4 h. Additional 1.0 M solution of borane THF complex in THF (0.40 mL, 0.40 mmol) was added and stirring was continued for 18 h. Another 1.0 M solution of borane THF complex in THF (0.40 mL, 0.40 mmol) was added and the mixture was stirred for an additional 24 h. Then water (1.0 mL) was added followed by 10% sodium hydroxide (1.0 mL), and 30% hydrogen peroxide (2.2 mL). The reaction mixture was stirred at room temperature for another 90 min, then cooled to 0 °C, and sodium thiosulfate (3.40 g, 21.5 mmol) was added carefully. The ice bath was removed and the mixture was stirred at room temperature for 30 min. The mixture was acidified to pH3 with 1N hydrochloric acid, and extracted with ethyl acetate (3 x 40 mL). The organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated to afford crude ethyl 6-[3-endo-({[2-(3-

hydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (258 mg). MS (EI) for $C_{26}H_{33}N_3O_5$: 468 (MH^+).

[00623] STEP 3: A suspension of ethyl 6-[3-endo-({[2-(3-hydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (240 mg, 0.51 mmol) and potassium hydroxide (58 mg, 1.02 mmol) in methanol (6 mL) and water (2 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, water was added to the resulting mixture, and the pH adjusted to 5 with 1N aqueous hydrochloric acid. Extraction with ethyl acetate (3 x 30 mL), drying over sodium sulfate then filtration and concentration provided crude 6-[3-endo-({[2-(3-hydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (120 mg, 53% yield). MS (EI) for $C_{24}H_{29}N_3O_5$: 440 (MH^+).

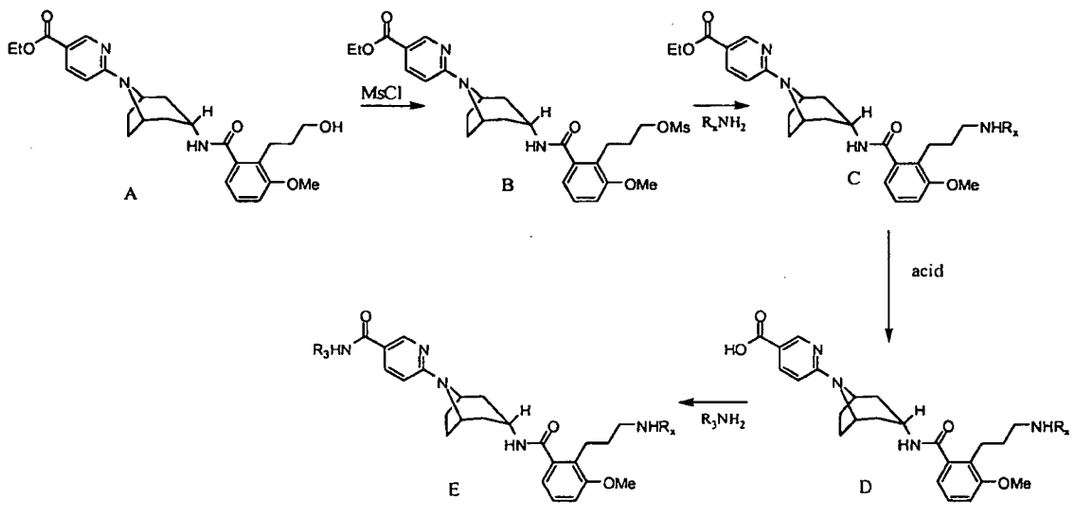
[00624] STEP 4: A solution of 6-[3-endo-({[2-(3-hydroxypropyl)-3-(methyloxy)-phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (35 mg, 0.08 mmol), N-methylmorpholine (26 µl, 0.24 mmol), benzylamine (10 µl, 0.08 mmol) and HATU (30 mg, 0.08 mmol) in dimethylformamide (1 mL) was stirred at 40 °C for 15 h. The mixture was cooled to room temperature and diluted with ethyl acetate. The organic portion was washed with 5% aqueous lithium chloride, 20% aqueous citric acid, brine, dried over sodium sulfate then filtered and concentrated. Purification by preparatory reverse phase HPLC (0.1% trifluoroacetic acid buffered aqueous acetonitrile eluent) afforded 6-[3-endo-({[2-(3-hydroxypropyl)-3-(methyl-oxy)phenyl]carbonyl}-amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)-pyridine-3-carboxamide as the trifluoroacetate salt (17 mg, 38% yield). ^1H NMR (400 MHz, d_6-DMSO): 8.98 (br s, 1H), 8.56 (s, 1H), 8.30 (d, 1H), 8.14 (d, 1H), 7.35-7.31 (m, 5H), 7.26-7.21 (m, 2H), 7.05-7.02 (m, 2H), 6.85 (d, 1H), 4.63 (br s, 2H), 4.47 (d, 2H), 3.90-3.83 (m, 1H), 3.80 (s, 3H), 3.35 (t, 2H), 2.64-2.59 (m, 2H), 2.28-1.90 (m, 8H), 1.68-1.60 (m, 2H). MS (EI) for $C_{31}H_{36}N_4O_4$: 529 (MH^+).

[00625] Using analogous synthetic techniques and substituting with alternative starting reagents, compound (13B) was prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00626] (13B): 6-[3-endo-({[2-(3-hydroxypropyl)-3-(methyloxy)phenyl] carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide. Prepared according to the method of example 13 by using ammonia in step 4. ^1H NMR (400

MHz, d_4-MeOH): 8.62 (d, 1H), 8.34-8.31 (m, 1H), 7.99 (dd, 1H), 7.25 (t, 1H), 7.03 (d, 1H), 6.91 (d, 1H), 6.76 (d, 1H), 4.61 (br s, 2H), 4.04-3.97 (m, 1H), 3.84 (s, 3H), 3.51 (t, 2H), 2.75 (t, 2H), 2.35-2.07 (m, 6H), 1.92 (d, 2H), 1.85-1.76 (m, 2H); MS (EI) for $C_{24}H_{30}N_4O_4$: 439 (MH^+).

SYNTHETIC SCHEME 14:



[00627] Scheme 14 generally describes the synthesis of all of the compound(s) listed in Example 14, wherein R_3 is as defined in the specification and R_x is alkyl.

[00628] In Scheme 14, MsCl is added to compound (A) under appropriate reaction conditions to arrive at compound (B). To compound (B) is added R_xNH_2 under appropriate reaction conditions to arrive at compound (C). The carboxylate of compound (C) is then hydrolyzed with a base to arrive at compound (D). To compound (D) is added R_3NH_2 under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (E).

[00629] EXAMPLE 14: 6-[3-endo-({[2-{3-[(1-methylethyl)amino]propyl}-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide.

[00630] STEP 1: A solution of ethyl 6-[3-endo-({[2-(3-hydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (synthesized in example 13) (90 mg, 0.19 mmol, example 13, step 2),

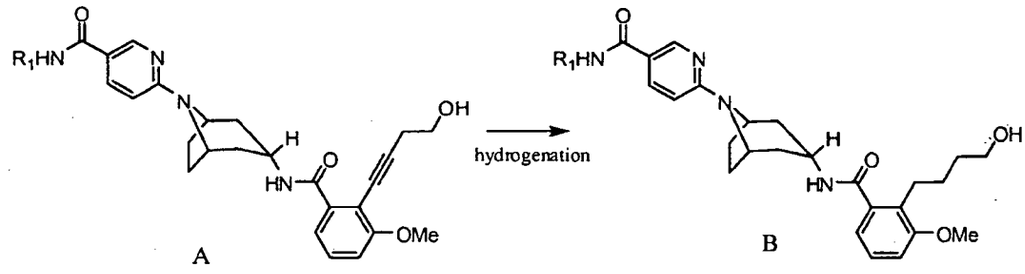
triethylamine (51 mg, 0.50 mmol), and mesyl chloride (29 mg, 0.26 mmol) in dichloromethane (5 mL) was stirred at room temperature for 2.5 h. The reaction mixture was concentrated and isopropylamine (5 mL) was added. The resulting mixture was stirred at 50 °C for 17 h and then concentrated. The residue was partitioned between ethyl acetate (50 mL) and saturated sodium bicarbonate (50 mL). The layers were separated and the organic layer was washed with brine (20 mL), dried over sodium sulfate, then filtered and concentrated to give crude ethyl 6-[3-endo-({[2-{3-[(1-methylethyl)amino]propyl}-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (87 mg, 89% yield) as a yellow oil. MS (EI) for $C_{29}H_{40}N_4O_4$: 509 (MH^+).

[00631] STEP 2: A suspension of ethyl 6-[3-endo-({[2-{3-[(1-methylethyl)amino]-propyl}-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo-[3.2.1]oct-8-yl]pyridine-3-carboxylate (83 mg, 0.16 mmol) and potassium hydroxide (18 mg, 0.32 mmol) in methanol (3 mL) and water (1 mL) was stirred at 60 °C for 1 h. After cooling to room temperature, some of the methanol was evaporated, water was added to the resulting mixture and the pH adjusted to 7 with 1N aqueous hydrochloric acid. The resulting mixture was concentrated and purified by preparatory HPLC (0.1% trifluoroacetic acid-aqueous acetonitrile) to afford 6-[3-endo-({[2-{3-[(1-methylethyl)amino]propyl}-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo-[3.2.1]oct-8-yl]pyridine-3-carboxylic acid trifluoroacetate salt (39 mg, 41% yield) as a colorless oil. MS (EI) for $C_{27}H_{36}N_4O_4$: 481 (MH^+).

[00632] STEP 3: A solution of 6-[3-endo-({[2-{3-[(1-methylethyl)amino]propyl}-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid trifluoroacetate salt (39 mg, 0.08 mmol), benzylamine (10 mg, 0.09 mmol), HATU (31 mg, 0.08 mmol), and diisopropylethylamine (26 mg, 0.20 mmol) in DMF (2 mL) was stirred at room temperature for 5 h. The reaction mixture was purified by preparatory reverse phase HPLC (0.1% trifluoroacetic acid-aqueous acetonitrile) to provide 6-[3-endo-({[2-{3-[(1-methylethyl)amino]propyl}-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide trifluoroacetate salt (25 mg, 45% yield). ^1H NMR (400 MHz, methanol-d_4): 8.57 (d, 1H), 8.46 (d, 1H), 8.26 (dd, 1H), 7.35 (m, 5H), 7.26 (m, 1H), 7.19 (d, 1H), 7.14 (d, 1H), 7.02 (d, 1H), 4.70 (br s, 2H), 4.57 (s,

2H), 4.10 (m, 1H), 3.88 (s, 3H), 3.25 (m, 1H), 2.88 (t, 2H), 2.81 (t, 2H), 2.39-2.20 (m, 6H), 2.10 (m, 2H), 1.26 (d, 6H); MS (EI) for $C_{34}H_{43}N_5O_3$: 570 (MH^+).

SYNTHETIC SCHEME 15:



[00633] Scheme 15 generally describes the synthesis of all of the compound(s) listed in Example 15, wherein R_1 is as defined in the specification.

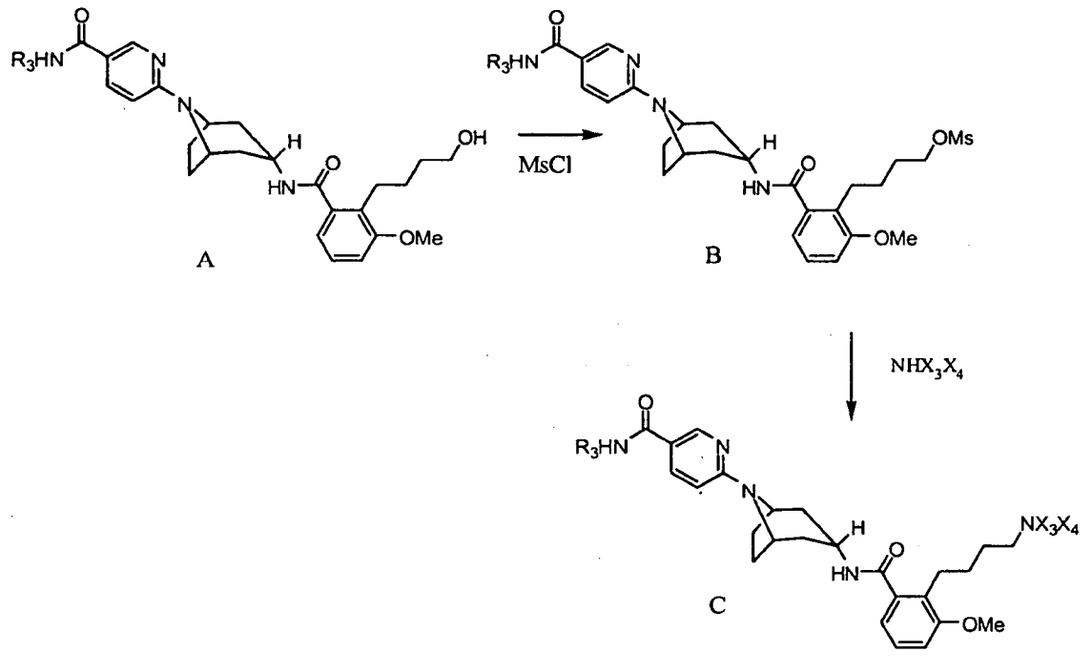
[00634] In Scheme 15, compound (A) is hydrogenated, such as being placed under a hydrogen balloon or in a pressure vessel under a hydrogen atmosphere in the presence of a suitable catalyst such as palladium on carbon, to arrive at compound (B).

[00635] EXAMPLE 15: 6-[3-endo-({[2-(4-hydroxybutyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide.

[00636] STEP 1: 6-[3-endo-({[2-(4-hydroxybut-1-yn-1-yl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide (synthesized in example 3) (0.069 g, 0.152 mmol) in methanol (20 ml) was stirred under a hydrogen balloon overnight at room temperature. The mixture was filtered through Celite and the filter cake rinsed with ethyl acetate (2x10ml). The filtrate was dried over anhydrous sodium sulfate, filtered and the solution was concentrated. The solid residue was purified by preparatory reverse phase HPLC (0.1% ammonium acetate buffered aqueous acetonitrile mobile phase) and the combined pure fractions were lyophilized to yield 6-[3-endo-({[2-(4-hydroxybutyl)-3-(methyloxy)phenyl]carbonyl}-amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide as a white powder (0.047 g; 68% yield). ^{1}H NMR (400 MHz, d_4-MeOH): 8.56 (d, 1H), 8.34 (d, 1H), 8.10 (dd, 1H), 7.24 (t, 1H), 7.02 (d, 1H), 6.96-

6.88 (m, 2H), 4.65 (br s, 2H), 4.06-3.99 (m, 1H), 3.53 (t, 2H), 2.73 (t, 2H), 2.37-2.10 (m, 6H), 1.98 (d, 2H), 1.66-1.50 (m, 4H); MS (EI) for $C_{25}H_{32}N_4O_4$: 453 (MH^+).

SYNTHETIC SCHEME 16:



[00637] Scheme 16 generally describes the synthesis of all of the compound(s) listed in Example 16, wherein R_3 is as defined in the specification and X_3 and X_4 are each independently H or alkyl.

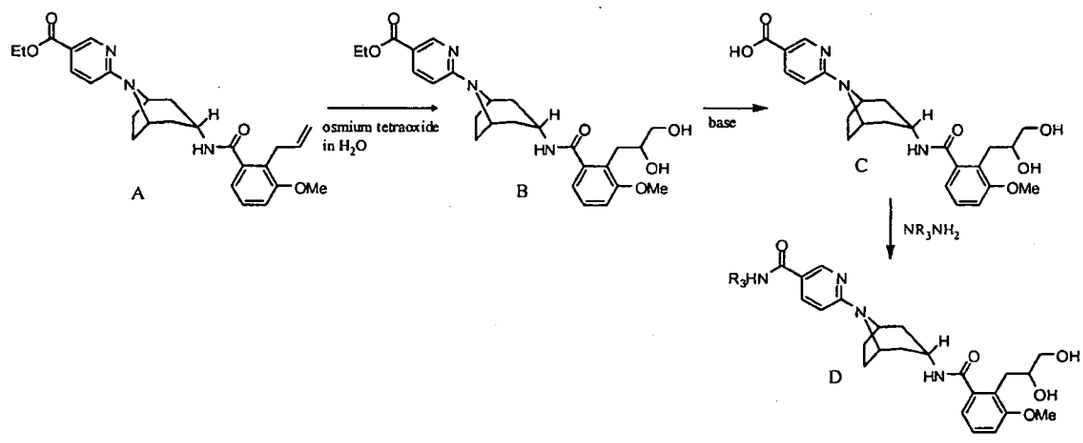
[00638] In Scheme 16, MsCl is added to compound (A) under appropriate reaction conditions to arrive at compound (B). To compound (B) is added NHX_3X_4 under appropriate reaction conditions to arrive at compound (C).

[00639] EXAMPLE 16: 6-{3-endo-[({2-[4-(dimethylamino)butyl]-3-(methyloxy)phenyl}carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}pyridine-3-carboxamide.

[00640] STEP 1: To a stirred solution of 6-[3-endo-({[2-(4-hydroxybutyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide (synthesized in example 15) (0.038 g, 0.0823 mmol) in dichloromethane (3 ml) was added triethylamine (0.034 ml, 0.250 mmol) followed by methanesulfonyl chloride (0.008 ml; 0.110 mmol) and the reaction mixture was stirred at room

temperature overnight. More triethylamine (0.034 ml, 0.250 mmol) and methanesulfonyl chloride (0.008 ml; 0.110 mmol) were added to the solution and the mixture was stirred at room temperature for two additional hours. The mixture was rotary evaporated and to the residue was added dimethylamine (4ml, 2 M solution in tetrahydrofuran, 2 mmol). The resulting solution was stirred in a sealed tube vessel at 60 °C for 2h, cooled to room temperature and concentrated. The residue was purified by preparatory reverse phase HPLC (0.1% ammonium acetate in aqueous acetonitrile mobile phase) and the combined pure fractions were lyophilized to yield 6-{3-endo-[({2-[4-(dimethylamino)butyl]-3-(methyloxy)phenyl}carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}pyridine-3-carboxamide (0.006 g; 15% yield). ^{1}H NMR (400 MHz, d_4-MeOH): 8.62 (d, 1H), 8.01 (dd, 1H), 7.28 (t, 1H), 7.05 (d, 1H), 6.94 (d, 1H), 6.78 (d, 1H), 4.62 (br s, 2H), 4.05-3.95 (m, 1H), 3.24-3.17 (m, 2H), 3.11 (t, 2H), 2.85 (s, 6H), 2.37-2.08 (m, 6H), 1.91 (d, 2H), 1.80-1.60 (m, 4H); MS (EI) for $C_{27}H_{37}N_5O_3$: 480 (MH^+).

SYNTHETIC SCHEME 17:



[00641] Scheme 17 generally describes the synthesis of all of the compound(s) listed in Example 17, wherein R_3 is as defined in the specification.

[00642] In Scheme 17, compound (A) is hydroxylated with an oxidizing agent, such as osmium tetroxide, under appropriate reaction conditions to form compound (B). The carboxylate of compound (B) is then hydrolyzed with a base, such as KOH, to form compound (C). The carboxylic acid thus formed is converted to carboxamide

(D) by treatment with an amine R_3NH_2, or ammonia in the case of R_3 selected to be hydrogen, in the presence of a suitable coupling agent such as HATU.

[00643] EXAMPLE 17: 6-[3-endo-({[2-(2,3-dihydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide.

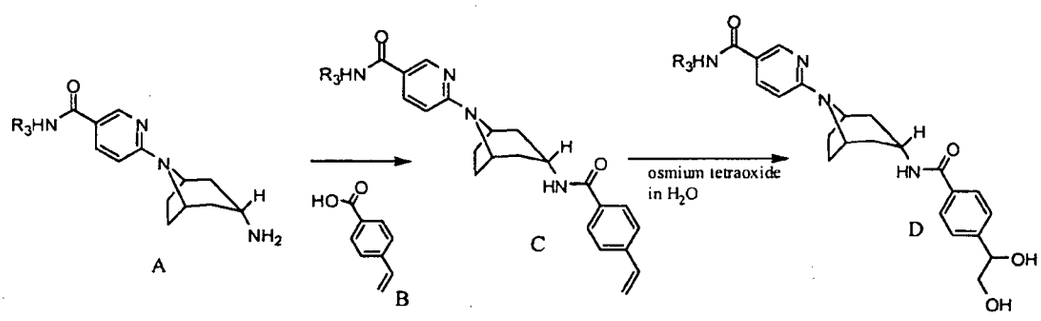
[00644] STEP 1: To a stirred solution of ethyl 6-[3-endo-({[3-(methyloxy)-2-prop-2-en-1-ylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (synthesized in example 13) (0.210 g, 0.470 mmol) and 4-methylmorpholine N-oxide (0.137 g; 1.17 mmol) in a mixture of acetone (0.8 ml) and water (0.2 ml) was added a catalytic amount of osmium tetroxide (0.020 ml, 4 wt % solution in water). The reaction mixture was stirred at 40 °C for 5 h and then quenched by addition of a 10% aqueous solution of sodium bisulfite (0.5 ml). The water phase was extracted with ethyl acetate (2x2ml) and the organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to give ethyl 6-[3-endo({[2-(2,3-dihydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (0.191 g; 85% yield). MS (EI) for $C_{26}H_{33}N_3O_6$: 484 (MH^+).

[00645] STEP 2: To a stirred solution of ethyl 6-[3-endo({[2-(2,3-dihydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (0.191 g, 0.395 mmol) in methanol (4.5 ml) was added potassium hydroxide (0.044 g; 0.79 mmol) in water (1.5ml) and the reaction mixture was stirred at 60 °C for 3h. The solvent was partially evaporated and the solution was acidified to pH 4 by addition of 1.5 M aqueous hydrochloric acid. The water phase was extracted with ethyl acetate (2x5ml) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give 6-[3-({[2-(2,3-dihydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (0.117 g; 65% yield). MS (EI) for $C_{24}H_{29}N_3O_6$: 454 (M-H).

[00646] STEP 3: A stirred solution of 6-[3-({[2-(2,3-dihydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (0.117 g, 0.257 mmol) and HATU in dimethylformamide was saturated with NH_3(g) for 0.5h,and the reaction mixture was stirred in a sealed tube at room temperature overnight. The crude mixture was purified by preparatory reverse phase HPLC (0.1% ammonium acetate buffered aqueous acetonitrile eluent) and the

combined pure fractions were lyophilized to yield 6-[3-endo-({[2-(2,3-dihydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide (0.047 g, 40% yield). ^{1}H NMR (400 MHz, d_4-MeOH): 8.89-8.85 (m, 1H), 8.62 (d, 1H), 7.98 (dd, 1H), 7.30 (t, 1H), 7.07 (d, 1H), 7.03 (d, 1H), 6.74 (d, 1H), 4.60 (br s, 2H), 4.07-3.94 (m, 2H), 3.87 (s, 3H), 3.56-3.52 (m, 2H), 3.03 (dd, 1H), 2.71-2.63 (m, 1H), 2.36-1.92 (m, 8H); MS (EI) for $C_{24}H_{30}N_4O_5$: 454 (MH^+).

SYNTHETIC SCHEME 18:



[00647] Scheme 18 generally describes the synthesis of all of the compound(s) listed in Example 18, wherein R_3 is as defined in the specification.

[00648] In Scheme 18, compound (B) is added to compound (A) under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (C). Compound (C) is then hydroxylated with an oxidizing agent, such as osmium tetroxide, under appropriate reaction conditions to form compound (D).

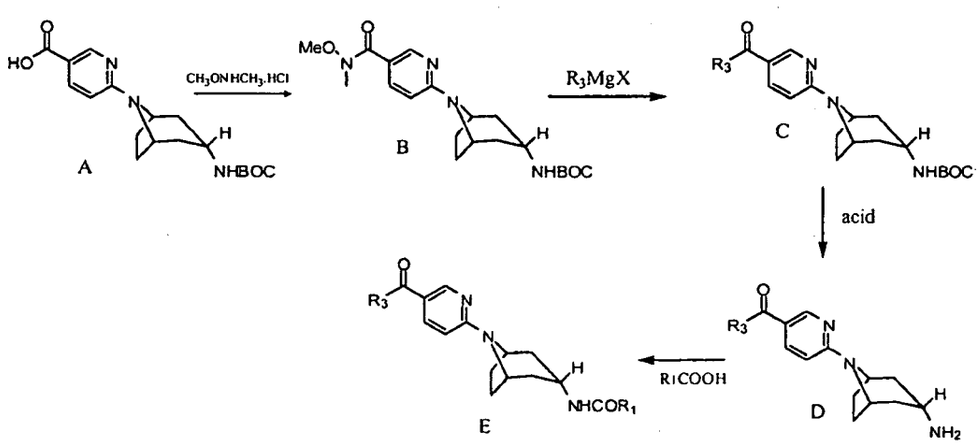
[00649] EXAMPLE 18: 6-[3-endo-({[4-(1,2-dihydroxyethyl)phenyl]carbonyl}-amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide

[00650] STEP 1: To a stirred solution of 4-vinylbenzoic acid (0.036 mg; 0.244 mmol) and N-methylmorpholine (0.098 g, 0.976 mmol) in dimethylformamide (1 ml) was added HOAt (0.490 ml; 0.5 M solution in dimethylformamide, 0.244 mmol), HATU (0.093 g, 0.244 mmol) and 6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide (synthesized in example 2) (0.100 g, 0.244 mmol). The reaction mixture was stirred at room temperature overnight followed by addition of water (3ml) and the resulting solid was collected by filtration and dried

under vacuum to give 6-(3-endo{[(4-ethenylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide (0.081; 71% yield). MS (EI) for $C_{29}H_{30}N_4O_2$: 467 (MH^+).

[00651] STEP 2: To a stirred solution of 6-(3-endo{[(4-ethenylphenyl)carbonyl]-amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide (0.081 g, 0.174 mmol) and 4-methylmorpholine N-oxide (0.053 g; 0.452 mmol) in a mixture of acetone (0.5 ml) and water (0.13 ml) was added a catalytic amount of osmium tetroxide (0.010 ml, 4 wt % solution in water). The reaction mixture was stirred at 40 °C overnight and then quenched by addition of a 10% aqueous solution of sodium bisulfite (0.5 ml). The water phase was extracted with ethyl acetate (2x 2 ml) and the organic layer was dried over anhydrous sodium sulfate then filtered and concentrated. The residue was purified by preparatory reverse phase HPLC (0.05% trifluoroacetic acid acid buffered aqueous acetonitrile mobile phase) and the combined pure fractions were lyophilized to yield 6-[3-endo-({[4-(1,2-dihydroxyethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide (0.052 g; 49% yield) as the trifluoroacetate salt. MS (EI) for $C_{29}H_{32}N_4O_4$: 499 (M-H).

SYNTHETIC SCHEME 19:



[00652] Scheme 19 generally describes the synthesis of all of the compound(s) listed in Example 19, wherein R_3 and R_1 are as defined in the specification.

[00653] In Scheme 19, $CH_3ONHCH_3.HCl$ N,O-dimethylhydroxylamine hydrochloride is added to compound (A) under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form compound (B). To compound (B) is added R_3MgX, (a Grignard reagent), wherein X represents a halogen, under appropriate reaction conditions to arrive at compound (C). Compound (C) is then deprotected with an acid, such as HCl, to remove the BOC and arrive at compound (D). To compound (D) is added R_1COOH under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (E).

[00654] EXAMPLE 19: N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-ethylpiperidin-4-yl)amino]benzene-1,4-dicarboxamide.

[00655] STEP 1: A mixture of 6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}-amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylic acid (7.96 g, 22.91 mmol, example 2, step 1), N,O-dimethylhydroxylamine hydrochloride (2.23 g, 22.91 mmol), HATU (8.71 g, 22.91 mmol), and diisopropylethylamine (11.84 g, 91.64 mmol) in DMF (50 mL) was stirred at roomtemperature for 3 h. The reaction mixture was poured into water (250 mL), filtered and the filter cake was washed with water (2 x 100 mL) then dried to give 1,1-dimethylethyl [8-(5-{[methyl(methyloxy)amino]carbonyl}pyridine-2-yl)-8- azabicyclo[3.2.1]oct-3-endo-yl]carbamate (8.55 g, 96% yield). ^1H NMR (400 MHz, DMSO-d_6): 8.46 (d, 1H), 7.79 (dd, 1H), 6.88 (br s, 1H), 6.69 (d, 1H), 4.49 (br s, 2H), 3.60 (s, 3H), 3.44 (m, 1H), 3.22 (s, 3H), 2.12 (m, 2H), 1.98 (m, 2H), 1.90 (m, 2H), 1.74 (d, 2H), 1.39 (s, 9H). MS (EI) for $C_{20}H_{30}N_4O_4$: 391 (MH^+).

[00656] STEP 2: To a suspension of 1,1-dimethylethyl [8-(5-{[methyl(methyloxy)amino]carbonyl}pyridine-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]carbamate (3.97 g, 10.17 mmol) in THF (70 mL) was added dropwise a 3M solution of methylmagnesium bromide in ether (17 mL, 51.00 mmol) at 0 °C. The ice bath was removed and the solution was stirred for 1 h. The solution was poured into saturated ammonium chloride (200 mL), extracted with ethyl acetate (3 x 100 mL) and the organic layers were washed with brine (100 mL), dried over sodium sulfate then filtered and concentrated. Column chromatography on silica (hexanes:ethyl acetate 1:1) afforded 1,1-dimethylethyl [8-(5-acetylpyridine-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]carbamate (2.55 g, 73% yield). ^1H NMR (400 MHz,

methanol-d_4): 8.71 (d, 1H), 8.03 (dd, 1H), 6.71 (d, 1H), 4.60 (br s, 2H), 3.59 (m, 1H), 2.49 (s, 3H), 2.20-2.04 (m, 6H), 1.81 (d, 2H), 1.44 (s, 9H).

[00657] STEP 3: To a solution of 1,1-dimethylethyl [8-(5-acetylpyridine-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]carbamate (2.00 g, 5.79 mmol) in methanol (5 mL) was added a solution of 4N hydrochloric acid in dioxane (5 mL) and the reaction mixture was refluxed for 2 min. After cooling to room temperature the mixture was concentrated, neutralized with saturated aqueous sodium bicarbonate, extracted with ethyl acetate (7 x 50mL), dried over sodium sulfate, then filtered and concentrated to provide 1-[6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-yl]ethanone (1.11 g, 78% yield). ^{1}H NMR (400 MHz, methanol-d_4): 8.70 (d, 1H), 8.01 (dd, 1H), 6.70 (d, 1H), 4.62 (br s, 2H), 3.01 (m, 1H), 2.48 (s, 3H), 2.29-2.06 (m, 6H), 1.60 (d, 2H). MS (EI) for $C_{14}H_{19}N_3O$: 246 (MH^+).

[00658] STEP 4: To a solution of 1-[6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-yl]ethanone (135 mg, 0.55 mmol) and 4-(aminocarbonyl)-3-[(1-{[(1,1-dimethylethyl)oxy]carbonyl}piperidin-4-yl)amino]benzoic acid (200 mg, 0.55 mmol) in DMF (5 mL) were added HATU (418 mg, 1.1 mmol) and diisopropylethylamine (142 mg, 1.1 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The solution was poured into saturated aqueous sodium chloride solution (30 mL), extracted with ethyl acetate (3 x 30 mL), dried over sodium sulfate then filtered and concentrated to provide 1,1-dimethylethyl (4-{[5-({[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1] oct-3-endo-yl]aminocarbonyl)-2-(aminocarbonyl)phenyl]amino}-piperidine-1-carboxylate (285 mg, 87% yield). ^{1}H NMR (400 MHz, methanol-d_4): 8.70 (d, 1H), 8.01 (d, 1H), 7.96 (s, 3H), 7.65 (d, 1H), 7.1 (s, 1H), 6.9 (d, 1H), 6.70 (d, 1H), 4.65 (s, 1H), 4.0 (m, 3H), 3.65 (m, 1H), 3.1 (br s, 2H), 2.48 (s, 3H), 2.39-2.0 (m, 10H), 1.50 (s, 9H). MS (EI) for $C_{32}H_{42}N_6O_5$: 591 (MH^+).

[00659] STEP 5: To a solution of 1,1-dimethylethyl (4-{[5-({[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1] oct-3-endo-yl]aminocarbonyl)-2-(aminocarbonyl)phenyl]amino}piperidine-1-carboxylate (285 mg, 0.483 mmol) in methanol (2 mL) was added hydrogen chloride in dioxane solution (2M, 0.6 mL) at room temperature. The reaction mixture was stirred at 45°C for 2 h. After cooling to room temperature the mixture was concentrated. The residue was triturated with ethyl acetate then dried to give N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-

yl]-2-(piperidin-4-ylamino)benzene-1,4-dicarboxamide as the hydrochloride salt. ^{1}H NMR (400 MHz, methanol-d_4): 8.55 (s, 1H), 8.30 (m, 2H), 7.70 (d, 2H), 7.65 (d, 1H), 7.22 (d, 1H), 7.18 (s, 1H), 7.00 (d, 1H), 4.06 (s, 1H), 3.92 (s, 1H), 3.48 (m, 2H), 3.24 (m, 2H), 2.39-2.18 (m, 12H), 1.70 (m, 2H); MS (EI) for $C_{27}H_{34}N_6O_3$: 491 (MH^+).

[00660] STEP 6: To a solution of N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(piperidin-4-ylamino)benzene-1,4-dicarboxamide (130 mg, 0.28 mmol) in methanol were added acetaldehyde (12 mg, 0.28 mmol), sodium cyanoborohydride (18 mg, 0.28 mmol) and acetic acid (17 mg, 0.28 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was poured into water (250 mL), extracted with ethyl acetate (2 x 50 mL), dried over sodium sulfate, filtered and concentrated to a volume of 10 mL. The precipitate thus formed was collected by filtration to give N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-ethylpiperidin-4-yl)amino]benzene-1,4-dicarboxamide (16 mg, 12% yield). ^{1}H NMR (400 MHz, methanol-d_4): 8.70(s, 1H), 8.06 (d, J = 9.2Hz, 1H), 7.69 (d, J = 8.2Hz, 1H), 7.14(s, 1H), 6.98(d, J = 8.2Hz, 1H), 6.77(d, J = 9.2Hz, 1H), 4.70(br,s,2H), 4.02(m, 1H), 3.82-3.45 (m, 2H), 3.20-3.05 (m, 6H), 3.00(s, 6H), 2.53(s, 3H), 2.40-2.1(m, 10H), 2.05(m, 2H), 1.34(t, J = 7.2Hz, 3H). MS (EI) for $C_{29}H_{38}N_6O_3$: 519 (MH^+).

[00661] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [(19B)-(19(BE)] were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00662] (19B): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(piperidin-4-ylamino)benzene-1,4-dicarboxamide. Prepared in example 19 step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.55 (s, 1H), 8.30 (m, 2H), 7.70 (d, 2H), 7.65 (d, 1H), 7.22 (d, 1H), 7.18 (s, 1H), 7.00 (d, 1H), 4.06 (s, 1H), 3.92 (s, 1H), 3.48 (m, 2H), 3.24 (m, 2H), 2.39-2.18 (m, 12H), 1.70 (m, 2H). MS (EI) for $C_{27}H_{34}N_6O_3$: 491 (MH^+).

[00663] (19C): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({2-[(1-methylethyl)oxy]ethyl}amino)benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 19 by using 4-(aminocarbonyl)-3-({2-[(1-methylethyl)oxy]ethyl}amino)benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400

MHz, DMSO-d_6) 8.73 (d, 1H), 8.32 (t, 1H), 8.20 (d, 1H), 7.95 (dd, 1H), 7.91 (br s, 1H), 7.68 (d, 1H), 7.32 (br s, 1H), 7.01 (s, 1H), 6.91 (d, 1H), 6.76 (d, 1H), 4.65 (br s, 2H), 3.82 (br s 1H), 3.58 (m, 3H), 3.25 (m, 2H), 2.43 (s, 3H), 2.20 (m, 2H), (2.18 (m, 6H), 1.08 (d, 6H). MS(EI) for $C_{27}H_{35}N_5O_4$: 494 (MH^+).

[00664] (19D): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-methylethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-[(1-methylethyl)amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.75 (s, 1H), 8.20 (dd, 1H), 8.14 (dd, 1H), 7.98 (dd, 1H), 7.92 (bs, 1H), 7.67 (d, 1H), 7.27 (s, 1H), 7.00 (s, 1H), 6.86 (dd, 1H), 6.79 (dd, 1H), 4.64 (bs, 2H), 3.85 (bs, 1H), 3.69 (m, 1H), 2.46 (s, 3H), 2.23 (d, 2H), 2.09-1.95 (m, 6H), 1.20 (d, 6H). MS (EI) for $C_{25}H_{31}N_5O_3$: 450 (MH^+).

[00665] (19E): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-[(1-ethylpropyl)amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.26 (d, 1H), 8.23 (d, 1H), 7.96 (dd, 1H), 7.92 (bs, 1H), 7.66 (d, 1H), 7.26 (bs, 1H), 6.95 (s, 1H), 6.81 (dd, 2H), 4.63 (bs, 1H), 3.85 (bs, 1H), 3.32 (m, 1H), 2.44 (s, 3H), 2.25 (dd, 2H), 2.04 (m, 6H), 1.97 (m, 1H), 1.54 (m, 4H), 0.90 (t, 6H). MS (EI) for $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00666] (19F): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2-methylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-[(2-methylpropyl)amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.39 (t, 1H), 8.21 (d, 1H), 7.96 (dd, 1H), 7.95 (bs, 1H), 7.65 (dd, 1H), 7.30 (bs, 1H), 6.96 (s, 1H), 6.87 (d, 1H), 6.79 (d, 1H), 4.64 (bs, 1H), 3.85 (bs, 1H), 2.99 (t, 2H), 2.46 (s, 3H), 2.25 (d, 2H), 2.04 (m, 4H), 1.97 (m, 4H), 0.95 (d, 6H). MS (EI) for $C_{26}H_{33}N_5O_3$: 464 (MH^+).

[00667] (19G): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2-dimethylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-[(2,2-dimethylpropyl)-amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then

omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.73 (s, 1H), 8.51 (bs, 1H), 8.19 (d, 1H), 7.98 (m, 2H), 7.69 (dd, 1H), 7.31 (bs, 1H), 7.02 (s, 1H), 6.87 (dd, 1H), 6.83 (dd, 1H), 4.65 (bs, 2H), 3.84 (bs, 1H), 2.95 (s, 2H), 2.46 (s, 3H), 2.23 (d, 2H), 2.02 (m, 6H), 0.98 (s, 9H). MS (EI) for $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00668] (19H): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(tetrahydrofuran-2-ylmethyl)amino]benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 19 by using 4-(aminocarbonyl)-3-[(tetrahydrofuran-2-ylmethyl)amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.49 (s, 1H), 8.30 (d, 1H), 8.24 (d, 1H), 7.95 (bs, 1H), 7.70 (dd, 1H), 7.46 (s, 1H), 7.32 (s, 2H), 7.20 (s, 1H), 7.05 (s, 1H), 6.92 (d, 1H), 4.06 (m, 1H), 3.91 (bs, 1H), 3.79 (m, 1H), 3.71 (m, 1H), 3.66 (m, 1H), 3.49 (m, 1H), 3.30 (m, 1H), 3.18 (m, 1H), 2.55 (s, 3H), 2.34 (d, 2H), 2.13 (m, 6H), 1.99 (m, 1H), 1.85 (m, 2H), 1.65 (m, 1H). MS (EI) for $C_{27}H_{33}N_5O_4$: 492 (MH^+).

[00669] (19I): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2-aminoethyl)amino]benzene-1,4-dicarboxamide. Prepared as the HCl salt according to the method of example 19 by using 4-(aminocarbonyl)-3-{[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethyl]amino}benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of step 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.23 (m, 2H), 7.96 (dd, 2H), 7.68 (dd, 1H), 7.32 (bs, 1H), 7.02 (s, 1H), 6.91 (dd, 1H), 6.80 (dd, 1H), 4.65 (bs, 2H), 3.90 (bs, 1H), 3.20 (m, 2H), 2.85 (t, 2H), 2.45 (s, 3H), 2.22 (d, 2H), 2.05 (m, 4H), 1.96 (m, 2H). MS (EI) for $C_{24}H_{30}N_6O_3$: 451 (MH^+).

[00670] (19J): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-methylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-[(1-methylpropyl)amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.21 (m, 2H), 7.97 (dd, 1H), 7.92 (bs, 1H), 7.66 (d, 1H), 7.27 (bs, 1H), 6.97 (s, 1H), 6.84 (dd, 1H), 6.79 (dd, 1H), 4.64 (bs, 2H), 3.85 (bs, 1H), 3.50 (m, 1H), 2.45 (s, 3H), 2.25 (d, 2H), 2.04 (m, 4H), 1.96 (m, 2H), 1.54 (m, 2H), 1.16 (d, 3h), 0.98 (t, 3H). MS (EI) for $C_{26}H_{33}N_5O_3$: 464 (MH^+).

[00671] (19K): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-propylbutyl)amino]benzene-1,4-dicarboxamide. Prepared as the HCl salt according to the method of example 19 by using 4-(aminocarbonyl)-3-[(1-propylbutyl)amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.48 (d, 1h), 8.40 (d, 1H), 7.88 (d, 1H), 7.52 (s, 1H), 7.40 (m, 2H), 4.81 (bs, 2H), 4.13 (m, 1H), 3.62 (q, 1H), 2.57 (s, 3H), 2.43 (m, 2H), 2.31 (m, 6H), 1.60 (m, 4H), 1.43 (m, 4H), 0.94 (t, 6H); MS (EI) for $C_{29}H_{39}N_5O_3$: 506 (MH^+).

[00672] (19L): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1,2-dimethylpropyl)amino]benzene-1,4-dicarboxamide. Prepared as the HCl salt according to the method of example 19 by using 4-(aminocarbonyl)-3-[(1,2-dimethylpropyl)amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.51 (d, 1H), 8.39 (dd, 1H), 8.08 (d, 1H), 7.90 (s, 1H), 7.81 (dd, 1H), 7.39 (d, 1H), 4.14 (m, 1H), 3.74 (m, 1H), 2.57 (s, 3H), 2.44 (m, 2H), 2.37 (m, 2H), 2.31 (m, 4H), 2.21 (m, 1H), 1.11 (m, 9H); MS (EI) for $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00673] (19M): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1,2,2-trimethylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-[(1,2,2-trimethylpropyl)-amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.74 (d, 1H), 8.06 (dd, 1H), 7.64 (d, 1H), 7.12 (s, 1H), 6.84 (d, 1H), 6.76 (d, 1H), 4.70 (bs, 2H), 4.01 (t, 1H), 3.45 (quar, 1H), 2.51 (s, 3H), 2.26 (m, 4H), 2.19 (m, 2H), 2.01 (d, 2H), 1.15 (d, 3H), 1.00 (s, 9H). MS (EI) for $C_{28}H_{37}N_5O_3$: 492 (MH^+).

[00674] (19N): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({1-[(methyloxy)methyl]propyl}amino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-({1-[(methyloxy)methyl]propyl}amino)benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.74 (d, 1H), 8.06 (dd, 1H), 7.63 (d, 1H), 7.11 (s, 1H), 6.90 (d, 1H), 6.76 (d, 1H), 4.70 (bs, 2H), 4.01 (t, 1H), 3.61 (m, 1H), 3.52 (dd, 1H), 3.42 (dd, 1H), 3.36 (s, 3H), 2.51 (s, 3H), 2.26 (m, 4H), 2.18 (m, 2H), 2.01 (m, 2H), 1.76 (m, 1H), 1.59 (m, 1H), 1.00 (t, 3H). MS (EI) for $C_{27}H_{35}N_5O_4$: 494 (MH^+).

[00675] (19O): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-{[(1S)-1-methylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-{[(1S)-1-methylpropyl]amino} benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.74 (d, 1H), 8.24 (d, 1H), 8.06 (dd, 1H), 7.63 (d, 1H), 7.06 (s, 1H), 6.88 (dd, 1H), 6.76 (d, 1H), 4.69 (bs, 2H), 4.01 (m, 1H), 3.56 (m, 1H), 2.50 (s, 3H), 2.26 (m, 4H), 2.19 (m, 2H), 2.00 (m, 2H), 1.61 (m, 2H), 1.22 (m, 3H), 0.98 (t, 3H). MS (EI) for $C_{26}H_{33}N_5O_3$: 464 (MH^+).

[00676] (19P): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({3-[(1-methylethyl)amino]propyl}amino)benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 19 by using 4-(aminocarbonyl)-3-({3-[(1-methylethyl)amino]propyl}amino)benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.74 (d, 1H), 8.06 (dd, 1h), 7.67 (d, 1H), 7.12 (s, 1H), 6.97 (d, 1H), 6.77 (d, 1H), 4.70 (bs, 2H), 4.01 (m, 1H), 3.38 (t, 2H), 3.08 (t, 2H), 2.51 (s, 3H), 2.23 (m, 6H0, 1.99 (m, 4H), 1.89 (s, 3H), 1.31 (d, 6H); MS (EI) for $C_{28}H_{38}N_6O_3$: 507 (MH^+).

[00677] (19Q): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(trans-4-hydroxycyclohexyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-[(trans-4-hydroxycyclohexyl)amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.27 (m, 2H), 7.97 (dd, 1H), 7.91 (br s, 1H), 7.66 (d, 1H), 7.27 (br s, 1H), 6.96 (s, 1H), 6.83 (d, 1H), 6.79 (d, 1H), 4.64 (br s, 2H), 4.60 (d, 1H), 3.85 (br s, 1H), 3.48 (m, 1H), 2.45 (s, 3H), 2.26 (m, 2H), 2.02 (m, 9H), 1.84 (m, 2H), 1.25 (m, 4H). MS (EI) for $C_{28}H_{35}N_5O_4$: 506 (MH^+).

[00678] (19R): N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-methyl-3-(methyloxy)benzamide. Prepared according to the method of example 19 by using 2-methyl-3-methoxybenzoic acid in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.25 (d, 1H), 7.96 (dd, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.78 (d, 1H), 4.62 (br s, 2H), 3.86 (m, 1H), 3.80 (s,

3H), 2.45 (s, 3H), 2.22 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.98 (m, 2H), 1.89 (d, 2H). MS (EI) for $C_{23}H_{27}N_3O_3$: 394 (MH^+).

[00679] (19S): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-[(cyclopropylmethyl)amino]-benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.26 (t, 1H), 8.18 (d, 1H), 7.96 (dd, 1H), 7.93 (br s, 1H), 7.67 (d, 1H), 7.29 (br s, 1H), 6.99 (d, 1H), 6.89 (dd, 1H), 6.79 (d, 1H), 4.64 (br s, 2H), 3.84 (m, 1H), 3.03 (m, 2H), 2.45 (s, 3H), 2.22 (m, 2H), 2.11-1.92 (m, 6H), 1.11 (m, 1H), 0.52 (m, 2H), 0.24 (m, 2H). MS (EI) for $C_{26}H_{31}N_5O_3$: 462 (MH^+).

[00680] (19T): N4-{8-[5-(cyclopentylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using cyclopentylmagnesium chloride in step 2 and 4-(aminocarbonyl)-3-[(cyclopropylmethyl)amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.77 (d, 1H), 8.26 (t, 1H), 8.13 (d, 1H), 8.00 (dd, 1H), 7.94 (br s, 1H), 7.67 (d, 1H), 7.30 (br s, 1H), 6.99 (d, 1H), 6.89 (dd, 1H), 6.79 (d, 1H), 4.64 (br s, 2H), 3.85 (m, 1H), 3.70 (m, 1H), 3.03 (m, 2H), 2.22 (m, 2H), 2.12-1.92 (m, 6H), 1.85 (m, 2H), 1.72 (m, 2H), 1.60 (m, 4H), 1.11 (m, 1H), 0.51 (m, 2H), 0.24 (m, 2H). MS (EI) for $C_{30}H_{37}N_5O_3$: 516 (MH^+).

[00681] (19U): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(butylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 3-(butylamino)-4-(aminocarbonyl)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (s, 1H), 8.27-8.20 (m, 2H), 7.97 (dd, 1H), 7.94 (br s, 1H), 7.67 (d, 1H), 7.30 (d, 1H), 6.97 (d, 1H), 6.87 (dd, 1H), 6.79 (d, 1H), 4.63 (br s, 2H), 3.87-3.81 (m, 1H), 3.16 (q, 2H), 2.45 (s, 3H), 2.27-2.20 (m, 2H), 2.10-1.92 (m, 6H), 1.62-1.54 (m, 2H), 1.44-1.33 (m, 2H),0.93 (t, 3H). MS (EI) for $C_{26}H_{33}N_5O_3$: 464 (MH^+).

[00682] (19V): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({4-(methyloxy)-3-[(2-morpholin-4-ylethyl)oxy]phenyl}amino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-({4-(methyloxy)-3-[(2-morpholin-4-ylethyl)oxy]phenyl}-amino)benzoic acid (synthesized according to reagent preparation 40) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 9.93 (s, 1H), 8.73 (d, 1H), 8.20 (d, 1H), 8.13 (br s, 1H), 7.95 (dd, 1H), 7.76 (d, 1H), 7.56 (br s, 1H), 7.41 (d, 1H), 7.00 (dd, 1H), 6.92 (d, 1H), 6.85-6.81 (m, 2H), 6.76 (d, 1H), 4.59 (br s, 2H), 4.06 (t, 2H), 3.83-3.77 (m m, 1H), 3.74 (s, 3H), 3.56 (t, 4H), 3.50 (s, 1H), 2.68 (t, 2H), 2.44 (s, 3H), 2.34-2.31 (m, 1H), 2.14-2.07 (m, 2H), 2.04-1.85 (m, 7H), 1.23 (br s, 1H). MS (EI) for $C_{35}H_{42}N_6O_6$: 643 (MH^+).

[00683] (19W): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-methylbutanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using isobutyl magnesium bromide in step 2 and 4-(aminocarbonyl)-3-(cyclopropylmethylamino)benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.75 (s, 1H), 8.29-8.24 (m, 1H), 8.19 (s, 1H), 8.01-7.91 (m, 2H), 7.70-7.65 (d, 1H), 7.35-7.26 (br. s, 1H), 6.99 (s, 1H), 6.92-6.86 (d, 1H), 6.81-6.76 (d, 1H), 4.71-4.53 (br. s, 2H), 3.88-3.81 (m, 1H), 3.06-3.00 (m, 2H), 2.77-2.71 (d, 2H), 2.26-2.19 (m, 2H), 2.17-1.91 (m, 7H), 1.15-1.06 (m, 1H), 0.95-0.90 (d, 6H), 0.55-0.48 (m, 2H), 0.28-0.21 (m, 2H). MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00684] (19X): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(4,4,4-trifluorobutanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using trifluoropropylmagnesium bromide in step 2 and 4-(aminocarbonyl)-3-(cyclopropylmethylamino)benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.78 (s, 1H), 8.29-8.24 (m, 1H), 8.19 (s, 1H), 8.04-8.00 (d, 1H), 7.94 (s, 1H), 7.69-7.65 (d, 1H), 7.29 (s, 1H), 6.99 (s, 1H), 6.91-6.87 (d, 1H), 6.82-6.78 (d, 1H), 4.73-4.55 (br. s, 2H), 3.88-3.81 (m, 1H), 3.23-3.16 (m, 2H), 3.06-3.01 (m, 2H), 2.68-2.55 (m, 2H), 2.27-2.19 (m, 2H), 2.11-1.93 (m, 6H), 1.15-1.06 (m, 1H), 0.55-0.48 (m, 2H), 0.27-0.21 (m, 2H). MS (EI) for $C_{28}H_{32}F_3N_5O_3$: 544 (MH^+).

[00685] (19Y): N4-[8-(5-butanoylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 19 by using propylmagnesium bromide in step 2 and 4-(aminocarbonyl)-3-(cyclopropylmethylamino)benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.53 (s, 1H), 8.29-8.24 (m, 1H), 7.74-7.70 (d, 1H), 7.33-7.27 (d, 1H), 7.09 (s, 1H), 7.02-6.97 (d, 1H), 4.86-4.75 (br. s, 2H), 3.98-3.92 (m, 1H), 3.09-3.06 (d, 2H), 2.97-2.92 (m, 2H), 2.39-2.32 (m, 2H), 2.24-2.09 (m, 6H), 1.71-1.61 (m, 2H), 1.18-1.06 (m, 1H), 0.99-0.92 (m, 3H), 0.58-0.51 (m, 2H), 0.31-0.24 (m, 2H). MS (EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00686] (19Z): N4-{8-[5-(cyclobutylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 19 by using cyclobutylmagnesium bromide in step 2 and 4-(aminocarbonyl)-3-(cyclopropylmethylamino)benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.64 (s, 1H), 8.28-8.23 (m, 1H), 8.18 (s, 1H), 7.95-7.81 (m, 2H), 7.70-7.65 (d, 1H), 7.33-7.26 (br. s, 1H), 6.98 (s, 1H), 6.90-6.87 (d, 1H), 6.81-6.76 (d, 1H), 4.70-4.55 (br. s, 2H), 4.05-3.95 (m, 1H), 3.89-3.81 (m, 1H), 3.06-3.00 (m, 2H), 2.27-2.15 (m, 6H), 2.12-1.91 (m, 6H), 1.83-1.73 (m, 2H), 1.14-1.06 (m, 1H), 0.55-0.48 (m, 2H), 0.28-0.21 (m, 2H); MS (EI) for $C_{29}H_{35}N_5O_3$: 502 (MH^+).

[00687] (19AA): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(cyclohexylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-(cyclohexylamino)benzoic acid (synthesized according to reagent prep 40) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.74 (d, 1H), 8.05 (dd, 1H), 7.62 (d, 1H), 7.07 (d, 1H), 6.87 (dd, 1H), 6.75 (d, 1H), 4.69 (br s, 2H), 4.01 (m, 1H), 3.44 (m, 1H), 2.50 (s, 3H), 2.30-2.14 (m, 6H), 2.09-1.96 (m, 1H), 1.82-1.75 (m, 2H), 1.68-1.61 (m, 1H), 1.50-1.26 (m, 5H). MS (EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00688] (19AB): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(cyclopentylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-(cyclopentylamino)benzoic acid

(synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.74 (d, 1H), 8.06 (dd, 1H), 7.63 (d, 1H), 7.09 (d, 1H), 6.89 (dd, 1H), 6.76 (d, 1H), 4.69 (br s, 2H), 4.01 (m, 1H), 3.91 (m, 1H), 2.51 (s, 3H), 2.30-2.15 (m, 6H), 2.10-1.96 (m, 4H), 1.81-1.52 (m, 6H). MS (EI) for $C_{27}H_{33}N_5O_3$: 476 (MH^+).

[00689] (19AC): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(ethylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-(ethylamino)benzoic acid (synthesized according to reagent prep 40) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.17 (d, 1H), 8.09 (t, 1H), 7.96 (dd, 1H), 7.91 (br s, 1H), 7.67 (d, 1H), 7.28 (br s, 1H), 6.98 (d, 1H), 6.89 (dd, 1H), 6.79 (d, 1H), 4.64 (br s, 2H), 3.85 (m, 1H), 3.18 (m, 2H), 2.45 (s, 3H), 2.25-2.20 (m, 2H), 2.11-1.94 (m, 6H), 1.21 (t, 3H). MS (EI) for $C_{24}H_{29}N_5O_3$: 436 (MH^+).

[00690] (19AD): N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-5-[(1-ethylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-2-methyl-5-(pentan-3-ylamino)benzoic acid (synthesized according to reagent prep 42) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.57 (br s, 1H), 8.37 (d, 1H), 8.16 (d, 1H), 7.88 (br s, 1H), 7.51 (s, 1H), 7.18 (m, 2H), 6.59 (s, 1H), 4.42 (m, 2H), 3.89 (m, 1H), 3.23 (m, 1H), 2.52 (m, 2H), 2.36-2.31 (m, 2H), 2.19 (s, 3H), 2.15-2.01 (m ,4H), 2.08 (s, 3H), 1.52 (m, 4H), 0.88 (t, 6H). MS (EI) for $C_{28}H_{37}N_5O_3$: 492 (MH^+).

[00691] (19AE): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}-benzoic acid (synthesized according to reagent prep 40) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.49 (d, 0.5H), 8.37 (dd, 0.5H), 7.97 (dd, 0.5H), 7.87 (d, 0.5H), 7.74 (d, 1H), 7.45 (s, 1H), 7.34 (dd, 1H), 7.09-6.96 (m, 4H), 4.81 (br s, 1H), 4.70 (br s, 1H), 4.34 (m, 2H), 4.05 (m, 1H), 3.88 (s, 3H), 3.58 (m, 3H), 3.02 (s, 6H), 2.56 (s, 1.5H), 2.32-2.12 (m, 8H), 1.54 (s, 1.5H). MS (EI) for $C_{33}H_{40}N_6O_5$: 601 (MH^+).

[00692] (19AF): N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-5-[(1-ethylpropyl)amino]-2-fluorobenzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-2-fluoro-5-(pentan-3-ylamino)benzoic acid (synthesized according to reagent prep 45) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.54 (m, 1H), 8.47 (d, 1H), 8.39 (dd, 1H), 7.59 (d, 1H), 7.37 (d, 1H), 7.15 (d, 1H), 4.79 (br s, 2H), 4.18 (m, 1H), 3.37 (m, 1H), 2.57 (s, 3H), 2.46-2.18 (m, 8H), 1.72-1.51 (m, 4H), 0.95 (t, 6H). MS (EI) for $C_{27}H_{34}FN_5O_3$: 496 (MH^+).

[00693] (19AG): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(piperidin-1-ylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-(piperidin-1-ylamino)benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.79 (d, 1H), 8.33 (d, 1H), 8.05 (dd, 1H), 7.80 (d, 1H), 7.42 (d, 1H), 6.99 (dd, 1H), 6.72 (d, 1H), 6.55 (d, 1H), 4.71 (br s, 2H), 4.28 (q, 1H), 2.74 (br s, 4H), 2.52 (s, 3H), 2.38-2.25 (m, 4H), 2.22-2.15 (m, 2H), 1.95-1.87(m, 2H), 1.73-1.63 (m, 6H). MS (EI) for $C_{27}H_{34}N_6O_3$: 491 (MH^+).

[00694] (19AH): N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-methyl-5-(pentylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-2-methyl-5-(pentylamino)benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.64 (d, 1H), 8.49 (d, 1H), 8.39 (dd, 1H), 7.74 (s, 1H), 7.36 (d, 1H), 7.16 (s, 1H), 4.79 (br s, 2H), 4.15 (q, 1H), 3.30 (m, 2H masked by solvent), 2.57 (s, 3H), 2.43-2.33 (m, 7H), 2.30-2.17 (m, 4H), 1.77-1.70 (m, 2H), 1.46-1.36 (m, 4H), 0.95 (t, 3H); MS (EI) for $C_{28}H_{37}N_5O_3$: 492 (MH^+).

[00695] (19AI): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-yl]-2-(pyrrolidin-3-ylamino)benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 19 by using 4-(aminocarbonyl)-3-[(1-{[(1,1-dimethylethyl)oxy]carbonyl}pyrrolidin-3-yl)amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of step 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.74 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 2.0, 9.2Hz, 1H), 7.71 (d, J = 8.0Hz, 1H), 7.08(s, 1H), 7.05 (dd, J = 1.2, 8.0Hz, 1H), 6.77 (d, J = 9.2Hz, 1H), 4.70 (s, 1H), 4.33(m, 1H), 4.02 (s, 1H), 3.58-3.40 (m, 4H), 2.51 (s, 3H), 2.40(m, 1H), 2.12-2.36 (m, 4H), 2.10-1.98 (m, 2H). MS (EI) for $C_{26}H_{32}N_6O_3$: 479 (MH^+).

[00696] (19AJ): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-yl]-2-[(piperidin-3-ylmethyl)amino]benzene-1,4-dicarboxamide. Prepared as the HCl salt according to the method of example 19 by using 4-(aminocarbonyl)-3-{[(1-{[(1,1-dimethylethyl)oxy]carbonyl}piperidin-3-yl)methyl]amino}benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of step 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.50(s, 1H), 8.39 (d, J = 9.2Hz, 1H), 7.69 (d, J = 8.4Hz, 1H), 7.37(d, J = 9.2 Hz, 1H), 7.14 (s, 1H), 7.00 (m, 1H), 4.80 (br, s, 1H), 4.10(br, s, 1H), 3.72 (m, 2H), 3.50-3.10 (m, 6H), 2.99-2.76 (m, 4H), 2.43-2.0(m, 4H). MS (EI) for $C_{28}H_{36}N_6O_3$: 505 (MH^+).

[00697] (19AK): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-yl]-2-[(pyrrolidin-3-ylmethyl)amino]benzene-1,4-dicarboxamide. Prepared as the HCl salt according to the method of example 19 by using 4-(aminocarbonyl)-3-{[(1-{[(1,1-dimethylethyl)oxy]carbonyl}pyrrolidin-3-yl)methyl]amino}benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of step 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.50(s, 1H), 8.39 (d, J = 9.2Hz, 1H), 7.69 (d, J =8.4Hz, 1H), 7.38(d, J = 9.2 Hz, 1H), 7.19 (s, 1H), 7.00 (m, 1H), 4.82 (br, s, 1H), 4.07(br, s, 1H), 3.72 (m, 1H), 3.50-3.30 (m, 6H), 3.05 (m, 1H), 2.78(m, 1H), 2.60(s, 3H), 2.42-2.20(m, 8H), 1.85(m, 1H), 1.40(m, 2H). MS (EI) for $C_{27}H_{34}N_6O_3$: 491 (MH^+).

[00698] (19AL): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-yl]-2-[(3-{[2-(dimethylamino)ethyl]oxy}phenyl)amino]benzene-1,4-dicarboxamide. Prepared as the acetate salt according to the method of example 19 by using 4-(aminocarbonyl)-3-[(3-{[(2-dimethylamino)ethyl]oxy}phenyl)amino]benzoic acid (synthesized according to reagent prep 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, methanol-d_4): 8.70 (s, 1H), 8.29 (s, 1H), 8.11 (d, J = 6.0Hz, 1H), 7.73 (m, 2H), 7.38-6.6 (m, 6H), 4.70 (br,s,2H), 4.46 (br, s, 1H), 4.07 (m, 1H), 3.82-3.45 (m, 3H), 3.05 (m, 2H), 3.00 (s, 6H), 2.86 (m, 2H), 2.53 (s, 3H), 2.20 (m, 4H), 2.05 (m, 2H). MS (EI) for $C_{32}H_{38}N_6O_4$: 571 (MH^+).

[00699] (19AM): 2-[(cyclopropylmethyl)amino]-N4-[8-(5-propanoylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using ethylmagnesium chloride in step 2 and 4-(aminocarbonyl)-3-(cyclopropylmethylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6.

^{1}HNMR (400 MHz, DMSO-d_6): 8.76 (s, 1H), 8.27-8.18 (m, 1H), 7.99-7.93 (m, 1H), 7.68-7.66 (d, 1H), 7.23 (s, 1H), 6.98 (s, 1H), 6.89 (d, 1H), 6.78 (d, 1H), 4.64 (s, 2H), 3.84 (s, 1H), 3.05 (t, 2H), 2.92 (t, 2H), 2.22-2.21 (m, 2H), 2.08-1.97 (m, 6H), 1.11-1.04 (m, 5H), 0.53-0.49 (m, 2H), 0.26-0.24 (m, 2H). MS (EI) for $C_{27}H_{33}N_5O_3$: 476 (MH^+).

[00700] (19AN): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(2-methylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared as the HCl salt according to the method of example 19 by using isopropylmagnesium chloride in step 2 and 4-(aminocarbonyl)-3-(cyclopropylmethylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}HNMR (400MHz, DMSO-d_6): 8.63 (s,1H), 8.25 (d, 1H), 8.16 (d, 1H), 7.96 (s, 1H), 7.70-7.68 (m, 1H), 7.32-7.30 (m, 1H), 7.12-7.10 (m, 1H), 6.93 (s, 1H), 6.90 (d, 1H), 4.77 (s, 2H), 3.89 (s, 1H), 3.16-3.01 (m, 2H), 2.28 (s, 6H), 2.11-2.07 (m, 2H), 2.05-2.04 (m, 6H), 1.12 (s, 1H), 1.08-1.06 (m, 4H), 0.53-0.5 (m, 2H), 0.27-0.24 (m, 2H). MS (EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00701] (19AO): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(ethylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 using 4-cyano-5-[(trans-4-hydroxycyclohexyl)amino]-2-methylbenzoic acid (synthesized according to reagent prep 41) in step 3 followed by nitrile hydrolysis as described in example 11 step 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.28 (d, 1H), 7.98-7.95 (m, 2H), 7.83 (br s, 1H), 7.47 (s, 1H), 7.16 (br s, 1H), 6.78 (d, 1H), 6.61 (s, 1H), 4.64 (br s, 2H), 4.57 (d, 1H), 3.87-3.82 (m, 1H), 3.51-3.42 (m, 1H), 3.26-3.17 (m ,1H), 2.45 (s, 3H), 2.32-2.26 (m, 2H), 2.19 (s, 3H), 2.08-1.91 (m, 8H), 1.86-1.80 (m, 2H), 1.32-1.15 (m, 4H). MS (EI) for $C_{29}H_{37}N_5O_4$: 520 (MH^+).

[00702] (19AP): N4-[8-(5-Acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(cyclopropylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-(cyclopropylamino)benzoic acid (synthesized according to reagent preparation 40) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.32 (br, 1H), 8.25 (d, 1H), 7.97 (dd, 2H), 7.68 (d, 1H), 7.41 (d, 1H), 7.34 (br, 1H), 6.93 (dd, 1H), 6.79 (d, 1H), 4.64 (br, 2H), 3.87 (br, 1H), 2.45 (s, 3H), 2.32-2.23 (m, 2H), 2.12-1.92 (m, 7H), 0.79-0.73 (m, 2H), 0.50-0.43 (m, 2H). MS (EI) for $C_{25}H_{29}N_5O_3$: 448 (MH^+).

[00703] (19AQ): N4-[8-(5-Acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(tetrahydrofuran-3-ylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-(tetrahydrofuran-3-ylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.75 (d, 1H), 8.38 (d, 1H), 8.23 (d, 1H), 8.01-7.94 (m, 2H), 7.70 (d, 1H), 7.36 (br s, 1H), 6.97 (s, 1H), 6.92 (dd, 1H), 6.80 (d, 1H), 4.64 (br s, 2H), 4.18-4.10 (m, 1H), 3.94-3.72 (m, 4H), 3.56 (dd, 1H), 2.45 (s, 3H), 2.30-2.19 (m, 3H), 2.12-1.92 (m, 6H), 1.82-1.72 (m, 1H). MS (EI) for $C_{26}H_{31}N_5O_4$: 478 (MH^+).

[00704] (19AR): N4-[8-(5-Acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2,3,3,3-pentafluoropropyl)amino]benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 19 by using 4-(aminocarbonyl)-3-(2,2,3,3,3-pentafluoropropylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.72-8.60 (m, 2H), 8.28 (d, 1H), 8.14-8.07 (m, 2H), 7.74 (d, 1H), 7.51 (br s, 1H), 7.20 (s, 1H), 7.12-7.03 (m, 1H), 7.03 (dd, 1H), 4.78 (br s, 2H), 4.28 (br t, 2H), 3.90 (br s, 1H), 2.51 (s, 3H), 2.35-2.24 (m, 2H), 2.18-1.97 (m, 6H). MS (EI) for $C_{25}H_{26}F_5N_5O_3$: 540 (MH^+).

[00705] (19AS): N-[8-(5-Acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-methyl-5-{[4-(trifluoromethyl)cyclohexyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-2-methyl-5-(4-(trifluoromethyl)cyclohexylamino)benzoic acid (synthesized according to reagent preparation 42) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.96 (dd, 1H), 7.90 (br s, 1H), 7.52 (s, 1H), 7.25 (br s, 1H), 6.78 (d, 1H), 6.60 (s, 1H), 4.62 (br s, 2H), 3.88-3.81 (m, 1H), 3.77-3.70 (m, 1H), 2.45 (s, 3H), 2.40-2.30 (m, 1H), 2.29-2.21 (m, 2H), 2.19 (s, 3H), 2.12-1.95 (m, 4H), 1.95-1.85 (m, 4H), 1.77-1.57 (m, 4H), 1.54-1.40 (m, 2H). MS (EI) for $C_{30}H_{36}F_3N_5O_3$: 572 (MH^+).

[00706] (19AT): N4-[8-(5-Acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2,3,3,4,4,4-heptafluorobutyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-(2,2,3,3,4,4,4-heptafluorobutylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d,

1H), 8.67 (t, 1H), 8.24 (d, 1H), 8.09 (br s, 1H), 7.97 (dd, 1H), 7.74 (d, 1H), 7.51 (s, 1H), 7.19 (s, 1H), 7.03 (dd, 1H), 6.79 (d, 1H), 4.65 (br s, 2H), 4.32 (td, 2H), 3.87 (br s, 1H), 2.46 (s, 3H), 2.29-2.20 (m, 2H), 2.13-1.90 (m, 6H). MS (EI) for $C_{26}H_{26}F_7N_5O_3$: 588 (MH^+).

[00707] (19AU): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-aminobenzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-aminobenzoic acid (synthesized according to reagent preparation 43) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.16 (d, 1H), 7.96 (dd, 1H), 7.84 (br s, 1H), 7.60 (d, 1H), 7.22 (br s, 1H), 7.07 (d, 1H), 6.80 (m, 4H), 4.63 (br s, 2H), 3.84 (s, 1H), 2.45 (s, 3H), 2.24 (m, 2H), 2.09-1.91 (m, 6H). MS (EI) for $C_{22}H_{25}N_5O_3$: 408 (MH^+).

[00708] (19AV): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(tetrahydro-2H-pyran-4-ylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-(tetrahydro-2H-pyran-4-ylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO):8.74 (d, 1H), 8.31 (d, 1H), 8.23 (d, 1H), 7.98-7.95 (m, 2H), 7.69 (d, 1H), 7.32 (br s, 1H), 7.00 (s, 1H), 6.87 (dd, 1H), 6.79 (d, 1H), 4.63 (br s, 2H), 3.88-3.86 (m, 3H), 3.66-3.56 (m, 1H), 3.45 (t, 2H), 2.46 (s, 3H), 2.24 (d, 2H), 2.07-1.92 (m, 8H), 1.46-1.36 (m, 2H). MS (EI) for $C_{27}H_{33}N_5O$: 492 (MH^+).

[00709] (19AW): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(phenylamino)benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 19 by using 4-(aminocarbonyl)-3-(phenylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 10.13(br s, 1H), 8.64 (s, 1H), 8.31 (d, 1H), 8.19 (s, 1H), 8.07 (d, 1H), 7.80 (d, 1H), 7.65 (s, 1H), 7.64 (s, 1H), 7.35-7.31 (m, 2H), 7.25 (d, 2H), 7.11 (dd, 1H), 7.04-7.00 (m, 2H), 4.71 (br s, 2H), 3.84 (br s, 1H), 2.49 (s, 3H), 2.22 (d, 2H), 2.09-2.00 (m, 6H). MS (EI) for $C_{28}H_{29}N_5O_3$: 484 (MH^+).

[00710] (19AX): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(phenylmethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 3-(phenylmethyl)-4-(aminocarbonyl)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5

and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 10.13(br s, 1H), 8.72-8.68 (m, 2H), 8.13 (br s, 1H), 7.99-7.94 (m, 2H), 7.69 (d, 1H), 7.37 (br s, 1H), 7.32 (br s, 4H), 7.24 (br s, 1H), 6.91-6.88 (m, 2H), 6.77 (d, 1H), 4.59 (br s, 2H), 4.48 (d, 2H), 3.79 (br s, 1H), 2.44 (s, 3H), 2.09 (d, 2H), 2.02-1.88 (m, 6H). MS (EI) for $C_{29}H_{31}N_5O_3$: 498 (MH^+).

[00711] (19AY): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(3S)-tetrahydrofuran-3-ylamino]benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 19 by using (S)-4-(aminocarbonyl)-3-(tetrahydrofuran-3-ylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (s, 1H), 8.29 (s, 1H), 8.14 (d, 1H), 8.00 (br s, 1H), 7.72 (d, 1H), 7.37 (br s, 1H), 7.13 (d, 1H), 6.97 (s, 1H), 6.93 (d, 1H), 4.81 (br s, 2H), 4.16 (br s, 1H), 3.90-3.75 (m, 4H), 3.57 (d, 1H), 2.52 (s, 3H), 2.35-2.19 (m, 4H), 2.09 (br s, 6H), 1.76 (m, 1H). MS (EI) for $C_{26}H_{31}N_5O_4$: 478 (MH^+).

[00712] (19AZ): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2,2-trifluoroethyl)amino]benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 19 by using 4-(aminocarbonyl)-3-(2,2,2-trifluoroethylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.64 (s, 2H), 8.24 (d, 1H), 8.12-8.05 (m, 2H), 7.73 (d, 1H), 7.51 (br s, 1H), 7.23 (s, 1H), 7.04 (d, 2H), 4.74 (br s, 2H), 4.26-4.15 (m, 2H), 3.89 (br s, 1H), 2.51 (s, 3H), 2.31-2.22 (m, 2H), 2.16-1.99 (m, 6H). MS (EI) for $C_{27}H_{33}N_5O$: 490 (MH^+).

[00713] (19BA): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(3R)-tetrahydrofuran-3-ylamino]benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 19 by using (R)-4-(aminocarbonyl)-3-(tetrahydrofuran-3-ylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.50 (s, 1H), 8.34 (d, 1H), 8.23 (d, 1H), 8.02 (br s, 1H), 7.72 (d, 1H), 7.36 (br s, 1H), 7.33 (d, 1H), 6.98 (s, 1H), 6.94 (d, 1H), 4.87 (br s, 2H), 4.19-4.13 (m, 1H), 3.92-3.87 (m, 2H), 3.86-3.73 (m, 2H), 3.59 (dd, 1H), 2.55 (s, 3H), 2.38-2.21 (m, 4H), 2.18-2.07 (m, 6H), 1.82-1.73 (m, 1H). MS (EI) for $C_{26}H_{31}N_5O_4$: 478 (MH^+).

[00714] (19BB): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(propylamino)benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 19 by using 4-(aminocarbonyl)-3-(propylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (s, 1H), 8.39 (s, 1H), 8.22-8.15 (m, 1H), 7.98 (br s, 1H), 7.74-7.67 (m, 1H), 7.34 (br s, 1H), 7.25 (br s, 1H), 7.01 (s, 1H), 6.94-6.88 (m, 1H), 4.54 (br s, 2H), 3.90 (s, 1H), 3.18-3.10 (m, 2H), 2.54 (s, 3H), 2.35-2.27 (m, 2H), 2.15-2.06 (m, 6H), 1.65-1.56 (m, 2H), 0.99-0.92 (m, 3H). MS (EI) for $C_{25}H_{31}N_5O_3$: 450 (MH^+).

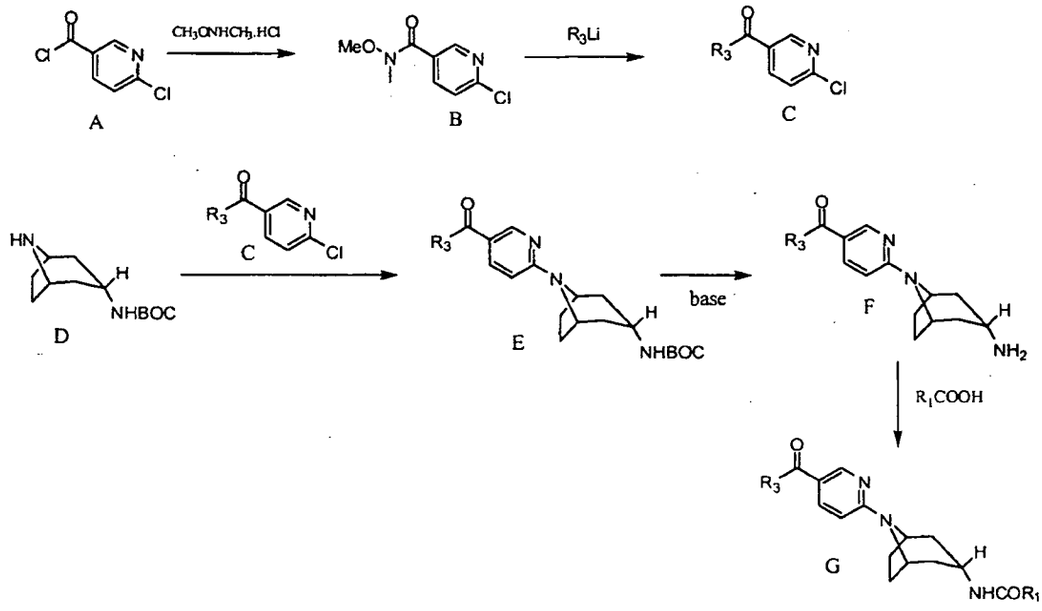
[00715] (19BC): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-azetidin-1-ylbenzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 3-(azetidin-1-yl)-4-(aminocarbonyl)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (s, 1H), 8.39 (s, 1H), 8.22-8.15 (m, 1H), 7.98 (br s, 1H), 7.74-7.67 (m, 1H), 7.34 (br s, 1H), 7.25 (br s, 1H), 7.01 (s, 1H), 6.94-6.88 (m, 1H), 4.54 (br s, 2H), 3.90 (s, 1H), 3.18-3.10 (m, 2H), 2.54 (s, 3H), 2.35-2.27 (m, 2H), 2.15-2.06 (m, 6H), 1.65-1.56 (m, 2H), 0.99-0.92 (m, 3H). MS (EI) for $C_{25}H_{29}N_5O_3$: 448 (MH^+).

[00716] (19BD): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-bromobenzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 3-bromo-4-(aminocarbonyl)benzoic acid (synthesized according to reagent preparation 44) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.37 (d, 1H), 8.02 (d, 1H), 7.98-7.95 (m, 2H), 7.82 (dd, 1H), 7.70 (br s, 1H), 7.50 (d, 1H), 6.80 (d, 1H), 4.65 (br s, 2H), 3.89-3.83 (m, 1H), 2.46 (s, 3H), 2.20-2.19 (m, 2H), 2.14-1.92 (m, 6H). MS (EI) for $C_{22}H_{23}BrN_4O_3$: 471, 473 (MH^+).

[00717] (19BE): N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(3,3,3-trifluoropropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 19 by using 4-(aminocarbonyl)-3-(3,3,3-trifluoropropylamino)benzoic acid (synthesized according to reagent preparation 39) in step 4, then omission of steps 5 and 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.38-8.34 (m, 1H), 8.26 (d, 1H), 7.99-7.95 (m, 2H), 7.70 (d, 1H), 7.36 (br s, 1H), 6.97 (s, 1H), 6.93 (dd, 1H), 6.89 (d, 1H), 4.64 (br s, 2H), 3.89-3.83 (m, 1H), 3.48 (q,

2H), 2.68-2.58 (m, 2H), 2.45 (s, 3H), 2.28-2.21 (m, 2H), 2.11-1.91 (m, 6H). MS (EI) for $C_{25}H_{28}F_3N_5O_3$: 504 (MH^+).

SYNTHETIC SCHEME 20:



[00718] Scheme 20 generally describes the synthesis of all of the compound(s) listed in Example 20, wherein R_3 and R_1 are as defined in the specification.

[00719] In Scheme 20, CH_3ONHCH_3.HCl N,O-dimethylhydroxylamine hydrochloride is added to compound (A) under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form compound (B). To compound B is added R_3Li under appropriate reaction conditions to arrive at compound (C). To compound (D) is added compound (C) in the presence of a weak base, such as tribasic potassium phosphate, and appropriate reaction conditions to undergo an aromatic nucleophilic substitution reaction and arrive at compound (E). Compound (E) is then deprotected with an acid, such as HCl, to remove the BOC and arrive at compound (F). To compound (F) is added R_1COOH under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (G).

[00720] EXAMPLE 20: N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide.

[00721] STEP 1: To a solution of 6-chloronicotinoyl chloride (2 g, 11.4 mmol) and diethylisopropylamine (5 mL, 28.5 mmol) in dichloromethane (100 mL) was added *N,O*-dimethylhyroxylamine hydrochloride (1.22 g, 12.5 mmol) at 0 °C. The solution was allowed to warm to room temperature then was stirred for 48 hours. The mixture was washed with 20% aqueous citric acid (2 x 100 mL), 1N aqueous sodium hydroxide (2 x 100 mL), brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford 6-chloro-*N*-methyl-*N*-(methyloxy)pyridine-3-carboxamide (2.05 g, 92% yield) as a yellow oil. ^{1}H NMR (400 MHz, d_6-DMSO): 8.65 (d, 1H), 8.08 (dd, 1H), 7.63 (d, 1H), 3.67 (s, 3H), 3.30 (s, 3H); MS (EI) for $C_8H_9ClN_2O_2$: 201 (MH^+).

[00722] STEP 2: To a solution of cyclopropylbromide (1.24 g, 10.24 mmol) in THF (10 mL) was added dropwise a 2.5M solution of n-butyllithium in hexanes (4.0 mL, 10.00 mmol) at -78 °C and the reaction mixture was stirred for 1 h at this temperature. Then a solution of 6-chloro-*N*-methyl-*N*-(methyloxy)pyridine-3-carboxamide (1.00 g, 4.98 mmol) in THF (5 mL) was added quickly at -78 °C, and the cooling bath was removed. Stirring was continued for 1 h, then the solution was poured into saturated ammonium chloride (100 mL), extracted with ethyl acetate (3 x 50 mL) and the organic layers were washed with brine (50 mL), dried over sodium sulfate then filtered and concentrated. Column chromatography on silica (hexanes:ethyl acetate 9:1 to 8:2) afforded (6-chloropyridin-3-yl)(cyclopropyl)-methanone (0.62 g, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 9.04 (d, 1H), 8.22 (dd, 1H), 7.46 (d, 1H), 2.61 (m, 1H), 1.32 (m, 2H), 1.15 (m, 2H).

[00723] STEP 3: To a solution of 1,1-dimethylethyl 8-azabicyclo[3.2.1]oct-3-endo-ylcarbamate hydrochloride (synthesized in reagent preparation 1) (795 mg, 3.03 mmol) and (6-chloropyridin-3-yl)(cyclopropyl)methanone (500 mg, 2.75 mmol) in diethylene glycol dimethyl ether (5 mL) was added an aqueous solution of potassium phosphate tribasic (1.75 g, 8.25 mmol in 5 mL of water). The biphasic mixture was stirred at 125 °C for 60 h. The mixture was cooled to room temperature and was diluted with water (25 mL). The precipitate thus formed was filtered, washed several times with water followed by hot hexane, and dried to afford 1,1-dimethylethyl{8-[5-

(cyclopropylcarbonyl)pyridine-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (943 mg, 96% yield). ^{1}H NMR (400 MHz, d_6-DMSO): 8.85 (d, 1H), 8.00 (dd, 1H), 6.89 (br s, 1H), 6.73 (d, 1H), 4.53 (br s, 2H), 3.44-3.40 (m, 1H), 2.80-2.73 (m, 1H), 2.15-2.08 (m, 2H), 2.00-1.87 (m, 4H), 1.78-1.71 (m, 2H), 1.37 (s, 9H), 0.94-0.88 (m, 4H); MS (EI) for $C_{21}H_{29}N_3O_3$: 372 (MH^+).

[00724] STEP 4: To a solution of 1,1-dimethylethyl{8-[5-(cyclopropylcarbonyl)pyridine-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (1.00 g, 2.69 mmol) in dioxane (18 mL) was added concentrated sulfuric acid (2.0 mL) and the mixture was stirred at room temperature for 30 min. The mixture was carefully poured into saturated aqueous sodium bicarbonate (300 mL), and extracted with 10% methanol in chloroform (3 x 100 mL). The combined organic layers were washed with water (50 mL), dried over sodium sulfate then filtered and concentrated to give [6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridin-3-yl](cyclopropyl)-methanone (0.71 g, 97% yield). ^{1}H NMR (400 MHz, d_4-methanol): 8.80 (d, 1H), 8.07 (dd, 1H), 6.72 (d, 1H), 4.63 (br s, 2H), 3.02 (m, 1H), 2.70 (m, 1H), 2.30-2.06 (m, 7H), 1.60 (d, 2H), 1.08 (m, 2H), 1.02 (m, 2H).

[00725] STEP 5: A solution of [6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridin-3-yl](cyclopropyl)methanone (100 mg, 0.37 mmol), HATU (210 mg, 0.55 mmol), 4-(aminocarbonyl)-2-methyl-5-{[(1R)-1-methylpropyl]amino}benzoic acid (synthesized in reagent preparation 41) (138 mg, 0.55 mmol), and diisopropylethyl-amine (256 µl, 1.47 mmol) in DMF (3 mL) was stirred at room temperature for 2 h. Concentration and column chromatography on silica (dichloromethane:methanol 100:0 then 95:5) followed by trituration of the residue obtained on concentration of the combined pure fractions with ethyl acetate afforded N-{8-[5-(cyclopropyl-carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide (179 mg, 96% yield) as a pale yellow powder. ^{1}H NMR (400 MHz, methanol-d_4): 8.84 (d, 1H), 8.11 (dd, 1H), 7.45 (s, 1H), 6.78 (d, 1H), 6.68 (s, 1H), 4.68 (br s, 2H), 4.02 (t, 2H), 3.77-3.67 (m, 1H), 3.25-3.19 (m, 2H), 2.76-2.70 (m, 1H), 2.32-2.25 (m, 7H), 2.18-2.14 (m, 2H), 1.97 (br s, 1H), 1.70-1.59 (m, 1H), 1.60-1.50 (m, 1H), 1.25-1.18 (m, 4H), 1.12-1.09 (m, 2H), 1.06-1.01 (m, 2H), 0.97 (t, 3H); MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00726] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [(20B)-(20BF)] were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00727] (20B): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-[(cyclopropylmethyl)amino]benzoic acid (synthesized according to reagent prep 39) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.26 (t, 1H), 8.18 (d, 1H), 8.05 (dd, 1H), 7.93 (br s, 1H), 7.67 (d, 1H), 7.29 (br s, 1H), 6.99 (d, 1H), 6.89 (dd, 1H), 6.81 (d, 1H), 4.64 (br s, 2H), 3.85 (m, 1H), 3.03 (m, 2H), 2.80 (m, 1H), 2.22 (m, 2H), 2.12-1.93 (m, 6H), 1.11 (m, 1H), 0.95 (m, 4H), 0.51 (m, 2H), 0.24 (m, 2H); MS (EI) for $C_{28}H_{33}N_5O_3$: 588 (MH^+).

[00728] (20C): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 20 by using 4-(aminocarbonyl)-3-[(1-ethylpropyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.61 (d, 1H), 8.45 (dd, 1H), 8.42 (d, 1H), 7.73 (d, 1H), 7.39 (d, 1H), 7.23 (s, 1H), 7.06 (d, 1H), 4.81 (br s, 2H), 4.12 (m, 1H), 3.44 (m, 1H), 2.74 (m, 1H), 2.46-2.23 (m, 8H), 1.74-1.53 (m, 4H), 1.16 (m, 4H), 0.97 (t, 6H); MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00729] (20D): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(pyridin-4-ylamino)benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 20 by using 4-(aminocarbonyl)-3-(pyridin-4-ylamino)benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.64 (d, 1H), 8.55 (d, 1H), 8.42 (dd, 1H), 8.22 (d, 2H), 7.88 (m, 3H), 7.32 (d, 1H), 7.18 (d, 2H), 4.81 (br s, 2H), 4.14 (m, 1H), 2.74 (m, 1H), 2.43-2.20 (m, 8H), 1.15 (m, 4H); MS (EI) for $C_{29}H_{30}N_6O_3$: 511 (MH^+).

[00730] (20E): 2-(cyclopentylamino)-N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 20 by using 4-(aminocarbonyl)-3-(cyclopentylamino)benzoic acid (synthesized according to reagent

preparation 39) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.76 (s, 1H), 8.29 (d, 1H), 8.22 (d, 1H), 7.96 (br s, 1H), 7.69 (d, 1H), 7.31 (br s, 1H), 7.15 (br d, 1H), 7.02 (s, 1H), 6.87 (d, 1H), 4.80 (br s, 2H), 3.90 (m, 1H), 3.85 (m, 1H), 2.86 (m, 1H), 2.31 (m, 2H), 2.09 (m, 6H), 1.98 (m, 2H), 1.65 (m, 4H), 1.46 (m, 2H), 1.02 (d, 4H); MS (EI) for $C_{29}H_{35}N_5O_3$: 502 (MH^+).

[00731] (20F): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cis-4-hydroxy-4-methylcyclohexyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-[(cis-4-hydroxy-4-methyl-cyclohexyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.88 (d, 1H), 8.23 (d, 2H), 8.06 (dd, 1H), 7.92 (br s, 1H), 7.67 (d, 1H), 7.29 (br s, 1H), 6.97 (s, 1H), 6.83 (d, 2H), 4.66 (br s, 2H), 3.85 (br s, 1H), 2.80 (m, 1H), 2.26 (m, 2H), 2.03 (m, 7H), 1.77 (m, 2H), 1.57 (m, 4H), 1.39 (m, 2H), 1.13 (s, 3H), 0.96 (m, 4H); MS (EI) for $C_{31}H_{39}N_5O_4$: 546 (MH^+).

[00732] (20G): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1R)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-{[(1R)-1,2-dimethylpropyl]amino}benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.85 (d, 1H), 8.11 (dd, 1H), 7.97 (d, 1H), 7.64 (d, 1H), 7.07 (s, 1H), 6.86 (d, 1H), 6.78 (d, 1H), 4.70 (br s, 2H), 4.02 (m, 1H), 3.53 (m, 1H), 2.73 (m, 1H), 2.31-2.16 (m, 6H), 2.02 (m, 2H), 1.90 (m, 1H), 1.16 (d, 3H), 1.10 (m, 2H), 1.04 (m, 2H), 1.01 (d, 3H), 0.96 (d, 3H); MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00733] (20H): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-({2-[(1-methylethyl)oxy]ethyl}amino)benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-({2-[(1-methylethyl)oxy]ethyl}amino)benzoic acid (synthesized according to reagent preparation 39) in step 5. MS (EI) for $C_{29}H_{37}N_5O_4$: 520.6 (MH^+).

[00734] (20I): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[1-(trifluoromethyl)propyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-{[1-

(trifluoromethyl)propyl]amino}benzoic acid (synthesized according to reagent preparation 39) in step 5. MS (EI) for $C_{29}H_{34}F_3N_5O_3$: 558 (MH^+).

[00735] (20J): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(3,3,3-trifluoro-1-methylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-[(3,3,3-trifluoro-1-methylpropyl)amino]benzoic acid (synthesized according to reagent preparation 42) in step 5. MS (EI) for $C_{29}H_{34}F_3N_5O_3$: 558 (MH^+).

[00736] (20K): 2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(2-methylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-[(2-methylpropyl)amino] benzoic acid (synthesized according to reagent preparation 50) in step 5. MS (EI) for $C_{28}H_{34}BrN_5O_3$: 568 (MH^+).

[00737] (20L): 5-(cyclobutylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-[(cyclobutylamino)-2-methylbenzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.90 (s, 1H), 8.32 (s, 1H), 8.05 (m, 1H), 8.04 (m, 1H), 7.84 (br, s, 1H), 7.50 (s, 1H), 7.22 (s, 1H), 6.80 (d, J = 9.2Hz, 1H), 6.46 (s, 1H), 4.64 (br s, 2H), 3.89 (m, 2H), 2.80 (m, 1H), 2.30 (m, 4H), 2.10-1.90 (m, 10H); MS (EI) for $C_{29}H_{35}N_5O_3$: 502 (MH^+).

[00738] (20M): N5-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-3-[(1-ethylpropyl)amino]-6-methylpyridine-2,5-dicarboxamide. Prepared according to the method of example 20 by using 6-(aminocarbonyl)-5-[(1-ethylpropyl)amino]-2-methylpyridine-3-carboxylic acid (synthesized according to reagent preparation 49) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.84 (s, 1H), 8.11 (d, J = 8.80Hz), 7.97 (s, 2H), 7.09 (s, 1H), 6.78 (d, J = 8.80Hz, 1H), 4.69 (br, s, 2H), 4.04 (br, s, 1H), 3.32(m, 1H), 2.73 (m, 1H), 2.43 (s, 3H), 2.30-2.06 (m, 6H), 2.03-1.98 (m, 2H), 1.80-1.50 (m, 4H), 1.30 (m, 2H), 1.12-1.01(m, 4H), 0.96 (t, J = 7.2Hz, 6H); MS (EI) for $C_{29}H_{38}N_6O_3$: 519 (MH^+).

[00739] (20N): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-{[(1*S*)-1-methylpropyl]amino}benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.84 (d, 1H), 8.11 (dd, 1H), 7.63 (d, 1H), 7.06 (s, 1H), 6.87 (dd, 1H), 6.78 (d, 1H), 4.69 (bs, 2H), 4.02 (t, 1H), 3.55 (q, 1H), 2.73 (m, 1H), 2.27 (m, 4H), 2.20 (m, 2H), 2.01 (m, 2H), 1.62 (m, 2H), 1.23 (d, 3H), 1.10 (m, 2H), 1.04 (m, 2H), 0.99 (t, 3H); MS (EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00740] (20O): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(1-methylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-[(1-methylpropyl)amino]benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.84 (d, 1H), 8.11 (dd, 1H), 7.63 (d, 1H), 7.06 (s, 1H), 6.87 (dd, 1H), 6.78 (d, 1H), 4.71 (bs, 2H), 4.03 (t, 1H), 3.56 (q, 1H), 2.72 (m, 1H), 2.27 (m, 4H), 2.20 (m, 2H), 2.01 (m, 2H), 1.62 (m, 2H), 1.23 (d, 3H), 1.10 (m, 2H), 1.04 (m, 2H), 0.99 (t, 3H); MS (EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00741] (20P): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-{[(1*R*)-1-methylpropyl]amino}benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.84 (d, 1H), 8.11 (dd, 1H), 7.63 (d, 1H), 7.06 (s, 1H), 6.84 (dd, 1H), 6.78 (d, 1H), 4.71 (bs, 2H), 4.02 (m, 1H), 3.56 (m, 1H), 2.73 (m, 1H), 2.27 (m, 4H), 2.20 (m, 2H), 2.00 (m, 2H), 1.62 (m, 2H), 1.23 (d, 3H), 1.10 (m, 2H), 1.04 (m, 2H), 0.99 (t, 3H); MS (EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00742] (20Q): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(2-methylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-[(2-methylpropyl)amino]benzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (s, 1H), 8.27 (d, 1H), 8.19 (t, 1H), 8.04 (dd, 1H), 7.86 (bs, 1H), 7.49 (s, 1H), 7.19 (bs,

1H), 6.79 (d, 1H), 6.57 (s, 1H), 4.63 (bs, 2H), 3.85 (m, 1H), 3.32 (m, 1H), 2.93 (t, 2H), 2.80 (m, 1H), 2.27 (m, 2H), 2.19 (s, 3H), 2.04 (m, 4H), 1.93 (m, 2H), 0.94 (m, 10H); MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00743] (20R): 5-[(cyclopentylmethyl)amino]-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-[(cyclopentylmethyl)amino]-2-methylbenzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.26 (d, 1H), 8.12 (t, 1H), 8.04 (dd, 1H), 7.84 (bs, 1H), 7.48 (s, 1H), 7.17 (bs, 1H), 6.79 (d, 1H), 6.58 (s, 1H), 4.64 (bs, 2H), 3.85 (m, 1H), 3.32 (m, 1H), 3.02 (m, 2H), 2.26 (m, 2H), 2.19 (s, 3H), 2.04 (m, 4H), 1.92 (m, 2H), 1.73 (m, 2H), 1.60 (m, 2H), 1.52 (m, 2H), 1.24 (m, 2H), 0.95 (m, 4H); MS (EI) for $C_{31}H_{39}N_5O_3$: 530 (MH^+).

[00744] (20S): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[1-(1-methylcyclopropyl)ethyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-{[1-(1-methylcyclopropyl)ethyl]amino}benzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.27 (d, 1H), 8.17 (d, 1H), 8.04 (dd, 1H), 7.85 (s, 1H), 7.47 (s, 1H), 7.17 (bs, 1H), 6.79 (d, 1H), 6.56 (s, 1H), 4.63 (bs, 1H), 3.85 (m, 1H), 3.09 (t, 1H), 2.81 (m, 1H), 2.27 (m, 2H), 2.18 (s, 3H), 2.03 (m, 4H), 1.93 (m, 2H), 1.15 (d, 3H), 1.07 (s, 3H), 0.95 (m, 4H), 0.37 (m, 2H), 0.26 (m, 2H); MS (EI) for $C_{31}H_{39}N_5O_3$: 530 (MH^+).

[00745] (20T): 2-chloro-*N*-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-chloro-5-[(1-ethylpropyl)amino]benzoic acid (synthesized according to reagent preparation 46) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.71 (d, 1H), 8.59 (d, 1H), 8.45 (dd, 1H), 7.68 (s, 1H), 7.38 (d, 1H), 6.76 (s, 1H), 4.77 (br s, 2H), 4.17-4.12 (m, 1H), 2.77-2.71 (m, 1H), 2.50-2.17 (m, 8H), 1.70-1.48 (m, 4H), 1.21-1.10 (m ,4H), 0.94 (t, 6H); MS (EI) for $C_{29}H_{36}ClN_5O_3$: 538 (MH^+).

[00746] (20U): 2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-(propylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-(propylamino)benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.42 (d, 1H), 8.33-8.28 (m, 1H), 8.04 (dd, 2H), 7.84 (s, 1H), 7.35 (br s, 1H), 6.79 (d, 1H), 6.59 (s, 1H), 4.63 (br s, 2H), 3.90-3.83 (m, 1H), 3.12-3.05 (m, 2H), 2.84-2.76 (m, 1H), 2.34-2.26 (m, 2H), 2.15-2.05 (m, 2H), 2.02-1.87 (m, 4H), 1.64-1.52 (m, 2H),1.00-0.90 (m, 2H); MS (EI) for $C_{29}H_{34}F_3N_5O_3$: 554, 556 (MH^+).

[00747] (20V): 2-(butylamino)-N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-(butylamino)benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.25-8.20 (m, 2H), 8.05 (dd, 1H), 7.94 (br s, 1H), 7.68 (d, 1H), 7.30 (br s, 1H), 6.97 (d, 1H), 6.87 (dd, 1H), 6.81 (d, 1H), 4.65 (br s, 2H), 3.86 (br s, 1H), 3.17 (q, 2H), 2.85-2.76 (m, 1H), 2.28-2.20 (m, 2H), 2.13-1.92 (m, 6H), 1.63-1.53 (m, 2H), 1.45-1.34 (m, 2H), 0.99-0.90 (m, 7H); MS (EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00748] (20W): *N*-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[2-methyl-1-(trifluoromethyl)propyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-{[2-methyl-1-(trifluoromethyl)propyl]amino}benzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.84 (d, 1H), 8.30 (d, 1H), 8.11 (dd, 1H), 7.53 (s, 1H), 6.87 (s, 1H), 6.78 (d, 1H), 4.69 (br s, 2H), 4.14-4.00 (m, 2H), 2.76-2.69 (m ,1H), 2.34-2.12 (m, 9H), 2.01-1.93 (m, 2H), 1.12-1.01 (m, 10H); MS (EI) for $C_{30}H_{36}F_3N_5O_3$: 572 (MH^+).

[00749] (20X): 2-bromo-*N*-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(2,2-dimethylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-[(2,2-dimethylpropyl)amino]benzoic acid (synthesized according to reagent preparation 50 in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.58 (t, 1H), 8.40 (d, 1H), 8.04 (m, 2H), 7.85 (s, 1H), 7.35 (s, 1H), 6.79 (d, 1H), 6.63 (s, 1H), 4.62 (br s, 2H), 3.89-3.84 (m, 1H), 3.17 (d, 1H), 2.90 (d, 1H), 2.84-

2.77 (m, 1H), 2.34-2.28 (m, 2H), 2.14-1.87 (m, 6H), 0.99-0.92 (m, 13H); MS (EI) for $C_{29}H_{36}BrN_5O_3$: 582, 584 (MH^+).

[00750] (20Y): *N*-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[2-fluoro-1-(fluoromethyl)ethyl]amino}-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-{[2-fluoro-1-(fluoromethyl)ethyl]amino}-2-methylbenzoic acid (synthesized according to reagent preparation 42) in step 5. ^1H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.37 (d, 1H), 8.28 (d, 1H), 8.04 (dd, 1H), 7.94 (s, 1H), 7.53 (s, 1H), 6.80 (d, 1H), 6.73 (s, 1H), 4.69-4.48 (m, 6H), 4.15-3.99 (m, 1H), 3.90-3.84 (m, 1H), 2.83-2.77 (m, 1H), 2.30-2.19 (m, 5H), 2.14-1.87 (m, 6H); MS (EI) for $C_{28}H_{33}F_2N_5O_3$: 526 (MH^+).

[00751] (20Z): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(trans-4-piperidin-1-ylcyclohexyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-[(trans-4-(piperidin-1-ylcyclohexyl)amino]benzoic acid (synthesized according to reagent preparation 47) in step 5. ^1H NMR (400 MHz, methanol-d_4): 8.78 (s, 1H), 8.28 (s, 1H), 8.24-8.20 (d, 1H), 7.69-7.65 (d, 1H), 7.13 (s, 1H), 7.00-6.91 (m, 1H), 4.77-4.70 (br. s, 2H), 4.10-4.02 (m, 1H), 3.54-3.44 (m, 4H), 3.27-3.24 (m, 1H), 3.09-3.01 (m, 1H), 2.76-2.69 (m, 1H), 2.37-2.26 (m, 4H), 2.26-2.14 (m, 2H), 2.14-2.04 (d, 2H), 2.03-1.96 (d, 2H), 1.88-1.66 (m, 4H), 1.58-1.47 (m, 2H), 1.44-1.32 (m, 4H), 1.17-1.10 (m, 4H), 1.09-1.03 (m, 2H); MS (EI) for $C_{35}H_{46}N_6O_3$: 599 (MH^+).

[00752] (20AA): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1S)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-{[(1S)-1,2-dimethylpropyl]amino}benzoic acid (synthesized according to reagent preparation 39) in step 5. ^1H NMR (400 MHz, d_6-DMSO): 8.90 (s, 1H), 8.40-8.34 (d, 1H), 8.23 (s, 1H), 8..07-8.02 (d, 1H), 7.96-7.89 (s, 1H), 7.70-7.63 (d, 1H), 7.31-7.24 (br. s, 1H), 6.97 (s, 1H), 6.85-6.78 (m, 2H), 4.72-4.53 (br. s, 2H), 3.88-3.81 (m, 1H), 3.52-3.43 (m, 1H), 2.85-2.77 (m, 1H), 2.31-2.19 (m, 4H), 2.12-1.92 (m, 6H), 1.91-1.82 (m, 1H), 1.12-1.05 (d, 3H), 0.99-0.92 (m, 5H), 0.91-0.85 (d, 2H); MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00753] (20AB): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(1-cyclopropylethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-(1-cyclopropylethylamino)benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.84 (s, 1H), 8.14-8.09 (d, 1H), 7.65-7.60 (d, 1H), 7.08 (s, 1H), 6.92-6.86 (d, 1H), 6.81-6.75 (d, 1H), 4.76-4.64 (br. s, 2H), 4.05-3.98 (m, 1H), 3.28-3.20 (m, 1H), 2.77-2.68 (m, 1H), 2.33-2.15 (m, 6H), 2.05-1.96 (d, 2H), 1.30-1.26 (d, 3H), 1.14-1.07 (m, 2H), 1.06-0.95 (m, 3H), 0.55-0.45 (m, 2H), 0.37-0.22 (m, 2H); MS (EI) for $C_{29}H_{35}N_5O_3$: 502 (MH^+).

[00754] (20AC): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1R)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-3-{[(1R)-1,2-dimethylpropyl]amino}benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.84 (s, 1H), 8.14-8.09 (d, 1H), 7.45 (s, 1H), 6.80-6.75 (d, 1H), 6.68 (d, 1H), 6.81-6.75 (d, 1H), 4.75-4.63 (br. s, 2H), 4.05-3.98 (m, 1H), 3.47-3.40 (m, 1H), 2.77-2.68 (m, 1H), 2.34-2.21 (m, 7H), 2.20-2.11 (m, 2H), 2.04-1.86 (m, 3),1.17-1.12 (d, 3H), 1.11-1.08 (m, 2H), 1.06-1.02 (m, 2H), 1.01-0.98 (d, 3H), 0.96-0.92 (d, 2H); MS (EI) for $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00755] (20AD): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[2-methyl-1-(1-methylethyl)propyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-{[2-methyl-1-(1-methylethyl)propyl]amino}benzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.84 (s, 1H), 8.15-8.07 (d, 1H), 7.45 (s, 1H), 6.82-6.73 (m, 2H), 4.75-4.63 (br. s, 2H), 4.05-3.98 (m, 1H), 3.38-3.34 (m, 3H), 3.12-3.05 (m, 1H), 2.74-2.67 (m, 1H), 2.35-2.11 (m, 6H), 2.04-1.86 (m, 2), 1.14-1.00 (m, 7H), 0.99-0.85 (m, 12H); MS (EI) for $C_{32}H_{45}N_5O_3$: 546 (MH^+).

[00756] (20AE): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(dicyclopropylmethyl)amino]-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-(dicyclopropylmethylamino)-2-methylbenzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90

(s, 1H), 8.31-8.26 (d, 1H), 8.09-7.95 (m, 2H), 7.84 (s, 1H), 7.48 (s, 1H), 7.19 (s, 1H), 6.82-6.76 (d, 1H), 6.57 (s, 1H), 5.54-5.44 (m, 1H), 5.13-5.03 (m, 1H), 4.73-4.53 (m, 2H), 3.89-3.81 (m, 1H), 3.14-3.08 (m, 1H), 2.85-2.77 (m, 1H), 2.31-2.23 (m, 4H), 2.19 (s, 3H), 2.13-1.98 (m, 6H), 1.96-1.88 (m, 2H), 1.40-1.31 (m, 1H), 0.99-0.92 (m, 4H), 0.66-0.59 (m, 2H), 0.35-0.28 (m, 2H); MS (EI) for $C_{32}H_{39}N_5O_3$: 542 (MH^+).

[00757] (20AF): 2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(3,3,3-trifluoropropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-(3,3,3-trifluoropropylamino)benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.84 (s, 1H), 8.15-8.07 (d, 1H), 7.84 (s, 1H), 6.82-6.75 (d, 2H), 6.73 (s, 1H), 4.74-4.61 (br. s, 2H), 4.08-4.00 (m, 1H), 3.53-3.46 (m, 2H), 2.76-2.68 (m, 1H), 2.61-2.47 (m, 2H), 2.37-2.25 (m, 4H), 2.17-2.07 (m, 2H), 2.03-1.94 (d, 2H), 1.14-1.07 (m, 2H), 1.06-0.99 (m, 2H); MS (EI) for $C_{27}H_{29}BrN_5O_3$: 609 (MH^+).

[00758] (20AG): 2-bromo-5-(cyclobutylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-(cyclobutylamino)benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (s, 1H), 8.46-8.43 (d, 1H), 8.40-8.36 (d, 1H), 8.07-8.02 (d, 2H), 7.85 (s, 1H), 7.42-7.37 (br. s, 1H), 6.82-6.77 (d, 1H), 6.47 (s, 1H), 4.72-4.54 (br. s, 2H), 3.95-3.83 (m, 2H), 2.84-2.76 (m, 1H), 2.43-2.26 (m, 4H), 2.13-2.04 (m, 2H), 2.03-1.96 (m, 2H), 1.93-1.87 (d, 2H), 1.85-1.71 (m, 4H), 1.00-0.91 (m, 4H); MS (EI) for $C_{28}H_{32}BrN_5O_3$: 567 (MH^+).

[00759] (20AH): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[(1R)-1,2,2-trimethylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-{[(1R)-1,2,2-trimethylpropyl]amino}benzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.32 (s, 1H), 8.30 (t, 1H), 8.04 (dd, 1H), 7.85 (s, 1H), 7.48 (s, 1H), 7.16 (s, 1H), 6.80 (d, 1H), 6.61 (s, 1H), 4.63 (br s, 1H), 3.82-3.88 (m, 1H), 3.35 (s, 3H), 3.22-3.28 (m, 1H), 2.77-2.84 (m, 1H), 2.28 (d, 2H), 2.19 (t, 3H), 2.00-2.10 (m, 4H), 1.90-1.95 (m, 2H), 1.05 (d, 3H), 0.94 (s, 12H); MS (EI) for $C_{31}H_{41}N_5O_3$: 532 (MH^+).

[00760] (20AI): 2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-methylethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-[(1-methylethyl)amino]benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.44 (d, 1H), 8.19 (d, 1H), 8.04 (dd, 2H), 7.83 (s, 1H), 7.35 (s, 1H), 6.79 (d, 1H), 6.61 (s, 1H), 3.85-3.88 (m, 1H), 3.60-3.64 (m, 2H), 2.78-2.82 (m, 1H), 2.31 (d, 2H), 1.88-2.11 (m, 6H), 1.12-1.18 (m, 7H), 0.93-0.97 (m, 4H); MS (EI) for $C_{27}H_{32}BrN_5O_3$: 555 (MH^+).

[00761] (20AJ): 2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-[(1-ethylpropyl)amino]benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.45 (d, 1H), 8.31 (d, 1H), 8.04 (dd, 2H), 7.83 (s, 1H), 7.33 (broad s, 1H), 6.79 (d, 1H), 6.60 (s, 1H), 4.60 (broad s, 2H), 3.85 (m, 1H), 3.28 (m, 1H), 2.80 (m, 1H), 2.30 (m, 2H), 2.10 (m, 2H), 1.99 (m, 2H), 1.93 (d, 2H), 1.50 (m, 4H), 0.95 (m, 4H), 0.89 (t, 6H); MS (EI) for $C_{29}H_{36}N_5O_3Br$: 584 (MH^+).

[00762] (20AK): 2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-{[(1*R*)-1-methylpropyl]amino}benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.44 (d, 1H), 8.26 (d, 1H), 8.04 (dd, 2H), 7.83 (s, 1H), 7.34 (broad s, 1H), 6.79 (d, 1H), 6.60 (s, 1H), 4.60 (broad s, 2H), 3.87 (m, 1H), 3.45 (m, 1H), 2.81 (m, 1H), 2.32 (m, 2H), 2.10 (m, 2H), 1.99 (m, 2H), 1.93 (d, 2H), 1.50 (m, 2H), 1.12 (d, 3H), 0.89 (m, 7H); MS (EI) for $C_{28}H_{34}N_5O_3$: 570 (MH^+).

[00763] (20AL): 2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1R)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-{[(1R)-1,2-dimethylpropyl]amino}benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H NMR (400 MHz,

DMSO- d_6): 8.85 (d, 1H), 8.42 (m, 2H), 8.06 (d, 1H), 8.02 (d, 1H), 7.83 (s, 1H), 7.31 (bs, 1H), 6.78 (d, 1H), 6.62 (s, 1H), 4.62 (bs, 2H), 3.86 (m, 1H), 3.40 (m, 1H), 2.81 (m, 1H), 2.32 (m, 2H), 2.08 (m, 2H), 1.98 (m, 2H), 1.90 (m, 2H), 1.83 (m, 1H), 1.06 (d, 3H), 0.94 (m, 7H), 0.87 (m, 3H); MS (EI) for $C_{29}H_{36}BrN_5O_3$: 584 (MH^+).

[00764] (20AM): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-aminocarbonyl-2-methyl-5-[(1-ethylpropyl)amino]benzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.31 (d, 1H), 8.07-8.02 (m, 2H), 7.85 (br s, 1H), 7.48 (s, 1H), 7.17 (br s, 1H), 6.79 (d, 1H), 6.57 (s, 1H), 4.62 (br s, 2H), 3.88-3.82 (m, 1H), 3.27-3.18 (m, 1H), 2.84-2.76 (m, 1H), 2.32-2.23 (m, 2H), 2.18 (s, 3H), 2.13-1.88 (m, 6H), 1.62-1.41 (m, 4H), 0.99-0.92 (m, 4H), 0.88 (t, 6H); MS (EI) for $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00765] (20AN): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(2,2,3,3,3-pentafluoropropyl)amino]benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 20 by using 4-(aminocarbonyl)-3-(2,2,3,3,3-pentafluoropropylamino)benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.65 (br s, 1H), 8.41-8.34 (m, 2H), 7.72 (d, 1H), 7.28 (br s., 1H), 7.25 (br s, 1H), 7.10 (dd, 1H), 4.78 (br s, 2H), 4.19-4.08 (m, 3H), 2.78-2.70 (m, 1H), 2.44-2.16 (m, 8H), 1.20-1.08 (m, 4H); MS (EI) for $C_{27}H_{28}F_5N_5O_3$: 566 (MH^+).

[00766] (20AO): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]-2-fluorobenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using using 4-aminocarbonyl-2-fluoro-5-[(1-ethylpropyl)amino]benzoic acid (synthesized according to reagent preparation 45) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.37 (d, 1H), 8.07-8.01 (m, 2H), 7.98 (br s, 1H), 7.56 (d, 1H), 7.40 (br s, 1H), 6.80 (d, 1H), 6.72 (d, 1H), 4.63 (br s, 2H), 3.93-3.86 (m, 1H), 3.29-3.20 (m, 1H), 2.84-2.76 (m, 1H), 2.30-2.21 (m, 2H), 2.12-1.86 (m, 6H), 1.61-1.37 (m, 4H), 0.99-0.91 (m, 4H), 0.87 (t, 6H); MS (EI) for $C_{29}H_{36}FN_5O_3$: 522 (MH^+).

[00767] (20AP): 5-amino-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 5-amino-4-(aminocarbonyl)-2-

methylbenzoic acid (synthesized according to reagent preparation 43) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.87 (d, 1H), 8.28 (d, 1H), 8.07 (dd, 1H), 7.79 (br s, 1H), 7.43 (s, 1H), 7.16 (br s, 1H), 6.85 (d, 1H), 6.67 (s, 1H), 4.65 (br s, 2H), 3.88-3.81 (m, 1H), 2.85-2.77 (m, 1H), 2.29-2.22 (m, 2H), 2.17 (s, 3H), 2.14-1.86 (m, 6H), 0.99-0.93 (m, 4H); MS (EI) for $C_{25}H_{29}N_5O_3$: 448 (MH^+).

[00768] (20AQ): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[(1S)-1-methylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-3-{[(1S)-1-methylpropyl]amino}benzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.85 (d, 1H), 8.12 (dd, 1H), 7.45 (s, 1H), 6.78 (d, 1H), 6.69 (s, 1H), 4.69 (br s, 2H), 4.02 (t, 1H), 3.51-3.43 (m, 1H), 2.76-2.70 (m, 1H), 2.33-2.25 (m, 7H), 2.19-2.14 (m, 2H), 2.01-1.95 (m, 3H), 1.69-1.62 (m, 1H), 1.59-1.52 (m, 1H), 1.22 (d, 3H), 1.13-1.09 (m, 2H), 1.06-1.02 (m, 2H), 0.98 (t, 3H); MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00769] (20AR): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-cyclopropylethyl)amino]-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-(1-cyclopropylethylamino)-2-methylbenzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.85 (d, 1H), 8.12 (dd, 1H), 7.45 (s, 1H), 6.79 (d, 1H), 6.69 (s, 1H), 4.69 (brs, 2H), 4.02 (t, 1H), 3.20-3.13 (m, 1H), 2.77-2.70 (m, 1H), 2.33-2.13 (m, 9H), 2.01-1.95 (m, 3H), 1.27 (d, 3H), 1.12-0.95 (m, 5H), 0.52-0.47 (m, 2H), 0.33-0.24 (m, 2H); MS (EI) for $C_{30}H_{37}N_5O_3$: 515 (MH^+).

[00770] (20AS): 2-bromo-5-(cyclopentylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-(cyclopentylamino)benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H NMR (DMSO-d_6): 8.89 (s, 1H), 8.44 (d, 1H), 8.33 (d, 1H), 8.06-8.05 (m, 2H), 7.83 (s, 1H), 7.34 (s, 1H), 6.79 (s, 1H), 6.63 (s, 1H), 4.63 (s, 2H), 3.88 (s, 1H), 3.88-3.77 (m, 1H), 2.95-2.93 (m, 1H), 2.41 (d, 2H), 2.21-1.98 (m, 8H), 1.66-1.59 (m, 4H), 1.46-1.41 (m, 2H), 0.95-0.93 (m, 4H); MS (EI) for $C_{29}H_{34}BrN_5O_3$: 581 (MH^+).

[00771] (20AT): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-(propylamino)benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-(propylamino)benzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H NMR (DMSO-d_6): 8.89 (s, 1H), 8.30 (d, 1H), 8.07 (t, 2H), 7.87 (s, 1H), 7.49 (s, 1H), 7.21 (s, 1H), 6.82 (d, 1H), 6.58 (s, 1H), 4.64 (s, 2H), 3.86-3.85 (m, 1H), 3.09 (t, 2H), 2.83-2.82 (m, 1H), 2.20-2.18 (m, 2H), 2.16 (s, 3H), 2.09-1.94 (m, 6H), 1.62-1.57 (m, 2H), 0.98-0.91 (m, 7H); MS (EI) for $C_{28}H_{35}N_5O_3$: 490(MH^+).

[00772] (20AU): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]-2-(trifluoromethyl)benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-[(1-ethylpropyl)amino]-2-(trifluoro-methyl)benzoic acid (synthesized according to reagent preparation **51**) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.82 (d, 1H), 8.50 (d, 1H), 8.20 (br s, 1H), 8.04 (dd, 1H), 7.96 (d, 1H), 7.40 (br s, 1H), 6.79 (d, 1H), 6.64 (s, 1H), 4.63 (br s, 2H), 3.89-3.81 (m, 1H), 3.45-3.33 (m, 1H), 2.84-2.76 (m, 1H), 2.30-2.20 (m, 2H), 2.14-1.92 (m, 4H), 1.88 (d, 2H), 1.66-1.43 (m, 4H), 0.99-0.92 (m, 4H), 0.89 (t, 6H); MS (EI) for $C_{30}H_{36}F_3N_5O_3$: 572 (MH^+).

[00773] (20AV): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(3,3,3-trifluoropropyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-(3,3,3-trifluoropropylamino)benzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.32 (d, 1H), 8.16 (t, 1H), 8.04 (dd, 1H), 7.89 (br s, 1H), 7.52 (s, 1H), 7.26 (br s, 1H), 6.80 (d, 1H), 6.60 (s, 1H), 4.62 (br s, 2H), 3.91-3.83 (m, 1H), 3.43 (q, 2H), 2.85-2.76 (m, 1H), 2.69-2.53 (m, 2H), 2.32-2.23 (m, 2H), 2.21 (s, 3H), 2.15-1.96 (m, 4H), 1.91 (d, 2H), 1.00-0.91 (m, 4H); MS (EI) for $C_{28}H_{32}F_3N_5O_3$: 544 (MH^+).

[00774] (20AW): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1R)-1-methylpropyl]amino}-2-(trifluoromethyl)benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-{[(1R)-1-methylpropyl]amino}-2-(trifluoromethyl)benzoic acid (synthesized according to reagent preparation 52) in

step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.78 (d, 1H), 8.49 (d, 1H), 8.19 (br s, 1H), 8.04 (dd, 1H), 7.96 (s, 1H), 7.41 (br s, 1H), 6.80 (d, 1H), 6.65 (s, 1H), 4.63 (br s, 2H), 3.89-3.82 (m, 1H), 3.58-3.49 (m, 1H), 2.85-2.76 (m, 1H), 2.28-2.20 (m, 2H), 2.14-2.03 (m, 2H), 2.03-1.95 (m, 2H), 1.88 (d, 2H), 1.63-1.47 (m, 2H), 1.17 (d, 3H), 0.99-0.88 (m, 7H); MS (EI) for $C_{29}H_{34}F_3N_5O_3$: 558 (MH^+).

[00775] (20AX): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethyl-2-methylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-[(1-ethyl-2-methylpropyl)amino]-2-methylbenzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, $CDCl_3$ w/ 20% methanol-d_4): 8.87 (d, 1H), 8.09 (dd, 1H), 7.34 (s, 1H), 7.21 (m, 1H) 6.66 (d, 1H), 6.62 (d, 1H), 4.67 (br s, 2H), 4.15 (m, 1H), 3.16 (m, 1H), 2.61 (m, 1H), 2.40-2.10 (br m, 8H), 1.92 (br d, 2H), 1.63 (m, 1H), 1.45 (m, 1H), 1.21 (m, 2H), 1.06 (m, 2H), 0.95 (m, 9H); MS (EI) for $C_{31}H_{41}N_5O_3$: 554 (M+Na).

[00776] (20AY): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-cyclopropylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-[(1-cyclopropylpropyl)amino]-2-methylbenzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8..89 (d, 1H), 8.28 (d, 1H), 8.04 (m, 2H), 7.83 (br s, 1H), 7.47 (s, 1H), 7.30 (br s, 1H), 6.80 d, 1H), 6.56 (s, 1H), 4.63 (br s, 2H), 3.88 (s, 1H), 2.94 (m, 1H), 2.81 (m, 1H), 22.228 (d, 2), 2.13-1.97 (br m, 4H), 1.92 (br d, 2H), 1.60 (m, 2H), 0.98-0.85 (br m, 5H), 0.44-.35 (br m, 2H), 0.20 (m, 2H); MS (EI) for $C_{31}H_{39}N_5O_3$: 530 (MH^+).

[00777] (20AZ): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(3S)-tetrahydrofuran-3-ylamino]benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-[(3S)-tetrahydrofuran-3-ylamino]benzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H NMR of Free Base (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.30 (d, 1H), 8.15 (d, 1H), 8.04 (dd, 1H), 7.90 (br s, 1H), 7.51 (s, 1H), 7.25 (br s, 1H), 6.80 (d, 1H), 6.57 (s, 1H), 4.63 (br s, 2H), 4.09-4.02 (m, 1H), 3.89-3.71 (m, 4H), 3.58 (dd, 1H), 2.84-2.77 (m, 1H), 2.30-2.15 (m, 6H), 2.12-1.98 (m, 4H), 1.96-1.88 (m, 2H), 1.83-1.74 (m, 1H),0.99-0.91 (m, 4H); MS (EI) for $C_{29}H_{35}N_5O_4$: 518 (MH^+).

[00778] (20BA): N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(propylamino)benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 20 by using 4-(aminocarbonyl)-3-(propylamino)benzoic acid (synthesized according to reagent preparation 39) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.83 (d, 1H), 8.24 (d, 1H), 8.12 (dd, 1H), 7.94 (br s, 1H), 7.68 (d, 1H), 7.31 (br s, 1H), 6.98 (d, 1H), 6.95 (br s, 2H), 6.88 (dd, 1H), 4.71 (br s, 2H), 3.90-3.84 (m, 1H), 3.13 (s, 1H), 2.88-2.80 (m, 2H), 2.30-2.23 (m, 2H), 2.12-1.99 (m, 6H), 1.66-1.56 (m, 2H), 1.00-0.93 (m, 2H); MS (EI) for $C_{27}H_{33}N_5O_3$: 476 (MH^+).

[00779] (20BB): 5-amino-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 5-amino-4-(aminocarbonyl)-2-methylbenzoic acid (synthesized according to reagent preparation 48) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.32 (d, 1H), 8.04 (dd, 1H), 7.75 (br s, 1H), 7.40 (s, 1H), 7.11 (br s, 1H), 7.79 (d, 1H), 6.64 (s, 1H), 6.52 (s, 2H), 4.63 (br s, 2H), 3.87-3.80 (m, 1H), 2.84-2.76 (m, 1H), 2.16 (s, 3H), 2.12-1.97 (m, 4H), 1.93-1.85 (m, 2H), 0.98-0.89 (m, 4H); MS (EI) for $C_{24}H_{29}N_5O_3$: 448 (MH^+).

[00780] (20BC): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(1-methylethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-[(1-methylethyl)amino]-2-methylbenzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.29 (d, 1H), 8.04 (dd, 1H), 7.92 (d, 1H), 7.84 (br s, 1H), 7.48 (s, 1H), 7.18 (br s, 1H), 6.80 (d, 1H), 6.59 (s, 1H), 4.63 (br s, 2H), 3.89-3.82 (m, 1H), 3.64-3.56 (m, 1H), 2.84-2.76 (m, 1H), 2.30-2.23 (m, 2H), 2.19 (s, 3H), 2.12-1.98 (m, 4H), 1.98-1.89 (m, 2H), 1.18 (s, 1H), 1.17 (s, 1H), 1.00-0.91 (m, 4H); MS (EI) for $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00781] (20BD): 5-(cyclopentylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-(cyclopentylamino)-2-methylbenzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.29 (d, 1H),

8.05-8.02 (m, 2H), 7.85 (br s, 1H), 7.48 (s, 1H), 7.18 (br s, 1H), 6.79 (d, 1H), 6.62 (s, 1H), 4.63 (br s, 2H), 3.88-3.83 (m, 1H), 3.78-3.71 (m, 1H), 2.84-2.24 (m, 1H), 2.32-2.24 (m, 2H), 2.19 (s, 3H), 2.11-1.90 (m, 8H), 1.73-1.53 (m, 4H), 1.50-1.41 (m, 2H), 0.99-0.92 (m, 4H); MS (EI) for $C_{30}H_{37}N_5O_3$: 516 (MH^+).

[00782] (20BE): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(2,2-dimethylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-[(2,2-dimethylpropyl)amino]-2-methylbenzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.29 (t, 1H), 8.24 (d, 1H), 8.04 (dd, 1H), 7.87 (br s, 1H), 7.49 (s, 1H), 7.18 (br s, 1H), 6.79 (d, 1H), 6.59 (s, 1H), 4.63 (br s, 2H), 3.88-3.82 (m, 1H), 2.89 (d, 2H), 2.84-2.77 (m, 1H), 2.29-2.22 (m, 2H), 2.18 (s, 3H), 2.14-1.97 (m, 4H), 1.95-1.88 (m, 2H), 1.98-0.90 (m, 13H); MS (EI) for $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00783] (20BF): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(cyclopropylmethyl)amino]-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-(cyclopropylmethylamino)-2-methylbenzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.24 (d, 1H), 8.05-8.03 (m, 2H), 7.85 (br s, 1H), 7.48 (s, 1H), 7.19 (br s, 1H), 6.78 (d, 1H), 6.57 (s, 1H), 4.63 (br s, 2H), 3.88-3.82 (m, 1H), 2.89 (t, 2H), 2.84-2.74 (m, 1H), 2.28-2.21 (m, 2H), 2.19 (s, 3H), 2.13-1.98 (m, 4H), 1.95-1.87 (m, 2H), 1.15-1.06 (m, 1H), 0.98-0.90 (m, 4H), 0.52-0.46 (m, 4H), 0.24-0.19 (m, 2H); MS (EI) for $C_{29}H_{35}N_5O_3$: 502 (MH^+).

[00784] (20BG): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(2,2-difluoro-1-methylethyl)amino]-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-[(2,2-difluoro-1-methylethyl)amino]-2-methylbenzoic acid (synthesized according to reagent preparation 42) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.90 (s, 1H), 8.24 (m, 2H), 8.06 (m, 1H), 7.94 (s, 1H), 7.52 (s, 1H), 7.30 (s, 1H), 6.81 (d, 1H), 6.73 (s, 1H), 6.11 (t, 1H), 4.63 (bs, 2H), 4.01 (m, 1H), 3.86 (s, 1H), 2.79 (m, 1H), 2.25 (m, 1H), 2.20 (s, 3H), 2.08 (m, 2H), 2.00 (m, 2H), 1.92 (m, 2H), 1.21 (m, 3H), 0.96 (m, 5H); MS (EI) for $C_{28}H_{33}F_2N_5O_3$: 526.3 (MH^+).

[00785] (20BH): 2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1,1-dimethylethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-[(1,1-dimethylethyl)amino]benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.52 (d, 1H), 8.48 (s, 1H), 8.03-8.06 (m, 2H), 7.82 (s, 1H), 7.36 (s, 1H), 6.78-6.80 (m, 2H), 4.63 (broad s, 2H), 3.82-3.85 (m, 1H), 3.34 (s, 3H), 2.77-2.83 (m, 1H), 2.31 (d, 2H), 1.92-2.09 (m, 6H), 1.35 (s, 9H), 0.94-0.97 (m, 3H). MS (EI) for $C_{28}H_{34}BrN_5O_3$: 569 (MH^+).

[00786] (20BI): 5-amino-2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 5-amino-4-(aminocarbonyl)-2-bromobenzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.85 (d, 1H), 8.42 (d, 1H), 8.04 (dd, 1H), 7.79 (s, 1H), 7.26 (bs, 1H), 6.85 (bs, 2H), 6.79 (d, 1H), 6.69 (s, 1H), 4.62 (bs, 2H), 3.86 (m, 1H), 2.82 (m, 1H) 2.30 (m, 2H), 2.10 (m, 2H), 2.00 (m 2H), 1.88 (m, 2H), 0.96 (m, 4H). MS (EI) for $C_{24}H_{26}BrN_5O_3$: 514 (MH^+).

[00787] (20BJ): 2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1S)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-{[(1S)-1,2-dimethylpropyl]amino}benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.85 (d, 1H), 8.42 (m, 2H), 8.02 (2d, 2H), 7.81 (s, 1H), 7.30 (bs, 1H), 6.78 (d, 1H), 6.61 (s, 1H), 4.60 (bs, 2H), 3.87 (m, 1H), 3.40 (m, 1H), 2.80 (m, 1H), 2.31 (m, 2H), 2.08 (m, 2H), 1.98 (m, 2H), 1.90 (m, 2H), 1.82 (m, 1H), 1.06 (d, 3H), 0.94 (m, 7H), 0.87 (d, 3H). MS (EI) for $C_{29}H_{36}BrN_5O_3$: 584 (MH^+).

[00788] (20BK): 2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-bromo-5-[(cyclopropylmethyl)amino]benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.95-8.88 (s,1H), 8.45-8.38 (d,1H), 8.35-8.28 (m, 1H), 8.12-8.00 (d, 1H), 7.88-7.81 (s, 1H), 7.40-7.31 (s, 1H), 6.83-6.77 (d, 1H), 6.63-6.58 (s, 1H), 4.77-4.53 (br. s, 2H),

3.93-3.83 (m, 1H), 3.05-2.95 (m, 2H), 2.85-2.76 (m, 1H), 2.38-2.26 (d, 2H), 2.20-1.84 (m, 6H), 1.18-1.04 (m, 1H), 1.03-0.91 (m, 4H), 0.57-0.46 (m, 2H), 0.29-0.19 (m, 2H). MS (EI) for $C_{28}H_{32}BrN_5O_3$: 567 (MH^+).

[00789] (20BL): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1,1-dimethylethyl)amino]-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-[(1,1-dimethylethyl)amino]-2-methylbenzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.88-8.83 (s,1H), 8.17-8.08 (d,1H), 7.47-7.44 (s, 1H), 6.98-6.95 (s, 1H), 6.83-6.76 (d, 1H), 4.66-4.59 (m, 2H), 4.07-4.00 (m, 1H), 2.77-2.70 (m, 1H), 2.34-2.24 (m, 5H), 2.22-2.09 (m, 2H), 2.07-1.86 (m, 4H), 2.85-2.76 (m, 4H), 1.43-1.37 (s, 9H), 1.30-1.00 (m, 4H). MS (EI) for $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00790] (20BM): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-(2-methylpropyl)benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-(2-methylpropyl)benzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.89 (s,1H), 8.26-8.25 (d,1H), 8.06-8.03 (m, 1H), 7.73 (s, 1H), 7.38 (s, 1H), 7.21 (s, 1H), 7.08 (s, 1H), 6.80 (d, 1H), 4.62 (br. s, 2H), 3.87-3.82 (m, 1H), 3.32-3.33 (m, 3H), 2.85-2.77 (m, 1H), 2.63-2.62 (d, 2H), 2.31 (s, 3H), 2.23-2.21 (m, 2H), 2.15-1.89 (m, 7H), 0.97-0.94 (m, 4H), 0.86-0.82 (d, 2H). MS (EI) for $C_{29}H_{36}N_4O_3$: 489 (MH^+).

[00791] (20BN): 2-chloro-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-3-[(1-cyclopropylethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-chloro-3-[(1-cyclopropylethyl)amino]benzoic acid (synthesized according to reagent preparation 46) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.87(d, 1H), 8.44 (d, 1H), 8.04-8.01(m, 2H), 7.58(s, 1H), 7.45(d, 1H), 6.82(d, 1H), 6.78(d, 1H), 6.40(d, 1H), 4.59(s, 2H), 3.84(s, 1H), 2.75-2.70(m, 1H), 2.42(d, 2H), 2.01-1.91(m, 4), 1.80(d, 2H), 1.06 (d, 3H), 0.93-0.91(m, 4H), 0.79-0.74(m, 2H), 0.28-0.25 (m, 2H), 0.03-0.02 (m, 2H); MS(EI) for $C_{29}H_{34}ClN_5O_3$: 537(MH^+).

[00792] (20BO): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-(methyloxy)benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-

methyl-5-(methyloxy)benzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.62 (s, 1H), 8.32 (s, 1H), 8.03-8.02 (d, 1H), 7.64 (s, 1H), 7.62 (s, 1H), 7.59 (s, 1H), 6.98 (s, 1H), 7.80-6.76 (d, 1H), 4.63 (b, 2H), 4.04(s, 2H), 3.88 (b, 4H), 3.80-2.75 (m, 1H), 2.26 (s, 3H), 2.24-2.20(q, 1H), 2.15-1.95 (m, 3H), 2.26 (s, 3H), 1.89 (s, 1H), 1.86 (s, 1H), 0.96-0.89 (m, 4H); MS (EI) for $C_{26}H_{30}N_4O_4$: 463 (MH^+).

[00793] (20BP): 5-bromo-3-chloro-N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-6-bromo-2-chloro-3-{[(1R)-1-methylpropyl]amino}benzoic acid (synthesized according to the method of reagent preparation 50) in step 5. ^{1}H-NMR (400 MHz, CD_3OD): 8.96(s, 1H), 8.64(s, 1H), 8.40(dd, 1H), 7.69(s, 1H), 7.31(d, 1H), 4.77(s, 2H), 4.16(t, 1H), 3.57-3.37(m, 1H), 2.74-2.67(m, 1H), 2.54-2.34(m, 3H), 2.19-2.09(m, 6H), 1.66-1.57(m, 1H), 1.54-1.44(m,1H), 1.32-1.21(m, 1H), 1.26-1.11(m, 6H), 1.00 (t, 2H); MS(EI) for $C_{28}H_{33}BrClN_5O_3$: 603 (MH^+).

[00794] (20BQ): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(methyloxy)-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-(methyloxy)-5-{[(1R)-1-methylpropyl]amino}benzoic acid (synthesized according to the method of reagent preparation 50) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.92-8.89 (s,1H), 8.68-8.63 (d,1H), 8.08-8.02 (m, 2H), 7.67-7.62 (d, 1H), 7.38-7.33 (s, 2H), 7.13-7.10 (s, 1H), 6.82-6.77 (d, 1H), 4.77-4.55 (br. s, 2H), 4.08-4.01 (m, 1H), 3.91-3.88 (s, 3H), 3.42-3.32 (m, 1H), 2.84-2.77 (m, 1H), 2.22-2.06 (m, 6H), 1.87-1.78 (d, 2H), 1.55-1.42 (m, 2H), 1.13-1.09 (d, 3H), 0.98-0.93 (m, 4H), 0.91-0.86 (m, 3H). MS (EI) for $C_{29}H_{37}N_5O_4$: 520 (MH^+).

[00795] (20BR): 3-chloro-N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-methyl-2-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-chloro-6-methyl-3-{[(1R)-1-methylpropyl]amino}benzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H-NMR (400 MHz, CD_3OD): 8.49(d, 1H), 8.62(d, 1H), 8.42(dd, 1H), 7.58(s, 1H), 7.32(dd, 1H), 4.78(s, 2H), 4.22(t, 1H), 3.62(q, 1H), 2.71-2.60(m, 1H), 2.50-2.37(m, 4H), 2.27(s, 3H), 2.25-

2.08(m, 6H), 1.75-1.61(m, 2H), 1.57-1.47(m, 1H), 1.22-1.08(m, 6H), 1.00-0.9 (m, 2H); MS(EI) for $C_{29}H_{36}ClN_{53}$: 539 (MH^+).

[00796] (20BS): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}thiophene-2,5-dicarboxamide. Prepared according to the method of example 20 by using 5-(aminocarbonyl)thiophene-2-carboxylic acid in step 5. ^{1}H-NMR (400 MHz, CD_3OD): 8.83(s, 1H), 8.31(d, 1H), 8.22-8.12(m, 2H), 7.73-7.69(m, 2H), 7.61(s, 1H), 6.99 (d, 1H), 4.72(s, 2H), 3.88(s, 1H), 2.82-2.78(m, 1H), 2.31-1.97(m, 8H), 1.00-0.95(m, 4H); MS(EI) for $C_{22}H_{24}N_4O_3S$: 425 (MH^+).

[00797] (20BT): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(ethylamino)-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-(ethylamino)-5-{[(1R)-1-methylpropyl]amino}benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.92-8.89 (s,1H), 8.45-8.41 (s,1H), 8.08-8.02 (d, 2H), 7.95-7.90 (s, 1H), 7.26-7.15 (m, 2H), 6.91-6.90 (s, 1H), 6.82-6.77 (d, 1H), 6.76-6.75 (s, 1H), 6.70-6.66 (s, 1H), 5.98-5.92 (m, 1H), 4.72-4.57 (m, 2H), 3.92-3.84 (m, 1H), 3.09-3.01 (m, 2H), 2.85-2.77 (m, 1H), 2.30-2.24 (m, 1H), 2.09-1.99 (m, 2H), 1.97-1.90 (m, 2H), 1.77-1.71 (m, 2H), 1.63-1.53 (m, 2H), 1.48-1.39 (m, 2H), 1.18-1.11 (m, 6H), 0.98-0.87 (m, 5H). MS (EI) for $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00798] (20BU): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(1-methylpropyl)oxy]benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-[(1-methylpropyl)oxy]benzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.89-8.87 (s,1H), 8.36-8.33 (s,1H), 8.04-8.00 (d, 1H), 7.69-7.67 (s, 1H), 7.66-7.54 (d, 2H), 6.98-6.96 (s, 1H), 6.80-6.76 (d, 1H), 4.69-4.49 (m, 3H), 3.91-3.84 (m, 1H), 2.81-2.74 (m, 1H), 2.28-2.20 (m, 5H), 2.13-1.95 (m, 4H), 1.92-1.85 (d, 2H), 1.79-1.60 (m, 4H), 1.32-1.27 (d, 3H), 0.96-0.88 (m, 5H). MS (EI) for $C_{29}H_{36}N_4O_4$: 505 (MH^+).

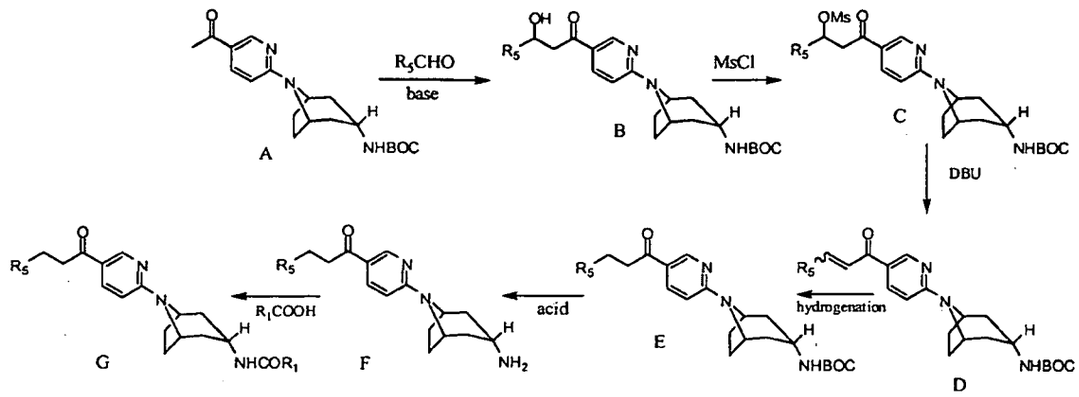
[00799] (20BV): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-ethyl-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-ethyl-5-{[(1R)-1-methylpropyl]amino}benzoic acid (synthesized according to reagent preparation 50) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): ^{1}H

NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.32 (d, 1H), 8.01-8.06 (m, 2H), 7.88 (s, 1H), 7.49 (s, 1H), 7.17 (s, 1H), 6.79 (d, 1H), 6.53 (s, 1H), 4.63 (broad s, 2H), 3.86 (s, 1H), 3.39-3.42 (m, 1H), 2.77-2.83 (m, 1H), 2.55 (d, 2H), 2.27 (d, 2H), 2.02-2.09 (m, 4H), 1.93 (d, 2H), 1.46-1.61 (m, 2H), 1.09-1.16 (m, 6H), 0.88-0.97 (m, 7H). MS (EI) for $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00800] (20BW): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-ethyl-2-methylbenzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-5-ethyl-2-methylbenzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.32 (d, 1H), 8.03 (dd, 1H), 7.88 (s, 1H), 7.49 (s, 1H), 7.20 (s, 1H), 7.17 (s, 1H), 6.81 (d, 1H), 4.63 (broad s, 2H), 3.85-3.91 (m, 1H), 3.35 (s, 5H), 2.77-2.84 (m, 1H), 2.73 (q, 2H), 2.31 (s, 3H), 2.24 (d, 2H), 2.08-2.14 (m, 2H), 2.00-2.04 (m, 2H), 1.91 (d, 2), 1.16 (t, 3H), 0.93-0.98 (m, 4H). MS (EI) for $C_{27}H_{32}N_4O_3$: 461 (MH^+).

[00801] (20BX): N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[2-(methyloxy)ethyl]oxy}benzene-1,4-dicarboxamide. Prepared according to the method of example 20 by using 4-(aminocarbonyl)-2-methyl-5-{[2-(methyloxy)ethyl]oxy}benzoic acid (synthesized according to reagent preparation 41) in step 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.34 (d, 1H), 8.03 (dd, 1H), 7.72 (s, 1H), 7.71 (s, 1H), 7.65 (s, 1H), 7.04 (s, 1H), 6.80 (d, 1H), 4.63 (broad s, 2H), 4.26-4.28 (m, 2H), 3.89-3.91 (m, 1H), 3.72-3.74 (m, 2H), 3.33 (d, 10H), 2.77-2.84 (m, 1H), 2.29 (s, 3H), 2.21-2.27 (m, 2H), 2.10-2.16 (m, 2H), 2.00-2.02 (m, 2H), 1.91 (s, 1H), 1.87 (s, 1H), 0.93-0.98 (m, 4H). MS (EI) for $C_{28}H_{34}N_4O_5$: 507 (MH^+).

SYNTHETIC SCHEME 21:



[00802] Scheme 21 generally describes the synthesis of all of the compound(s) listed in Example 21, wherein R_5 and R_1 are as defined in the specification.

[00803] In Scheme 21, R_5CHO and a strong base, such as lithium diisopropylamide, is added to compound (A) under appropriate reaction conditions to form compound (B). To compound (B) is added MsCl under appropriate reaction conditions to arrive at compound (C). To compound (C) is added DBU under appropriate reaction conditions to arrive at compound (D). Compound (D) is reduced with an appropriate reducing agent, such as 10% palladium on charcoal, and under appropriate reaction conditions, to arrive at compound (E). Compound (E) is deprotected under acidic conditions, such as with HCl, to remove BOC and arrive at compound (F). R_1COOH is added to compound (F) under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (G).

[00804] Example 21: 2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(1-methylpiperidin-4-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide acetate.

[00805] STEP 1: A solution of lithium diisopropylamide (0.87 mL, 2.0 M in tetrahydrofuran, 1.74 mmol) was added drop-wise to a mixture of 1,1-dimethylethyl [8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]carbamate (300 mg, 0.87 mmol) in tetrahydrofuran at -78°C. After stirring for 10 minutes, a solution of phenylmethyl 4-formylpiperidine-1-carboxylate (322 mg, 1.30 mmol) in

tetrahydrofuran was added drop-wise and stirred for 2 hours at -78°C. The reaction mixture was poured into saturated aqueous ammonium chloride solution (50 mL), extracted with ethyl acetate (3 x 20 mL), and the combined extract was washed with water (50 mL), then brine (20 mL), dried over sodium sulfate, filtered then concentrated. The residue was purified by flash chromatography (55% to 75% ethyl acetate in hexanes) to give phenylmethyl 4-(3 -{6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}-1-hydroxy-3-oxopropyl)piperidine-1-carboxylate (360 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.75 (d, 1H), 7.99 (dd, 1H), 7.37-7.30 (m, 5H), 6.49 (dd, 1H), 5.13 (s, 2H), 4.97 (br, 1H), 4.63 (br, 1H), 4.26 (br, 2H), 3.96 (br, 1H), 3.79 (br, 1H), 3.56 (br, 1H), 3.08 (d, 1H), 2.89 (dd, 1H), 2.77 (2H), 2.26-2.02 (m, 6H), 1.93 (m, 1H), 1.79 (br, 1H), 1.76 (br, 1H), 1.73-1.59 (m, 3H), 1.45 (s, 9H), 1.34 (m, 2H); MS (EI) for $C_{33}H_{44}N_4O_6$: 593 (MH^+).

[00806] STEP 2: Methanesulfonyl chloride (29 *u*L, 0.72 mmol) was added to a mixture of phenylmethyl 4-(3-{6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}-1-hydroxy-3-oxopropyl)piperidine-1-carboxylate (213 mg, 0.36 mmol) and triethylamine (51 *u*L, 0.72 mmol) in dichloromethane (20 mL) at 0°C. The reaction mixture was slowly warmed to room temperature. After stirring for 18 hours, it was washed with water (20 mL), then saturated aqueous sodium bicarbonate solution (20 mL), dried over sodium sulfate then filtered and concentrated. The residue was purified by flash chromatography (25% to 55% ethyl acetate in hexanes) to give phenylmethyl 4-(3-{6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}-1-[(methylsulfonyl)oxy]-3-oxopropyl)piperidine-1-carboxylate (212 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.75 (d, 1H), 7.97 (dd, 1H), 7.37-7.33 (m, 5H), 6.49 (dd, 1H), 5.22 (s, 1H), 5.13 (br, 2H), 4.97 (br, 1H), 4.26 (br, 2H), 3.79 (br, 1H), 3.36 (dd, 1H), 3.04 (d, 1H), 3.00 (s, 3H), 2.77 (br, 2H), 2.25-2.04 (m, 9H), 1.78 (m, 2H), 1.73-1.59 (m, 3H), 1.69 (br, 1H), 1.45 (s, 9H), 1.34 (m, 2H); MS (EI) for $C_{34}H_{46}N_4O_8S$: 671 (MH^+).

[00807] STEP 3: 1,8-Diazabicyclo[5.4.0]undec-7-ene (82 *u*L, 0.27 mmol) was added to a solution of phenylmethyl 4-(3-{6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}-1-[(methylsulfonyl)oxy]-3-oxopropyl)piperidine-1-carboxylate (183 mg, 0.27 mmol) in

dichloromethane (20 mL) and the resulting mixture was stirred for one hour at room temperature. The mixture was washed with saturated aqueous ammonium chloride solution (2x 20 mL), brine (20 mL), dried over sodium sulfate, filtered then concentrated. The residue was purified by flash chromatography (25% to 55% ethyl acetate in hexanes) to give phenylmethyl 4-[(1E,*Z*)-3-{6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}-amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}-3-oxoprop-1-en-1-yl]piperidine-1-carboxylate (147 mg, 94% yield). MS (EI) for $C_{33}H_{42}N_4O_5$: 575 (MH^+).

[00808] STEP 4: A mixture of phenylmethyl 4-[(1E,*Z*)-3-{6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}-3-oxoprop-1-en-1-yl]piperidine-1-carboxylate (107 mg, 0.19 mmol), 10% palladium on charcoal (Degussa type, 110 mg), and acetic acid (23 *u*L, 0.37 mmol) in ethyl acetate (50 mL) was hydrogenated at 1 atm for 18 hours. The mixture was filtered and concentrated to give the 1,1-dimethylethyl {8-[5-(3-piperidin-4-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate as the acetate salt (91 mg, 97% yield). MS (EI) for $C_{25}H_{38}N_4O_3$: 443 (MH^+).

[00809] STEP 5: Sodium triacetoxyborohydride (96 mg, 0.45 mmol) was added to a mixture of 1,1-dimethylethyl {8-[5-(3-piperidin-4-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endoyl}carbamate acetate salt (91 mg, 0.18 mmol), formaldehyde (73 *u*L, 37% aq. solution, 0.91 mmol) and acetic acid (55 *u*L, 0.92 mmol) in tetrahydrofuran (5 mL) at room temperature. After stirring for one hour, a saturated aqueous ammonium chloride solution (5 mL) was added and stirred for 5 minutes. The reaction mixture was diluted with water (15 mL), extracted with ethyl acetate (3 x 20 mL) and the combined extract was washed with water (50 mL), then brine (20 mL), dried over sodium sulfate, filtered, then concentrated to give 1,1-dimethylethyl (8-{5-[3-(1-methylpiperidin-4-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)carbamate (68 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.76 (d, 1H), 8.01 (dd, 1H), 6.49 (d, 1H), 4.99 (br, 1H), 4.63 (br, 2H), 3.78 (br, 1H), 3.53 (d, 2H), 2.89 (t, 2H), 2.76 (s, 3H), 2.66 (tr, 2H), 2.25-2.04 (m, 6H), 2.00-1.87 (m, 4H), 1.83-1.71 (m, 3H), 1.45 (s, 9H), 1.28 (m, 2H); MS (EI) for $C_{26}H_{40}N_4O_3$: 457 (MH^+).

[00810] STEP 6: A mixture of 1,1-dimethylethyl (8-{5-[3-(1-methylpiperidin-4-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)carbamate (60 mg, 0.13 mmol), methanol (1 mL) and hydrogen chloride in dioxane (4 M, 1 mL) was stirred at 60°C for 20 minutes. The reaction mixture was concentrated to give a white solid, which was washed with hexane and dried to give 1-[6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridin-3-yl]-3-(1-methylpiperidin-4-yl)propan-1-one hydrochloride salt (51 mg, 39% yield). MS (EI) for $C_{21}H_{32}N_4O$: 357 (MH^+).

[00811] STEP 7: N,N-Diisopropylethylamine (101 uL, 0.66 mmol) was added to a mixture of O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (53 mg, 0.14 mmol), and 4-(aminocarbonyl)-3-[(cyclopropylmethyl)amino]-benzoic acid (synthesized according to reagent preparation 39) (31 mg, 0.13 mmol) and the resulting mixture was stirred at room temperature for 30 minutes. A solution of 1-[6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridin-3-yl]-3-(1-methylpiperidin-4-yl)propan-1-one hydrochloride salt (51 mg, 0.13 mmol) in N,N-dimethylformamide (0.5 mL) was added and stirring was continued for 18 hours. The reaction mixture was diluted with methanol (1.5 mL), and purified by preparatory reverse phase HPLC (ammonium acetate buffered aqueous acetonitrile eluent) to give 2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(1-methylpiperidin-4-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide as the acetate salt, (54 mg, 66% yield). ^{1}H NMR (400 MHz, d_4-Methanol): 8.65 (d, 1H), 7.97 (dd, 1H), 7.54 (d, 1H), 6.96 (d, 1H), 6.82 (dd, 1H), 6.67 (d, 1H), 4.57, (Br, 2H), 3.89 (tr,1H), 3.04 (m, 2H), 2.95 (d, 2H), 2.87 (tr, 2H), 2.44 (s, 3H), 2.37 (tr, 2H), 2.21-2.01 (m, 6H), 1.91 (br, 1H), 1.88 (br, 1H), 1.80 (s, 3H), 1.78 (m, 1H), 1.58 (q, 4H), 1.38 (br, 1H), 1.22 (m, 2H), 1.02 (m, 1H), 0.47 (m, 2H), 0.20 (m, 2H); MS (EI) for $C_{33}H_{44}N_6O_3$: 573 (MH^+).

[00812] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [(21B)-(21H)] were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00813] (21B): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-hydroxy-4-methylpentanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 21 by using 2-methylpropanal in step 1 and omitting steps 2 through 5. ^{1}H NMR (400 MHz, d_4-Methanol): 8.67 (d, 1H), 8.00 (dd, 1H), 7.55 (d, 1H), 6.97 (d, 1H), 6.84 (dd, 1H),

6.68 (d, 1H), 4.60, (Br, 2H), 3.90 (m,1H), 3.83 (m, 1H), 2.95 (d, 2H), 2.93 (m, 1H), 2.82 (dd, 1H), 2.21-2.01 (m, 6H), 1.93 (br, 1H), 1.89 (br, 1H), 1.66 (m, 1H), 1.07 (m, 1H), 0.90 (d, 6H), 0.49 (m, 2H), 0.20 (m, 2H). MS (EI) for $C_{30}H_{39}N_5O_4$: 534 (MH^+).

[00814] (21C): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-phenylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 21 by using benzaldehyde in step 1 and omitting step 5. ^{1}H NMR (400 MHz, d_4-Methanol): 8.67 (d, 1H), 7.97 (dd, 1H), 7.56 (d, 1H), 7.08 (m, 5H), 6.98 (d, 1H), 6.84 (dd, 1H), 6.67 (d, 1H), 4.59, (Br, 2H), 3.90 (m,1H), 3.93 (tr, 1H), 3.15 (tr, 2H), 3.00 (d, 2H), 2.92 (tr, 2H), 2.18-2.11 (m, 6H), 1.93 (br, 1H), 1.90 (br, 1H), 1.66 (m, 1H), 1.07 (m, 1H), 0.51 (m, 2H), 0.22 (m, 2H); MS (EI) for $C_{33}H_{37}N_5O_3$: 552 (MH^+).

[00815] (21D): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-hydroxy-3-phenylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 21 by using benzaldehyde in step 1 and omitting steps 2 through 5. ^{1}H NMR (400 MHz, d_4-Methanol): 8.64 (d, 1H), 7.97 (dd, 1H), 7.55 (d, 1H), 7.34 (m, 2H), 7.25 (m, 2H), 7.17 (m 1H), 6.96 (d, 1H), 6.84 (dd, 1H), 6.65 (d, 1H), 5.18 (dd, 1H), 4.60, (br, 2H), 3.92 (m,1H), 3.31 (dd, 1H), 3.06 (dd, 1H), 3.00 (d, 2H), 2.18-2.09 (m, 6H), 1.93 (br, 1H), 1.90 (br, 1H), 1.86 (br, 1H), 1.66 (m, 1H), 1.04 (m, 1H), 0.48 (m, 2H), 0.19 (m, 2H); MS (EI) for $C_{33}H_{37}N_5O_4$: 568 (MH^+).

[00816] (21E): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(4-methylpentanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 21 by using 2-methylpropanal in step 1 and omitting step 5. ^{1}H NMR (400 MHz, d_4-Methanol): 8.67 (d, 1H), 8.01 (dd, 1H), 7.55 (d, 1H), 6.98 (d, 1H), 6.83 (dd, 1H), 6.68 (d, 1H), 4.60, (br, 2H), 3.93 (m,1H), 3.00 (d, 2H), 2.83 (dd, 1H), 2.18-2.05 (m, 7H), 1.93 (br, 1H), 1.90 (br, 1H), 1.59-1.46 (m, 3H), 1.05 (m, 1H), 0.87 (d, 6H), 0.49 (m, 2H), 0.20 (m, 2H); MS (EI) for $C_{30}H_{39}N_5O_3$: 518 (MH^+).

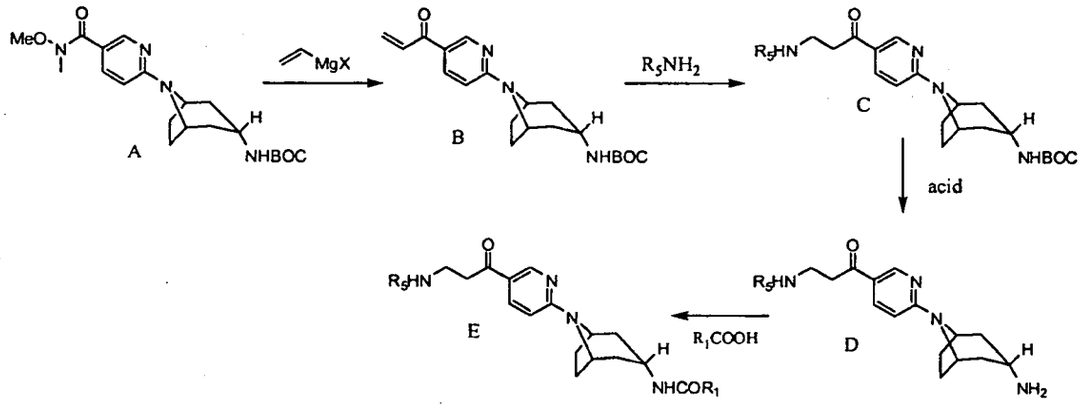
[00817] (21F): N4-{8-[5-(3-cyclohexylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide. Prepared according to the method of example 21 by using cyclohexanecarbaldehyde in step 1 and omitting step 5. ^{1}H NMR (400 MHz, d_4-Methanol): 8.67 (d, 1H), 7.99 (dd, 1H), 7.57 (d, 1H), 6.99 (d, 1H), 6.86 (dd, 1H),

6.68 (d, 1H), 4.61, (br, 2H), 3.91 (m,1H), 3.01 (d, 2H), 2.83 (dd, 1H), 2.12-2.10 (m, 6H), 1.95 (br, 1H), 1.91 (br, 1H), 1.76-1.59 (m, 5H), 1.51 (q, 2H), 1.05 (m, 5H), 0.87 (d, 2H), 0.51 (m, 2H), 0.23 (m, 2H); MS (EI) for $C_{33}H_{43}N_5O_3$: 558 (MH^+).

[00818] (21G): 5-[(1-ethylpropyl)amino]-2-methyl-N-(8-{5-[3-(1-methylpiperidin-4-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared as the hydrochloride salt according to the method of example 21 by using 4-aminocarbonyl-2-methyl-5-(pentan-3-ylamino)benzoic acid (prepared according to reagent preparation 42) in step 7. ^1H NMR (400 MHz, Methanol-d_4): 8.56 (d, 1H), 8.42 (dd, 1H), 7.93 (s, 1H), 7.48 (s, 1H), 7.39 (d, 1H), 4.88-4.81 (m, 2H), 4.21-4.12 (m, 1H), 3.60-3.48 (m, 3H), 3.15-2.93 (m, 4H), 2.86 (s, 3H), 2.53-2.16 (m, 9H), 2.06 (d, 2H), 1.88-1.61 (m, 7H), 1.55-1.39 (m, 2H), 1.01 (t, 6H); MS (EI) for $C_{35}H_{50}N_6O_3$: 604 (MH^+).

[00819] (21H): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-piperidin-4-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 21 by using phenylmethyl 4-formylpiperidine-1-carboxylate in step 1 and omitting step 5. ^1H NMR (400 MHz, CD_3OD): 8.65 (s, 1H), 8.33-8.29 (s, 1H), 8.26-8.19 (d, 1H), 7.68-7.63 (d, 1H), 7.10-7.03 (d, 1H), 6.97-6.92 (d, 1H), 4.77-4.70 (m, 2H), 4.08-4.02 (m, 1H), 3.45-3.35 (m, 2H), 3.11-3.07 (d, 2H), 3.05-2.92 (m, 4H), 2.35-2.19 (m, 6H), 2.14-2.07 (d, 2H), 2.05-1.96 (d, 2H), 1.75-1.66 (m, 2H), 1.45-1.32 (m, 2H), 1.21-1.09 (m, 1H), 0.62-0.55 (m, 2H), 0.32-0.26 (m, 2H), 0.11-0.08 (m, 1H). MS (EI) for $C_{32}H_{42}N_6O_3$: 559 (MH^+).

SYNTHETIC SCHEME 22:



[00820] Scheme 22 generally describes the synthesis of all of the compound(s) listed in Example 22, wherein R_5 and R_1 are as defined in the specification.

[00821] In Scheme 22, an appropriate Grignard reagent, such as vinyl magnesium bromide, is added to compound (A) under appropriate reaction conditions to form compound (B). To compound (B) is added R_5NH_2 under appropriate reaction conditions to form compound (C). Compound (C) is deprotected with an acid, such as trifluoroacetic acid in dichloromethane, to form compound (D). To compound (D) is added R_1COOH under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (E).

[00822] Example 22: 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-piperidin-1-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide

[00823] STEP 1: A solution of vinyl magnesium bromide (1.0 M in tetrahydrofuran, 6.5 mL) is added to a solution of 1,1-dimethylethyl [8-(5-{[methyl(methyloxy)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]carbamate (synthesized according to example 19 step 1) (0.5 g, 1.3 mmol) in tetrahydrofuran (20 mL) at 0°C and the resulting mixture was stirred at 0°C for one hour. The mixture was poured into saturated aqueous ammonium chloride solution (50 mL), extracted with ethyl acetate (3 x 20 mL) and the combined extract was washed with water (50 mL), brine (20 mL) then dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (50% to 65%

ethyl acetate in hexanes) to give 1,1-dimethylethyl [8-(5-acryloylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]carbamate (180 mg, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.81 (d, 1H), 8.09 (dd, 1H), 7.13 (dd, 1H), 6.55 (d, 1H), 6.43 (d, 1H), 5.85 (dd, 1H), 4.97 (br, 1H), 4.63 (b, 2H), 3.93 (m, 1H), 2.28-2.05 (m, 6H), 1.78 (d, 2H), 1.45 (s, 9H); MS (EI) for $C_{20}H_{27}N_3O_3$: 358 (MH^+).

[00824] STEP 2: To a solution of 1,1-dimethylethyl [8-(5-acryloylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]carbamate (45 mg, 13 mmol) in tetrahydrofuran (2 mL) was added piperidine (13 *u*L, 13 mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated and the residue was purified by flash chromatography (10% methanol in dichloromethane) to give 1,1-dimethylethyl {8-[5-(3-piperidin-1-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (41 mg, 74% yield). MS (EI) for $C_{25}H_{38}N_4O_3$: 443 (MH^+).

[00825] STEP 3: A solution of 1,1-dimethylethyl {8-[5-(3-piperidin-1-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (41 mg, 0.093 mmol) in 1:1 trifluoroacetic acid dichloromethane (1 mL) was stirred at room temperature for 15 min. The reaction mixture was concentrated and the residue was triturated with hexanes (3x 2 mL) and dried *in vacuo* to give the 1-[6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridin-3-yl]-3-piperidin-1-ylpropan-1-one as the trifluoroacetate salt (42 mg, 100% yield). MS (EI) for $C_{20}H_{30}N_4O$: 343 (MH^+).

[00826] STEP 4: N,N-Diisopropylethylamine (192 *u*L, 0.46 mmol) was added to a mixture of O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophos-phate (38 mg, 0.10 mmol), and 4-(aminocarbonyl)-3-[(cyclopropylmethyl)amino]benzoic acid (synthesized according to reagent preparation 39) (22 mg, 0.093 mmol) and the resulting mixture was stirred at room temperature for 30 minutes. A solution of 1-[6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridin-3-yl]-3-piperidin-1-ylpropan-1-one trifluoroacetate salt (42 mg, 0.093 mmol) in N,N-dimethylformamide (0.5 mL) was added and stirring was continued for 18 hours. The reaction mixture was diluted with methanol (1.5 mL) and purified by preparatory reverse phase HPLC (ammonium acetate buffered aqueous acetonitrile eluent) to afford 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-piperidin-1-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide as the acetate salt (4.6 mg, 12% yield). ^{1}H NMR (400MHz, D_4-

Methanol): 8.67 (d, 1H), 7.97 (dd, 1H), 7.54(d, 1H), 6.96 (d, 1H), 6.82 (dd, 1H), 6.67 (d, 1H), 4.60 (br, 2H), 3.89 (tr, 1H), 3.07 (tr, 3H), 2.98 (d, 2H), 2.84 (br,3), 2.16-2.10 (m, 6H), 1.84 (m, 3H), 1.67 (m, 4H), 1.50(m, 2H), 1.07(m, 1H), 0.48 (m, 2H), 0.18 (m, 2H); MS (EI) for $C_{32}H_{42}N_6O_3$: 559 (MH^+).

[00827] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds [(22B)-(22I)] were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00828] (22B): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(N,N-dimethyl-beta-alanyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 22 by using dimethylamine in step 2. ^{1}H NMR (400MHz, D_4-Methanol): 8.67 (d, 1H), 7.99 (dd, 1H), 7.54(d, 1H), 6.95 (d, 1H), 6.82 (dd, 1H), 6.68 (d, 1H), 4.61 (br, 2H), 3.90 (tr, 1H), 3.43-3.38 (m, 4H), 2.98 (d, 2H), 2.84 (s, 6H), 2.17-2.10 (m, 6H), 1.92 (m, 3H), 1.09 (m, 1H), 0.47 (m, 2H), 0.19 (m, 2H); MS (EI) for $C_{29}H_{38}N_6O_3$: 519 (MH^+).

[00829] (22C): 2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(methyloxy)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared according to the method of example 22 by using methanol in step 2. ^{1}H NMR (400MHz, D_4-Methanol): 8.67 (d, 1H), 7.98 (dd, 1H), 7.55 (d, 1H), 6.97 (d, 1H), 6.83 (dd, 1H), 6.68 (d, 1H), 4.61 (br, 2H), 3.90 (tr, 1H), 3.69 (tr, 2H), 3.25 (s, 3H), 3.06 (tr, 2H), 3.00 (d, 2H), 2.21-2.02 (m, 6H), 1.91 (m, 2H), 1.04 (m, 1H), 0.49 (m, 2H), 0.20 (m, 2H); MS (EI) for $C_{28}H_{35}N_5O_4$: 506 (MH^+).

[00830] (22D): 2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(ethyloxy)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared according to the method of example 22 by using ethanol in step 2. ^{1}H NMR (400MHz, $CDCl_3$): 8.81 (d, 1H), 8.06 (dd, 1H), 7.93 (b, 1H), 7.45 (d, 1H), 7.09 (d, 1H), 6.75 (dd, 1H), 6.58 (d, 1H), 6.54 (d, 1H), 5.70 (br, 1H), 4.70 (br, 2H), 4.23 (q, 1H), 3.86 (tr, 1H), 3.54 (q, 2H), 3.14 (tr, 2H), 3.07 (tr, 2H), 2.39-2.23 (m, 4H), 2.09 (m, 2H), 1.89 (d, 2H), 1.20 (tr, 3H), 1.13 (m, 1H), 0.59 (m, 2H), 0.28 (m, 2H); MS (EI) for $C_{29}H_{37}N_5O_4$: 520 (MH^+).

[00831] (22E): 2-[(cyclopropylmethyl)amino]-N4-(8-{5-[N-(4-fluorophenyl)-beta-alanyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide Prepared according to the method of example 22 by using 4-fluoroaniline in step 2. ^{1}H NMR (400MHz, D_4-Methanol): 8.74 (d, 1H), 8.06 (dd,

1H), 7.63 (b, 1H), 7.06 (d, 1H), 6.92 (dd, 1H), 6.86 (m, 21H), 6.75 (d, 1H), 6.65 (m, 2H), 4.57 (br, 2H), 3.90 (tr, 1H), 3.34 (m, 2H), 3.07 (tr, 2H), 3.02 (m 2H), 2.98 (d, 2H), 2.21-2.02 (m, 5H), 1.91 (m, 3H), 1.03 (m, 1H), 0.57 (m, 2H), 0.29 (m, 2H); MS (EI) for $C_{33}H_{37}FN_6O_3$: 585 (MH^+).

[00832] (22F): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-morpholin-4-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 22 by using morpholine in step 2. ^{1}H NMR (400MHz, D_4-Methanol): 8.67 (d, 1H), 7.98 (dd, 1H), 7.54 (d, 1H), 6.96 (d, 1H), 6.82 (dd, 1H), 6.68 (d, 1H), 4.60 (br, 2H), 3.90 (tr, 1H), 3.61 (tr, 4H), 3.05 (tr, 2H), 3.00 (d, 2H), 2.71 (tr, 2H), 2.47 (br, 4H), 2.22-2.04 (m, 6H), 1.91 (d, 2H), 1.06 (m, 1H), 0.48 (m, 2H), 0.19 (m, 2H); MS (EI) for $C_{31}H_{40}N_6O_4$: 561 (MH^+).

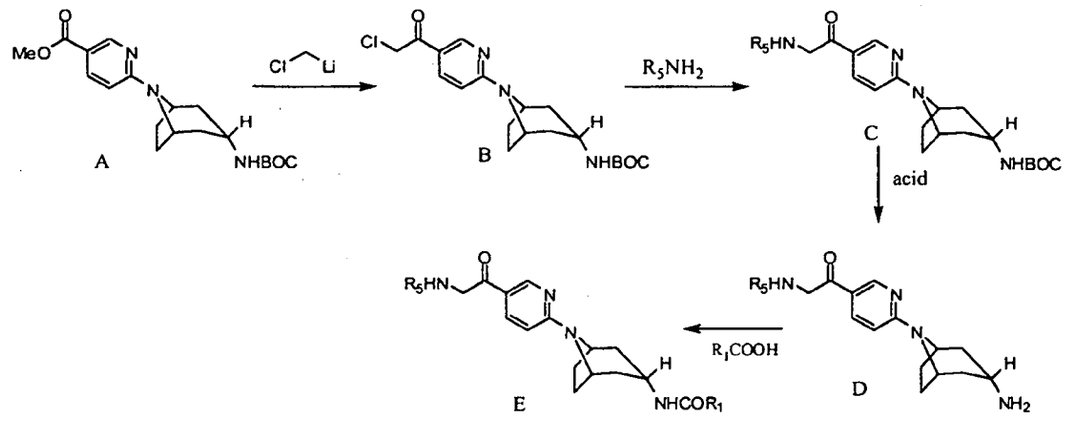
[00833] (22G): 2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(4-methylpiperazin-1-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared according to the method of example 22 by using 1-methylpiperazine in step 2. ^{1}H NMR (400MHz, D_4-Methanol): 8.69 (d, 1H), 7.99 (dd, 1H), 7.57 (d, 1H), 6.99 (d, 1H), 6.85 (dd, 1H), 6.70 (d, 1H), 4.63 (br, 2H), 3.93 (tr, 1H), 3.21 (m, 1H), 3.09 (tr, 2H), 3.02 (d, 2H), 2.71 (tr, 2H), 2.47 (br, 4H), 2.42 (s, 3H), 2.26-2.04 (m, 7H), 1.98-1.84 (m, 4H), 1.08 (m, 1H), 0.51 (m, 2H), 0.22 (m, 2H); MS (EI) for $C_{32}H_{43}N_7O_3$: 574 (MH^+).

[00834] (22H): 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-pyrrolidin-1-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide. Prepared according to the method of example 22 by using pyrrolidine in step 2. ^{1}H NMR (400MHz, D_4-Methanol): 8.69 (d, 1H), 8.00 (dd, 1H), 7.54 (d, 1H), 6.96 (d, 1H), 6.82 (dd, 1H), 6.70 (d, 1H), 4.61 (br, 2H), 3.90 (tr, 1H), 3.06-2.97 (m, 6H), 2.71 (tr, 2H), 2.47 (br, 4H), 2.42 (s, 3H), 2.19-2.08 (m, 6H), 1.82 (br, 2H),1.06 (m, 1H), 0.48 (m, 2H), 0.20 (m, 2H); MS (EI) for $C_{31}H_{40}N_6O_3$: 545 (MH^+).

[00835] (22I): 2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(4-phenylpiperazin-1-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide. Prepared according to the method of example 22 by using 1-phenylpiperazine in step 2. ^{1}H NMR (400MHz, D_4-Methanol): 8.80 (d, 1H), 8.10 (dd, 1H), 7.63 (d, 1H), 7.27 (m, 2H), 7.06 (d, 1H), 7.02 (d, 2H), 6.91 (m, 2H), 6.79 (d, 1H), 4.72 (br, 2H), 4.00 (tr, 1H), 3.47-3.32 (m, 11H), 3.08 (d, 2H), 2.32-2.15 (m, 6H),

2.02 (m, 3H), 1.14 (m, 1H), 0.58 (m, 2H), 0.29 (m, 2H); MS (EI) for $C_{37}H_{45}N_7O_3$: 636 (MH^+).

SYNTHETIC SCHEME 23:



[00836] Scheme 23 generally describes the synthesis of all of the compound(s) listed in Example 23, wherein R_5 and R_1 are as defined in the specification.

[00837] In Scheme 23, chloroiodomethane is added to compound (A) with a base, such as lithium diisopropylamide, under appropriate reaction conditions to form compound (B). To compound B is added R_5NH_2 under appropriate reaction conditions to form compound (C). Compound (C) is deprotected with an acid, such as trifluoroacetic acid in dichloromethane, to form compound (D). To compound (D) is added R_1COOH under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (E).

[00838] EXAMPLE 23: 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(piperidin-1-ylacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide.

[00839] STEP1: A solution of lithium diisopropylamide (0.36 mL, 2.0 M in tetrahydrofuran, 0.72 mmol) was added drop-wise to a mixture of methyl 6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (synthesized according to the method of example 1) (52 mg, 0.14 mmol) and chloroiodomethane (42 *u*L, 0.56 mmol) in tetrahydrofuran (2 mL) at -78°C. After stirring for 10 minutes, the reaction mixture was quenched with water (10 mL),

extracted with ethyl acetate (3 x 10 mL), and the combined extract was washed with water (15 mL), then brine (15 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (25% to 65% ethyl acetate in hexanes) to give the 1,1-dimethylethyl {8-[5-(chloroacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (45 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.78 (d, 1H), 8.01 (dd, 1H), 6.53 (d, 1H), 4.95 (br, 1H), 4.85 (br, 1H), 4.55 (s, 2H), 3.80 (br, 1H), 2.27-2.04 (m, 6H), 1.85-1.75 (m, 2H), 1.43 (s, 9H); MS (EI) for $C_{19}H_{26}ClNO_3$: 380 (MH^+).

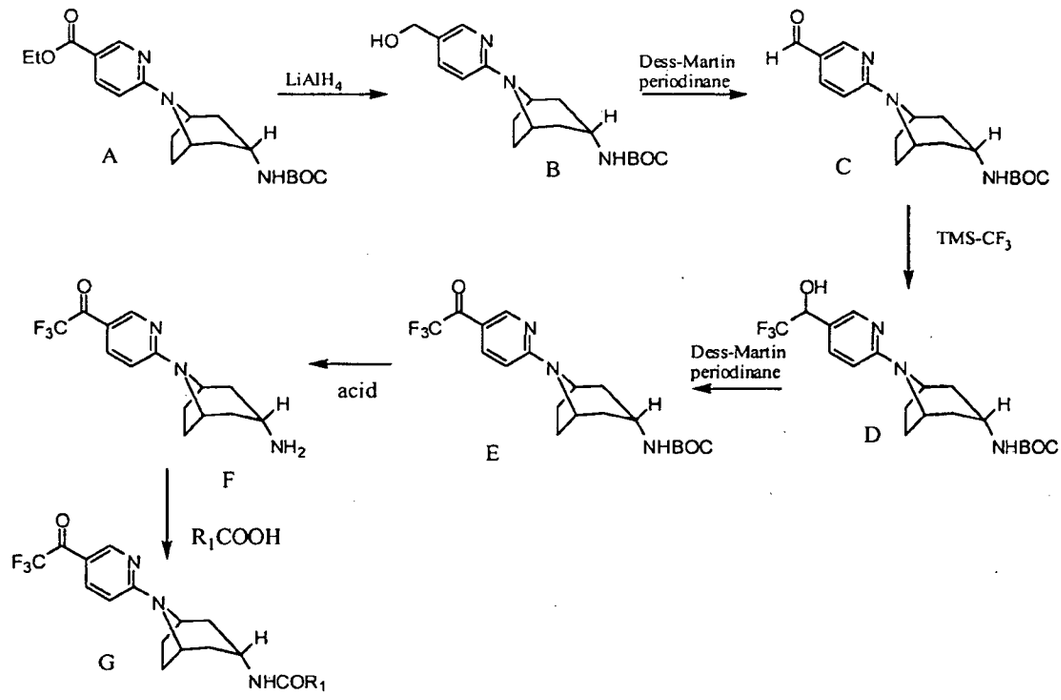
[00840] STEP 2: To a solution of {8-[5-(chloroacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (44 mg, 0.12 mmol) in tetrahydrofuran (2 mL) was added piperidine (13 *u*L, 13 mmol), and the resulting mixture was stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate (10 mL), washed with water (10 mL), then brine (10 mL) and dried over sodium sulfate. The organic solution was filtered and concentrated then dried *in vacuo* to afford 1,1-dimethylethyl {8-[5-(piperidin-1-ylacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (50 mg, 100% yield); MS (EI) for $C_{24}H_{36}N_4O_3$: 429 (MH^+).

[00841] STEP 3: A solution of 1,1-dimethylethyl {8-[5-(piperidin-1-ylacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (50 mg, 0.12 mmol) in 1:1 trifluoroacetic acid dichloromethane (1 mL) was stirred at room temperature for 15 min. The reaction mixture was concentrated, and the residue was triturated with hexanes (3x2 mL) then dried *in vacuo* to give 1-[6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridin-3-yl]-2-piperidin-1-ylethanone as the trifluoroacetate salt (51 mg, 99% yield). MS (EI) for $C_{19}H_{28}N_4O$: 329 (MH^+).

[00842] STEP 4: N,N-Diisopropylethylamine (78 *u*L, 0.58 mmol) was added to a mixture of O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophos-phate (47 mg, 0.12 mmol), and 4-(aminocarbonyl)-3-[(cyclopropylmethyl)amino]benzoic acid (synthesized according to reagent preparation 39) (22 mg, 0.093 mmol) and the resulting mixture was stirred at room temperature for 30 minutes. A solution of 1-[6-(3-endo-amino-8-azabicyclo[3.2.1]oct-8-yl)pyridin-3-yl]-2-piperidin-1-ylethanone trifluoroacetate salt (42 mg, 0.093 mmol) in N,N-dimethylformamide (0.5 mL) was added and stirring was continued for 18 hours. The reaction mixture was diluted with methanol (1.5 mL) and purified by preparatory reverse phase HPLC (ammonium acetate buffered

aqueous acetonitrile eluent) to give 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(piperidin-1-ylacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide as the acetate salt (24.4 mg, 39% yield). ^{1}H NMR (400 MHz, d_4-Methanol): 8.69 (d, 1H), 7.98 (dd, 1H), 7.54 (d, 1H), 6.96 (d, 1H), 6.83 (dd, 1H), 6.67 (d, 1H), 4.55 (br, 2H), 3.90 (br, 3H), 2.98 (d, 2H), 2.62 (m, 4H), 2.20-2.07 (m, 6H), 1.92 (m, 2H), 1.61 (m, 4H), 1.45.

SYNTHETIC SCHEME 24:



[00843] Scheme 24 generally describes the synthesis of all of the compound(s) listed in Example 24, wherein R_1 is as defined in the specification.

[00844] In Scheme 24, $LiAlH_4$ is added to compound (A) under appropriate reaction conditions to form compound (B). Compound (B) undergoes oxidation of the primary alcohol into an aldehyde to form compound (C) by treatment with an appropriate oxidizing agent such as Dess-Martin periodinane. TMS-CF_3 is then added to compound (C) under appropriate reaction conditions to form compound (D). Compound (D) undergoes oxidation of the secondary alcohol into a ketone to form

compound (E) by treatment with an appropriate oxidizing agent such as Dess-Martin periodinane. Compound (E) is deprotected with an acid, such as HCl, to form compound (F). To compound (F) is added R_1COOH under appropriate reaction conditions and with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (G).

[00845] EXAMPLE 24: 2-[(cyclopropylmethyl)amino]-N4-{8-[5-(trifluoroacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide.

[00846] STEP 1: To a suspension of ethyl 6-[3-endo-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxylate (synthesized in example 1) (1.47 g, 3.92 mmol) in THF (25 ml) was slowly added lithium aluminum hydride (1.96 ml, 2M solution in THF, 3.92 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 4 hours and then quenched by addition of water (0.15 ml), followed by 15% aqueous sodium hydroxide (0.15 ml) and then water (0.45 ml). After being stirred for 0.5 h at room temperature the mixture was diluted with ethyl acetate, filtered through Celite, washed with ethyl acetate and concentrated. Column chromatography on silica (dichloromethane:methanol 30:1 to 15:1) afforded 1,1-dimethylethyl {8-[5-(hydroxymethyl)pyridin-2-yl]- 8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (0.72 g, 55% yield). MS (EI) for $C_{18}H_{27}N_3O_3$: 334 (MH^+).

[00847] STEP 2: A suspension of 1,1-dimethylethyl {8-[5-(hydroxymethyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (105 mg, 0.31 mmol) and Dess-Martin periodinane (147 mg, 0.35 mmol) in dichloromethane (5 mL) was stirred at room temperature for 90 min. A 10% solution of sodium thiosulfate (5 mL) and then saturated sodium bicarbonate (5 mL) were added and stirring was continued for 30 min. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with saturated sodium bicarbonate (20 mL) and brine (20 mL), dried over sodium sulfate, and concentrated to give crude 1,1-dimethylethyl [8-(5-formylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]carbamate (100 mg, 96% yield) as a colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$): 9.76 (s, 1H), 8.55 (d, 1H), 7.92 (dd, 1H), 6.54 (d, 1H), 4.97 (d, 1H), 4.60 (br s, 2H), 3.81 (m, 1H), 2.20 (m, 4H), 2.08 (d, 2H), 1.80 (d, 2H).

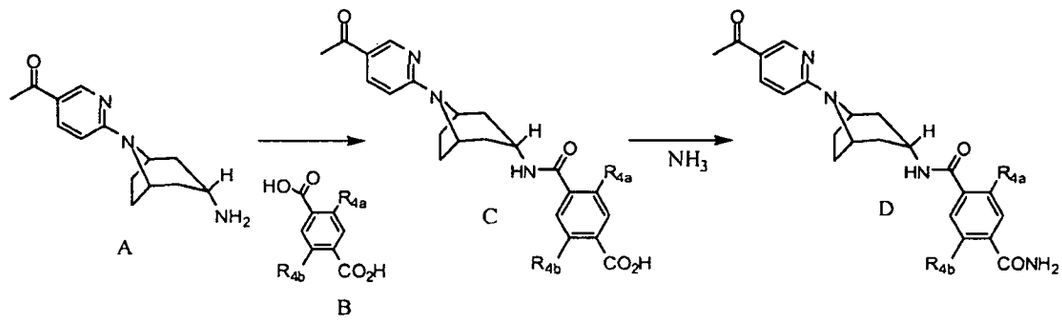
[00848] STEP 3: To a solution of 1,1-dimethylethyl [8-(5-formylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]carbamate (72 mg, 0.22 mmol) in DMF (1.5 mL) was added trimethyl(trifluoromethyl)silane (154 mg, 1.09 mmol) and cesium carbonate (85 mg, 0.26 mol), and the reaction mixture was stirred at room temperature for 1 h. Ethyl acetate (30 mL) was added, and the mixture was washed with water (3 x 10 mL) and brine (10 mL), dried over sodium sulfate, and concentrated. Column chromatography on silica (dichloromethane:methanol 95:5) afforded 1,1-dimethylethyl {8-[5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (45 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.17 (d, 1H), 7.59 (dd, 1H), 6.55 (d, 1H), 4.98 (br s, 1H), 4.91 (m, 1H), 4.51 (br s, 2H), 3.78 (m, 1H), 2.51 (d, 1H), 2.24 (m, 2H), 2.16 (m, 2H), 2.03 (m, 2H), 1.70 (d, 2H), 1.45 (s, 9H); MS (EI) for $C_{19}H_{26}F_3N_3O_3$: 402 (MH^+).

[00849] STEP 4: A suspension of 1,1-dimethylethyl {8-[5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (41 mg, 0.10 mmol) and Dess-Martin periodinane (52 mg, 0.12 mmol) in dichloromethane (2 mL) was stirred at room temperature for 3.5 h. A 10% solution of sodium thiosulfate (2 mL) and then saturated sodium bicarbonate (2 mL) were added and stirring was continued for 30 min. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, and concentrated to give crude 1,1-dimethylethyl {8-[5-(trifluoroacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (40 mg, 98% yield) as a colorless. MS (EI) for $C_{19}H_{24}F_3N_3O_3$: 400 (MH^+).

[00850] STEP 5: To a solution of 1,1-dimethylethyl {8-[5-(trifluoroacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}carbamate (38 g, 0.10 mmol) in methanol (2 mL) was added a solution of 4N hydrogen chloride in dioxane (2 mL), and the reaction mixture was refluxed for 2 min. After cooling to room temperature the mixture was concentrated and dried *in vacuo*. To the residue was added 4-(aminocarbonyl)-3-[(cyclopropylmethyl)amino]benzoic acid (synthesized according to reagent prep 39) (23 mg, 0.10 mmol), HATU (38 mg, 0.10 mmol), DMF (1 mL), and diisopropylethylamine (76 mg, 0.58 mmol), and the mixture was stirred at room temperature for 16 h. Purification by preparatory HPLC (0.1% ammonium

acetate buffered aqueous acetonitrile mobile phase) provided 2-[(cyclopropyl-methyl)amino]-N4-{8-[5-(trifluoroacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide (18 mg, 37% yield). ^{1}H NMR (400 MHz, DMSO-d_6): 8.77 (s, 1H), 8.26 (t, 1H), 8.23 (d, 1H), 7.99 (dd, 1H), 7.94 (br s, 1H), 7.67 (d, 1H), 7.30 (br s, 1H), 6.99 (d, 1H), 6.91 (m, 2H), 4.96 (br s, 1H), 4.56 (br s, 1H), 3.89 (m, 1H), 3.03 (t, 2H), 2.26 (m, 2H), 2.06 (m, 6H), 1.11 (m, 1H), 0.52 (m, 2H), 0.25 (m, 2H); MS (EI) for $C_{26}H_{28}F_3N_5O_3$: 516 (MH^+).

SYNTHETIC SCHEME 25:



[00851] Scheme 25 generally describes the synthesis of all of the compound(s) listed in Example 25, wherein R_{4a} and R_{4b} are as defined in the specification.

[00852] In Scheme 25, compound (B) is added to compound (A), with a suitable coupling reagent, such as HATU, to condense and form the amide bond in compound (C). This scheme is applicable when R_{4a} and R_{4b} are the same. To compound (C) is added NH_3 (g) under appropriate reaction conditions to form compound (D).

[00853] EXAMPLE 25: N-[8-(5-Acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2,5-dimethylbenzene-1,4-dicarboxamide.

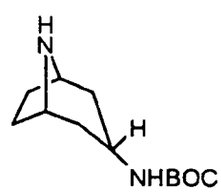
[00854] STEP 1: 2,5-Dimethylterephthalic acid (200 mg, 1.03 mmol) was dissolved in DMF (5 mL) and HATU (392 mg, 1.03 mmol) was added and the mixture was stirred at ambient for 15 minutes. N,N-Diisopropylethylamine (0.7 mL, 3.99 mmol) was added and after 5 minutes 1-[6-(3-endo-amino-8-azabicyclo-[3.2.1]oct-8-yl)pyridine-3-yl]ethanone (prepared in Example 19 Step 3) (250 mg, 1.02

mmol) was added and the mixture was stirred at 50 °C for 15 h. The mixture was cooled to ambient temperature and HATU (392 mg, 1.03 mmol) and N,N-diisopropylethylamine (0.2 mL, 1.14 mmol) were added and the mixture was stirred at ambient for 15 minutes. Ammonia gas was bubbled into the solution and a thick precipitate formed. The mixture was stirred at 50 °C for 0.5 h and then was cooled to ambient temperature and was concentrated. The residue was treated with 1N aqueous hydrochloric acid (~ 2mL) and DMSO. Water was added and the precipitate was collected by filtration then further purified by reverse phase HPLC. The pure fractions were combined and concentrated to an aqueous residue. The aqueous residue was basified with sodium bicarbonate and extracted with ethyl acetate (2x). The combined organic portion was dried over magnesium sulfate then filtered and was concentrated to afford N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2,5-dimethylbenzene-1,4-dicarboxamide (77 mg, 0.183 mmol, 18% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.74 (d, 1H), 8.28 (d, 1H), 7.97 (dd, 1H), 7.71 (br s, 1H), 7.41 (br s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.79 (d, 1H), 4.62 (br s, 2H), 3.87 (br s, 1H), 2.45 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 2.27-2.18 (m, 2H), 2.15-1.94 (m, 4H), 1.89 (d, 2H); MS (EI) for $C_{24}H_{28}N_4O_3$: 421 (MH^+).

REAGENT PREPARATIONS:

[00855] The following reagents referred to in the above examples were made as follows. The reagent numbers below correspond to the reagent numbers referred to in the above examples.

REAGENT PREPARATION 1: tert-butyl 8-azabicyclo[3.2.1]octan-3-endo-ylcarbamate:



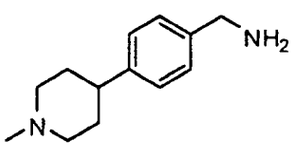
[00856] STEP 1: To a 5 L round-bottom flask was added 8-methyl-8-azabicyclo[3.2.1]octan-3-endo-amine (432 g, 3.1 mol), 2 L of dry 1,4-dioxane, 675 mL of deionized water and 468 g of dry triethylamine. Di-*tert*-butyl dicarbonate (solution in 1.2 L of dioxane) was added dropwise to the stirring solution at room temperature over 16 h. The reaction mixture was concentrated and the resulting residue suspended in 2.5 L of methylene chloride. then washed twice with 1 L of water, dried with anhydrous magnesium sulfate, filtered, and volatile organics removed by rotary evaporation to yield 617 g (83%) of tert-butyl 8-methyl-8-azabicyclo[3.2.1]octan-3-ylcarbamate (mp 79-81 °C).

[00857] STEP 2: To a 5 L round-bottom flask was added 480 g (2.0 mol) of tert-butyl 8-methyl-8-azabicyclo[3.2.1]octan-3-endo-ylcarbamate, 2 L of toluene, and 69 g (0.5 mol) of potassium carbonate. 2,2,2-Trichloroethyl chloroformate (347 mL, 2.4 mol) was added dropwise at room temperature over 6 h and the reaction heated at reflux temperature for 8 h. After the solution was cooled to room temperature, 1.2 L of water was added to the reaction solution and stirred 0.5 h. The organic layer was separated and washed with 1 L of brine, dried with anhydrous magnesium sulfate, filtered, and concentrated to yield a cloudy oil. The oil was titruated with 700 mL of a 3:2 ethyl ether/hexanes solution to yield 280 g (mp 131-135 °C) of 2,2,2-trichloroethyl 3-endo-(tert-butoxycarbonylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate that was collected by filtration. The mother liquour was concentrated and titruated further to yield a less pure sample of the Troc protected diamine (129 g, mp 116-118 °C).

[00858] STEP 3: To a 5 L round-bottom flask was added 360 g (0.9 mol) of 2,2,2-trichloroethyl 3-endo-(tert-butoxycarbonylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate, 2.8 L of methanol and 675 g (12.6 mol) of ammonium chloride. The solution was heated to reflux and 387 g (7.5 mol) of zinc dust was carefully added in small portions over 0.5 h. Upon complete addition of the zinc dust, the reaction was heated at reflux temperature for 2 h then cooled to room temperature. The reaction filtered through a thin pad a Celite 545, and the methanol removed by rotary evaporation. The resulting solid was dissolved in 800 mL of methylene chloride and stirred with 600 mL of concentrated ammonium hydroxide for 0.5 h. The organic layer was separated, washed with 600 mL of water, dried with anhydrous magnesium sulfate, filtered, and concentrated to yield an oil. The residue was dissolved in 200 mL

of methylene chloride and 1 L of ethyl ether then filtered. The resulting solution was chilled to 0 °C and 215 mL of 4N hydrogen chloride in dioxane were added slowly, dropwise over 0.5 h, being sure to maintain the reaction solution temperature close to 0 °C. After the addition was complete, 200 mL of methylene chloride and 1.4 L of ethyl ether were added to the cooled solution and a pale white precipitate formed. The resulting solid was collected by filtration to yield 173 g (85%) of tert-butyl 8-azabicyclo[3.2.1]octan-3-endo-ylcarbamate hydrochloride salt.

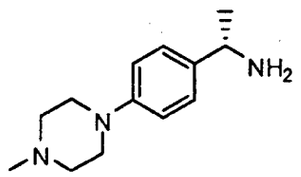
REAGENT PREPARATION 2: 4-(1-methylpiperidin-4-yl)benzylamine:



[00859] STEP 1: To a solution of 4-piperidin-4-ylbenzamide (200 mg, 1.00 mmol), 37% aqueous formaldehyde (162 μL, 2.00 mmol), and acetic acid (86 uL, 1.5 mmol) in a mixture of dichloromethane and methanol (2:1, 6 mL) was added sodium triacetoxylborohydride (318 mg, 1.5 mmol) in portions over fifteen minutes and stirring was continued for 2 hr at room temperature. The reaction was then quenched with water and adjusted to pH 9 with 2N aqueous sodium hydroxide then extracted with dichloromethane (2x 50 ml). The organic extracts were combined and dried over sodium sulfate, filtered and concentrated to give 4-(1-methylpiperidin-4-yl)benzamide (190 mg, 87 %). MS (EI) for $C_{13}H_{18}N_2O$: 218 (MH^+).

[00860] STEP 2: To an ice cold solution of 4-(1-methylpiperidin-4-yl)benzamide (190 mg, 0.87 mmol) in tetrahydrofuran (5 mL) was added 1.0M lithium aluminum hydride in tetrahydrofuran (1.79 mL, 1.79 mmol) and stirring continued overnight at room temperature. The reaction mixture was quenched by adding sodium sulfate decahydrate until gas evolution ceased. The suspension was filtered through Celite and and the filter cake washed with a mixture of ethyl acetate and chloroform (2:1, 50mL). The filtrate was concentrated to give 4-(1-methylpiperidin-4-yl)benzylamine (130 mg, 71%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.23 (dd, 4H), 3.86 (s, 3H), 2.98 (m, 2H), 2.49 (m, 1H), 2.11 (m, 2H), 1.83 (m, 4H).

REAGENT PREPARATION 3: (S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethylamine:

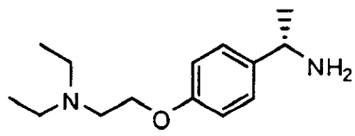


[00861] STEP 1: A solution of (1S)-1-(4-bromophenyl)ethylamine (10g, 50 mmol) and di-tert-butyl dicarbonate (13 g, 60 mmol) in dichloromethane (80 mL) was stirred at room temperature for 15 hours. Concentration of the reaction mixture afforded a solid residue that was then suspended in diethyl ether (100 mL). The mixture was diluted with hexane (100 mL) and the solid was isolated by filtration, then washed with hexane and dried to afford 14.4 g, 48 mmol (96%) of 1,1-dimethylethyl [(1S)-1-(4-bromophenyl)ethyl]carbamate. ^{1}H NMR (400 MHz, $CDCl_3$): 7.46-7.42 (m, 2H), 7.19-1.76 (m, 2H), 5.29 (s, 1H), 4.71 (br s, 1H), 1.43-1.39 (m, 12H). MS (EI) for $C_{13}H_{18}BrNO_2$: 301 (MH^+).

[00862] STEP 2: A mixture of 1,1-dimethylethyl [(1S)-1-(4-bromophenyl)-ethyl]carbamate (14.4 g, 48 mmol), tris(dibenzylideneacetone)dipalladium(0) (4.6 g, 4.8 mmol), N-methylpiperazine (22 mL, 200 mmol), BINAP (1.4 g, 4.8 mmol) and tribasic potassium phosphate in ethylene glycol dimethylether (120 mL) was refluxed for 15 hours. On cooling to room temperature, the mixture was diluted with ethyl acetate (100 mL). The organic mixture was extracted using 1N aqueous hydrochloric acid (3 x 100 mL). The pH of the combined aqueous portions was adjusted to 10 and was then extracted using ethyl acetate (3 x 100 mL). The combined organic portion was washed with brine then dried over anhydrous sodium sulfate. Filtration and concentration afforded a brown residue which was purified by silica gel column chromatography. Eluting with 0-20% methanol in ethyl acetate, purified fractions were pooled and concentrated to afford 12.9g, 40.5 mmol (84%) of 1,1-dimethylethyl {(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}carbamate. ^{1}H NMR (400 MHz, d_6-DMSO): 7.16 (d, 2H), 6.84 (d, 2H), 4.54 (m, 1H), 3.07 (m, 4H), 2.42 (m, 4H) 2.21 (s, 3H), 1.38 (s, 9H), 1.25 (d, 3H). MS (EI) for $C_{18}H_{29}N_3O_2$: 320 (MH^+).

[00863] STEP 3: A solution of 1,1-dimethylethyl {(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}carbamate (2g, 6.3 mmol) and 4N hydrogen chloride in dioxane (5 mL) in methanol (5 mL) was refluxed for 2 min. After cooling to room temperature the mixture was concentrated and rotary evaporated from benzene, and further dried *in vacuo* to afford 1.7 g, 5.9 mmol (95%) of (S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethylamine dihydrochloride. MS (EI) for $C_{13}H_{21}N_3$: 220 (MH^+).

REAGENT PREPARATION 4: (S)-2-[4-(1-aminoethyl)phenoxy]-N,N-diethylethylamine:



[00864] STEP 1: A solution of (S)-1-(4-methoxyphenyl)ethanamine (3.10 g, 20.5 mmol) in dichloromethane (30 ml) was cooled to -78 °C and a solution of boron tribromide (3.88 ml, 41 mmol) in dichloromethane (15 ml) was added dropwise. The reaction mixture was stirred at -78 °C for two hours and then at room temperature for 2 h. The solution was then cooled to 0 °C and water (15 ml) was added followed by saturated aqueous sodium carbonate to pH 8. The mixture was partially concentrated by rotary evaporation, tetrahydrofuran (50 ml) was then added followed by di-tert-butyl dicarbonate (4.47 g, 20.5 mmol) and the reaction mixture was stirred at room temperature overnight. The water layer was extracted with ethyl acetate (2x 150 ml) and the combined organic layers were washed with brine, dried over sodium sulfate then filtered and concentrated. The residue was purified by silica gel column chromatography using hexanes:ethyl acetate 4:1 to 3:1 as eluent to afford 1,1-dimethylethyl [(1S)-1-(4-hydroxyphenyl)ethyl]carbamate (2.90 g, 60 % yield). ^1H NMR (400 MHz, $CDCl_3$): 7.10 (br s, 2H), 6.73 (d, 2H), 6.07 (br s, 1H), 4.91-4.51 (m, 2H), 1.56-1.25 (m, 12H).

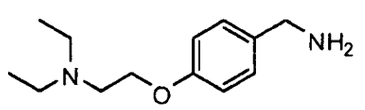
[00865] STEP 2: To a solution of 1,1-dimethylethyl [(1S)-1-(4-hydroxyphenyl)ethyl]carbamate (2.90 g, 12.2 mmol) in dimethylformamide (25ml) were added cesium carbonate (11.9 g, 36.6 mmol) and 2-bromo-N,N-diethylamine hydrobromide (3.18 g, 12.2 mmol) and the reaction mixture was stirred at 60 °C for 24h. The mixture was partitioned between ethyl acetate (150 ml) and water (75ml)

and the organic phase was washed with 1M aqueous sodium hydroxide (50 ml), 5% aqueous lithium chloride (50ml), dried over sodium sulfate then filtered and concentrated to give 1,1-dimethylethyl [(1S)-1-(4-{[2-(diethylamino)ethyl]oxy}phenyl)ethyl]carbamate (0.920 g, 22% yield) as a yellow oil. MS (EI) for $C_{19}H_{32}N_2O_3$: 337 (MH^+).

[00866] STEP 3: A solution of 1,1-dimethylethyl [(1S)-1-(4-{[2-(diethylamino)ethyl]oxy}phenyl)ethyl]carbamate (0.912 g, 2.7 mmol) in 4N hydrogen chloride in dioxane (5 mL) and methanol (5 mL) was refluxed for 2 min. After cooling to room temperature the mixture was concentrated to afford (S)-2-[4-(1-aminoethyl)phenoxy]-N,N-diethylethylamine as the hydrochloride salt (0.830 g, 99% yield). MS (EI) for $C_{14}H_{24}N_2O$: 237 (MH^+).

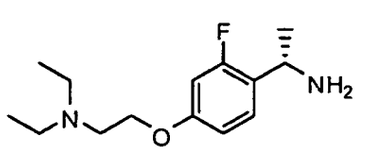
[00867] Using analogous synthetic techniques and substituting with alternative starting reagents, the following reagents were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00868] 2-[4-(aminomethyl)phenoxy]-N,N-diethylethylamine:



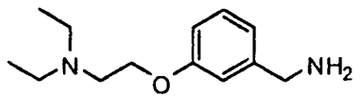
Synthesized according to the method of reagent preparation 4 using 4-(aminomethyl)phenol in step 1. ^1H NMR(CD_3OD): 7.45 (d, 2H), 7.10 (d, 2H), 4.40 (t, 2H), 4.06 (s, 2H), 3.70 (s, 2H), 3.65 (t, 2H), 3.32 (t, 2H), 1.39-1.36 (m, 6H). MS (EI) for $C_{13}H_{22}N_2O$: 223.

[00869] (S)-2-[4-(1-aminoethyl)-3-fluorophenoxy]-N,N-diethylethylamine:



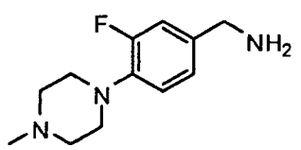
Synthesized according to the method of reagent preparation 4 using (S)-4-(1-aminoethyl)-3-fluorophenol in step 1. MS (EI) for $C_{14}H_{23}FN_2O$: 255 (MH^+).

[00870] 2-[3-(aminomethyl)phenoxy]-N,N-diethylethylamine:



[00871] Synthesized according to the method of reagent preparation 4 using 3-(aminomethyl)phenol in step 1. ^{1}H NMR(DMSO-d_6): 6.05 (t, 2H), 5.85 (s, 2H), 5.75-5.72 (m, 2H), 3.05-3.03 (m, 2H), 2.28 (s, 2H), 2.28-2.01 (m, 2H), 1.95-1.93 (m, 10H). MS(EI) for $C_{13}H_{22}N_2O$: 223.

REAGENT PREPARATION 5: [3-fluoro-4-(4-methylpiperazin-1-yl)phenyl]benzylamine:



[00872] STEP 1: To 4-bromo-3-fluorobenzoic acid (2.00 g, 9.13 mmol) in methanol (12 ml) was added sulfuric acid (500 µl) and heated to 80°C for 18 h then cooled to room temperature and concentrated. The residue was diluted with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and then concentrated to afford (2.07 g, 97%) of methyl 4-bromo-3-fluorobenzoate, which was used without further purification. ^{1}H NMR (400 MHz, CD_3OD): 7.80-7.73 (m, 3H), 3.91 (s, 3H). MS (EI) for $C_8H_6BrFO_2$: 234 (MH^+).

[00873] STEP 2: To 1-methylpiperazine (980 µl, 8.80 mmol) in toluene (15 ml) was added tris(dibenzylidene acetone)dipalladium (201 mg, 0.22 mmol), BINAP (550 mg, 0.88 mmol), and cesium carbonate (4.30 g, 13.2 mmol). The mixture was stirred for 30 minutes before the addition of methyl 4-bromo-3-fluorobenzoate (2.05 g, 8.80 mmol), after which, the temperature was increased to 105°C and stirred for an additional 18 h. The mixture was cooled and filtered through Celite, washed with ethyl acetate, and the resultant filtrate concentrated *in vacuo* to afford an orange oil. The residue was purified by column chromatography eluting with 5% methanol in

dichloromethane. Pure fractions were concentrated to afford (1.80 g, 81%) of methyl 3-fluoro-4-(4-methylpiperazin-1-yl)benzoate as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD): 7.78-7.73 (d, 1H), 7.64-7.59 (d, 1H), 7.09-7.03 (m, 1H), 3.86 (s, 3H), 3.26-3.20 (m, 4H), 2.65-2.59 (m, 4H), 2.35 (s, 3H). MS (EI) for $C_{13}H_{17}FN_2O_2$: 253 (MH^+).

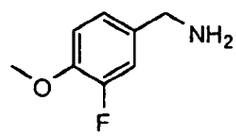
[00874] STEP 3: To methyl 3-fluoro-4-(4-methylpiperazin-1-yl)benzoate (1.80 g, 7.13 mmol) in methanol (40 ml) was added 1 M sodium hydroxide (25 ml, 25.0 mmol). The solution was stirred at 50°C for 3 h, at which point the mixture was concentrated. The residue was diluted with water (10 ml) and the pH adjusted to 6 with 1 N hydrochloric acid. The resultant precipitate was collected by filtration and dried *in vacuo* to afford (733 mg, 43%) of 3-fluoro-4-(4-methylpiperazin-1-yl)benzoic acid. ^{1}H NMR (400 MHz, CD_3OD): 7.73-7.68 (d, 1H), 7.62-7.57 (d, 1H), 7.03-6.97 (m, 1H), 3.26-3.20 (m, 4H), 2.83-2.76 (m, 4H), 2.47 (s, 3H). MS (EI) for $C_{12}H_{15}FN_2O_2$: 239 (MH^+).

[00875] STEP 4: To 3-fluoro-4-(4-methylpiperazin-1-yl)benzoic acid (250 mg, 1.05 mmol) in THF (10 ml) was added triethylamine (221 µl, 1.58 mmol) and isobutyl chloroformate (145 µl, 1.10 mmol). The mixture was stirred at 0°C for 1 hour, at which time concentrated aqueous ammonia (3 ml) was added. The reaction mixture was stirred for 3 hours then the volume was reduced *in vacuo*. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and then concentrated to afford (30.0 mg, 12%) of 3-fluoro-4-(4-methylpiperazin-1-yl)benzamide, which was used without further purification. MS (EI) for $C_{12}H_{16}FN_3O$: 238 (MH^+).

[00876] STEP 5: To 3-fluoro-4-(4-methylpiperazin-1-yl)benzamide (300 mg, 1.33 mmol) in THF (10 ml) was added sodium borohydride (252 mg, 6.67 mmol), followed by dropwise addition of boron trifluoride etherate (2.28 ml, 8.65 mmol) over 5 minutes. The mixture was stirred at 70°C for 16 h, at which point the mixture was cooled and quenched with 1N aqueous hydrochloric acid then THF was removed by rotary evaporation. The mixture was diluted with water (10 ml) and the pH adjusted to 10 with 1 N sodium hydroxide, extracted with ethyl acetate and the orgaic phase dried over sodium sulfate, filtered, and concentrated to afford (221 mg, 75%) of [3-fluoro-4-(4-methylpiperazin-1-yl)phenyl]benzylamine. ^{1}H NMR (400 MHz, CD_3OD): 7.23-7.11 (m, 3H), 4.05 (s, 2H), 3.49-3.40 (m, 2H), 3.26-3.20 (m, 2H),

3.17-3.08 (m, 2H), 2.99-2.91 (m, 2H), 2.68 (s, 3H). MS (EI) for $C_{12}H_{18}FN_3$: 224 (MH^+).

REAGENT PREPARATION 6: 3-fluoro-4-methoxybenzylamine:



[00877] STEP 1: A mixture of 3-fluoro-4-hydroxybenzoic acid (500 mg, 3.2 mmol), cesium carbonate (3.1 g, 9.6 mmol) and iodomethane (440 µl, 7.0 mmol) in dimethylformamide (7 mL) was stirred at room temperature for 4 hours. The mixture was diluted with ethyl acetate and washed with 5% aqueous lithium chloride, 1N aqueous sodium hydroxide, brine, then dried over anhydrous sodium sulfate. Filtration and concentration afforded 534 mg, 2.9 mmol (92%) of methyl 3-fluoro-4-(methyloxy)benzoate. MS (EI) for $C_9H_9FO_3$: 185 (MH^+).

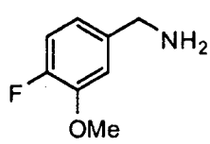
[00878] STEP 2: A solution of methyl 3-fluoro-4-(methyloxy)benzoate (534 mg, 2.9 mmol) in 35% aqueous potassium hydroxide:methanol (1:4, 10 mL) was stirred at reflux for 1 hour. The solution was cooled to room temperature and the methanol was evaporated. The pH of the aqueous portion was brought to 2 using concentrated hydrochloric acid. The precipitate which formed was collected by filtration and washed with water to afford 400 mg, 2.4 mmol (83%) of 3-fluoro-4-methoxybenzoic acid. MS (EI) for $C_8H_7FO_3$: 169 (M-H).

[00879] STEP 3: To a solution of 3-fluoro-4-methoxybenzoic acid (400 mg, 2.4 mmol) and triethylamine (560 µl, 3.5 mmol) in tetrahydrofuran (10 mL) cooled to 0°C was added isobutylchloroformate (320 µl, 2.4 mmol), and the mixture was stirred at 0°C for 1 hour. The solution was warmed to room temperature and was saturated with ammonia gas, then stirred for 15 hours at room temperature. The mixture was diluted with ethyl acetate, then washed with 20% aqueous citric acid, saturated aqueous sodium bicarbonate, and brine, then dried over anhydrous sodium sulfate. Filtration and concentration afforded 280mg, 1.7 mmol (70%) of 3-fluoro-4-(methyloxy)benzamide. MS (EI) for $C_8H_8FNO_2$: 170 (MH^+).

[00880] STEP 4: To a solution of 3-fluoro-4-(methyloxy)benzamide (100 mg, 0.60 mmol) in tetrahydrofuran (5 mL) was added sodium borohydride (115 mg, 3.0 mmol) followed by the drop-wise addition of a solution of borontrifluoride etherate (48% BF_3 ca., 475 µl, 3.8 mmol) in tetrahydrofuran (3 mL). The mixture was stirred at reflux for 15 hours, then was cooled to room temperature and diluted with ethyl acetate. The organic portion was extracted with 20% aqueous citric acid. The aqueous portion was brought to pH 8 using solid sodium bicarbonate, then was extracted several times using ethyl acetate. The combined organic portion was washed with brine then dried over anhydrous sodium sulfate. Filtration and concentration afforded a yellow residue, which was purified by silica gel column chromatography using 10% methanol in dichloromethane as eluent. Purified fractions were pooled and concentrated to afford 56 mg, 0.36 mmol (61%) of 3-fluoro-4-methoxybenzylamine as a colorless residue. MS (EI) for $C_8H_{10}FNO$: 156 (MH^+).

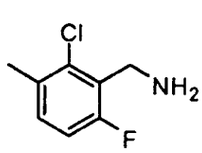
[00881] Using analogous synthetic techniques and substituting with alternative starting reagents, the following intermediate reagents were prepared. Alternative starting reagents were obtained commercially.

[00882] 4-fluoro-3-methoxybenzylamine:



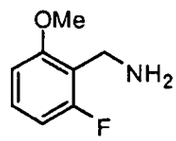
Prepared according to the method of reagent preparation 6 by omission of step 1 and 2 and using 2-fluoro-6-methoxybenzoic acid in step 3. MS (EI) for $C_8H_{10}FNO$: 156 (MH^+).

[00883] 2-chloro-6-fluoro-3-methylbenzylamine:



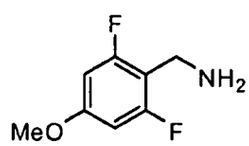
Prepared according to the method of reagent preparation 6 by omission of step 1 and 2 and using 2-chloro-6-fluoro-3-methylbenzoic acid in step 3. MS (EI) for C_8H_9ClFN: 178 (MH^+).

[00884] 2-fluoro-6-methoxybenzylamine:



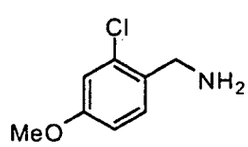
Prepared according to the method of reagent preparation 6 by omission of step 1 and 2 and using 2-fluoro-6-methoxybenzoic acid in step 3. MS (EI) for $C_8H_{10}FNO$: 156 (MH^+).

[00885] 2,6-difluoro-4-methoxybenzylamine:



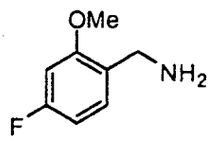
Prepared according to the method of reagent preparation 6 by omission of step 1 and 2 and using 2,6-difluoro-4-methoxybenzoic acid in step 3. MS (EI) for $C_8H_9F_2NO$: 174 (MH^+).

[00886] 2-chloro-4-methoxybenzylamine:



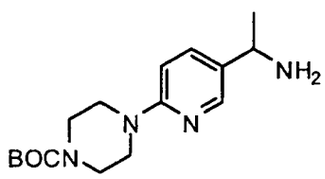
Prepared according to the method of reagent preparation 6 by using 2-chloro-4-hydroxybenzoic acid in step 1. MS (EI) for $C_8H_{10}ClNO$: 173 (MH^+).

[00887] 4-fluoro-2-methoxybenzylamine:



Prepared according to the method of reagent preparation 6 by using 4-fluoro-2-hydroxybenzoic acid in step 1. MS (EI) for $C_8H_{10}FNO$: 156 (MH^+).

REAGENT PREPARATION 7: tert-butyl 4-(5-(1-aminoethyl)pyridin-2-yl)piperazine-1-carboxylate:



[00888] STEP 1: A mixture of ethyl 6-chloronicotinate (2.67 g, 14.4 mmol), tert-butyl piperazine-1-carboxylate (2.5 g, 13.4 mmol) and N,N-diisopropylethylamine (3.5 mL, 20 mmol) in DME (15 mL) was heated at 120°C for 12 hours. The mixture was then cooled to room temperature and partitioned with ethyl acetate and 10% aqueous citric acid. The organic layer was washed twice with 10% aqueous citric acid then brine and dried over anhydrous sodium sulfate. Filtration and concentration followed by silica gel flash chromatography of the residue using 3:1 hexanes:ethyl acetate to 100% ethyl acetate afforded tert-butyl 4-(5-(ethoxycarbonyl)pyridin-2-yl)piperazine-1-carboxylate (3.65 g). ^{1}H NMR (400 MHz, $CDCl_3$): 8.81 (s, 1H), 8.04 (d, 1H), 6.58 (d, 1H), 4.33 (q, 2H), 3.70-3.67 (m, 4H), 3.56-3.53 (m, 4H), 1.49 (s, 9H), 1.37 (tr, 3H).

[00889] STEP 2: tert-Butyl 4-(5-(ethoxycarbonyl)pyridin-2-yl)piperazine-1-carboxylate (3.65 g, 10.9 mmol) was taken into methanol (40 mL) followed by addition of 1M aqueous sodium hydroxide (15 mL) and THF (15 mL), and the mixture was heated at 50°C for one hour. An additional portion of 1M aqueous sodium hydroxide (10 mL) was then added and heating was continued an additional two hours. The mixture was then cooled to room temperature and concentrated to remove organic solvents. The aqueous residue was partitioned with ethyl ether and

the organic layer was discarded. The aqueous phase has carefully brought to pH 5-6 by addition of 1M aqueous hydrochloric acid to give a thick white suspension. The solid was collected by filtration and dried to give 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)nicotinic acid (2.0 g). ^{1}H NMR (400 MHz, DMSO-d_6): 12.57 (br s, 1H), 8.64 (s, 1H), 7.95 (d, 1H), 6.86 (d, 1H), 3.67-3.62 (m, 4H), 3.45-3.40 (m, 4H), 1.43 (s, 9H).

[00890] STEP 3: 6-(4-(tert-Butoxycarbonyl)piperazin-1-yl)nicotinic acid (2.0 g, 6.5 mmol) was taken into DMF (10 mL) followed by addition of HATU (2.48 g, 6.5 mmol), N,N-diisopropylethylamine (2.5 mL, 14.1 mmol) and N,O-dimethylhydroxylamine hydrochloride (652 mg, 6.7 mmol), and the mixture was stirred at room temperature over 12 hours. The resulting solution was partitioned with ethyl acetate and water then the organic phase washed with water (3x), 10% aqueous citric acid (2x) then 0.5M aqueous sodium hydroxide and brine. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated, then purified by silica gel flash chromatography with ethyl ether as eluent to provide tert-butyl 4-(5-(methoxy(methyl)carbamoyl)pyridin-2-yl)piperazine-1-carboxylate (1.45 g). MS (EI) for $C_{17}H_{26}N_4O_4$: 351 (MH^+).

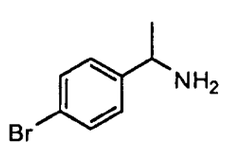
[00891] STEP 4: tert-Butyl 4-(5-(methoxy(methyl)carbamoyl)pyridin-2-yl)piperazine-1-carboxylate (1.45 g, 4.1 mmol) was taken into THF (20 mL) and the solution cooled to 0°C under a nitrogen atmosphere. Methyl magnesium bromide (3.0M in ethyl ether, 3.5 mL) was added in portions and the mixture was allowed to stir 10 minutes followed by addition of another 1.5 mL aliquot then the mixture was warmed to room temperature. The solution was then partitioned with ethyl ether and water and the organic phase washed with brine then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was taken into methanol (25 mL) followed by portion-wise addition of sodium borohydride solid (250 mg) over 10 minutes. The mixture was allowed to stir at room temperature another 10 minutes then concentrated. The residue was partitioned with ethyl ether and water and the aqueous phase extracted ethyl ethyl ether (2x). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl 4-(5-(1-hydroxyethyl)pyridin-2-yl)piperazine-1-carboxylate (1.48 g) which was carried forward without further purification.

[00892] STEP 5: tert-Butyl 4-(5-(1-hydroxyethyl)pyridin-2-yl)piperazine-1-carboxylate (1.48 g) as obtained in step 4 was taken into DMF (10 mL) followed by

addition of sodium azide (580 mg, 8.9 mmol), DPPA (1.6g, 5.7 mmol) and N,N-diisopropylethylamine (0.72 mL, 4.2 mmol) and the mixture was heated to 60°C for 12 hours. Additional aliquots of sodium azide and DPPA were then added to the reaction mixture and the temperature was raised to 75°C for an additional 12 hours. The mixture was then cooled to room temperature and partitioned with ethyl ether and water. The organic layer was washed with water (2x), 0.5M aqueous sodium hydroxide (2x) then with 10% aqueous citric acid brought to pH 1 with 1M aqueous hydrochloric acid. The organic phase was discarded and the acidic aqueous phase was quickly basified to pH 7 by portion-wise addition of solid sodium bicarbonate and 50% aqueous sodium hydroxide. The neutralized aqueous phase was extracted once with ethyl ether and the organic layer dried over anhydrous sodium sulfate, filtered, and concentrated to provide tert-butyl 4-(5-(1-azidoethyl)pyridin-2-yl)piperazine-1-carboxylate (1.21 g).

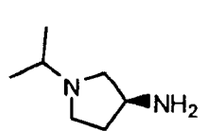
[00893] STEP 6: tert-Butyl 4-(5-(1-azidoethyl)pyridin-2-yl)piperazine-1-carboxylate (1.21 g), ,as obtained in step 5, was hydrogenated in methanol (50 mL) in the presence of 10% palladium on carbon (390 mg) at one atmosphere of hydrogen for 6 hours. The mixture was then filtered and concentrated to afford tert-butyl 4-(5-(1-aminoethyl)pyridin-2-yl)piperazine-1-carboxylate (1.1 g).

REAGENT PREPARATION 8: 1-(4-bromophenyl)ethylamine:



[00894] Synthesized according to the method of example 12 step 1 by using 1-(4-bromo-2-fluorophenyl)ethanone. MS (EI) for C_8H_9BrFN: 219 (MH^+).

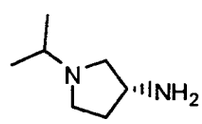
REAGENT PREPARATION 9: (3S)-1-(1-methylethyl)pyrrolidin-3yl-amine:



[00895] To a solution of 1,1-dimethylethyl (3S)-pyrrolidin-3yl carbamate (500 mg, 2.68 mmol) in acetone (0.5 mL, 6.80 mmol) was added sodium triacetoxyborohydride (1.50 g, 7.07 mmol). After 15 minutes stirring, additional sodium triacetoxyborohydride (750 mg, 3.53 mmol) was added and the mixture was stirred overnight at room temperature. Ethyl acetate (15 mL) was added to reaction mixture and the organic layer was washed with 0.5 M aqueous sodium hydroxide solution (10 mL) and brine, dried with anhydrous sodium sulfate then filtered and concentrated. The residue was diluted with acetonitrile (15 mL) and 4 M hydrogen chloride in dioxane (5 mL) was added. The mixture was stirred for 2 hr at 40 °C then concentrated and dried *in vacuo* to give the title compound hydrochloride salt (384 mg, 72.0%). ^{1}H NMR (400 MHz, d_4-methanol): 4.00-4.30 (m, 1H), 3.50-3.90 (m, 4H), 3.30 (m, 1H), 2.50-2.70 (m, 1H), 2.15 (m, 1H), 1.45 (d, 6H).

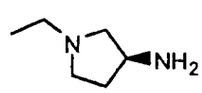
[00896] Using analogous synthetic techniques and substituting with alternative starting reagents, the following reagents were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00897] (3R)-1-(1-methylethyl)pyrrolidin-3-amine:



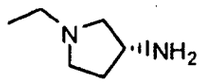
Synthesized according to the method of reagent preparation 9 by using 1,1-dimethylethyl (3R)-pyrrolidine-3yl carbamate. MS (EI) for $C_7H_{16}N_2$: 129 (MH^+).

[00898] (3S)-1-ethylpyrrolidin-3-amine:



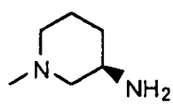
Synthesized according to the method of reagent preparation 9 by using acetaldehyde. MS (EI) for $C_6H_{14}N_2$: 115 (MH^+).

[00899] (3R)-1-ethylpyrrolidin-3-amine:



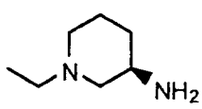
Synthesized according to the method of reagent preparation 9 by using acetaldehyde and 1,1-dimethylethyl (3R)-pyrrolidin-3yl carbamate. MS (EI) for $C_6H_{14}N_2$: 115 (MH^+).

[00900] (3R)-1-methylpiperidin-3-amine:



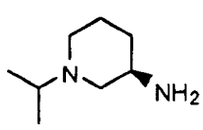
Synthesized according to the method of reagent preparation 9 by using aqueous formaldehyde and 1,1-dimethylethyl (3R)-piperidin-3-yl carbamate. MS (EI) for $C_6H_{14}N_2$: 115 (MH^+).

[00901] (3R)-1-ethylpiperidin-3-amine:



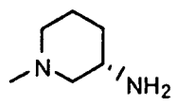
Synthesized according to the method of reagent preparation 9 by using acetaldehyde and 1,1-dimethylethyl (3R)-piperidin-3-yl carbamate. MS (EI) for $C_7H_{16}N_2$: 129 (MH^+).

[00902] (3R)-1-(1-methylethyl)piperidin-3-amine:



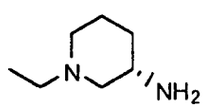
Synthesized according to the method of reagent preparation 9 by using 1,1-dimethylethyl (3R)-piperidin-3-yl carbamate. MS (EI) for $C_8H_{18}N_2$: 143 (MH^+).

[00903] (3S)-1-methylpiperidin-3-amine:



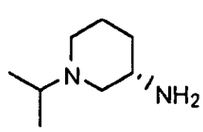
Synthesized according to the method of reagent preparation 9 by using aqueous formaldehyde and 1,1-dimethylethyl (3S)-piperidin-3-yl carbamate. MS (EI) for $C_6H_{14}N_2$: 113 (M-H).

[00904] (3S)-1-ethylpiperidin-3-amine:



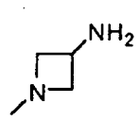
Synthesized according to the method of reagent preparation 9 by using acetaldehyde and 1,1-dimethylethyl (3S)-piperidin-3-yl carbamate. MS (EI) for $C_7H_{16}N_2$: 131 (MH^+).

[00905] (3S)-1-(1-methylethyl)piperidin-3-amine:



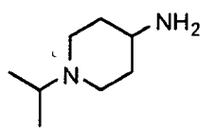
Synthesized according to the method of reagent preparation 9 by using 1,1-dimethylethyl (3S)-piperidin-3-yl carbamate. MS (EI) for $C_8H_{18}N_2$: 143 (MH^+).

[00906] 1-methylazetidin-3-amine:



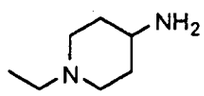
Synthesized according to the method of reagent preparation 9 by using formaldehyde and 1,1-dimethylethyl azetidin-3-ylcarbamate.

[00907] 1-(1-methylethyl)piperidin-4-amine:



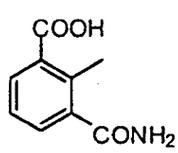
Synthesized according to the method of reagent preparation 9 by using acetone and 1,1-dimethylethyl piperidin-4-ylcarbamate. MS (EI) for $C_8H_{18}N_2$: 143 (MH^+).

[00908] 1-ethylpiperidin-4-amine:



Synthesized according to the method of reagent preparation 9 by using acetaldehyde and 1,1-dimethylethyl piperidin-4-ylcarbamate. MS (EI) for $C_7H_{16}N_2$: 131 (MH^+).

REAGENT PREPARATION 10: 3-(aminocarbonyl)-2-methylbenzoic acid:

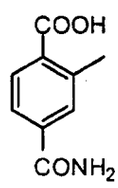


[00909] STEP 1: To a solution of methyl 3-bromo-2-methylbenzoate (0.646 g, 2.8 mmol) in 4 ml of dimethylamine was added $Pd(OAc)_2$ (0.5mol%), sodium carbonate (0.3 g, 2.8 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.262 g, 0.62 mmol). The mixture was heated to 120°C and stirred at this temperature for 4 hours then at RT for 18 hours. The reaction mixture was diluted with 30 ml of ethyl acetate and the resulting slurry was filtered through Celite. The filtrate was washed with water (2x15 ml) then 5% aqueous ammonium hydroxide (1x15 ml). The organic layer was dried over anhydrous sodium sufate then filtered and concentrated to provide methyl 3-cyano-2-

methylbenzoate (0.248 g, 50% yield) (*S.Weissman, D. Zewge, C. Chen; J. Org. Chem. 2005, 70, 1508-1510).* ^{1}H-NMR(400 MHz, DMSO-d_6): 8.09(d, 1H), 8.04(d, 1H), 7.53(t, 1H), 3.87 (s, 3H), 2.66 (s, 3H).

[00910] STEP 2: To a solution of methyl 3-cyano-2-methylbenzoate (0.111 g, 0.63 mmol) in 3 ml of t-butanol was added potassium hydroxide (0.29 g, 5.1 mmol). The mixture was refluxed for 6 hours and stirred at room temperature for 48 hours. The mixture was rotary evaporated to dryness and the residue dissolved in water then extracted with ethyl acetate (2x20 ml). The water layer was acidified with concentrated aqueous hydrochloric acid to pH 1-2 and extracted with ethyl acetate (3x20 ml). The ethyl acetate layer was dried over anhydrous sodium sulfate, then filtered and concentrated to yield 3-(aminocarbonyl)-2-methylbenzoic acid (86 mg).

REAGENT PREPARATION 11: 4-(aminocarbonyl)-2-methylbenzoic acid:

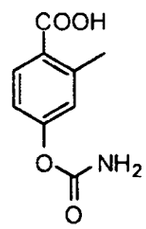


[00911] STEP 1: To a solution of 4-bromo-3-methylbenzonitrile (0.48 g, 2.43 mmol) in 1 ml of toluene at -78°C was added 1 ml of 2.6M n-BuLi in toluene followed by quenching with dry ice (0.5g, 12.5 mmol). The reaction mixture was warmed to room temperature, then taken into water and extracted with ethyl acetate (2x 15 ml). The water layer was acidified to pH 1-2 by addition of concentrated aqueous hydrochloric acid and extracted with ethyl acetate (3x 15 ml). The organic layer was dried over anhydrous sodium sulfate, then filtered and concentrated to give 4-cyano-2-methylbenzoic acid (0.08g, 20% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): 13.10 (br s, 1H), 7.92 (d, 1H), 7.84 (m, 1H), 7.76 (d, 1H), 2.53 (s, 3H).

[00912] STEP 2: To 4-cyano-2-methylbenzoic acid (0.071 g, 0.44 mmol) in 2 ml of t-butanol was added potassium hydroxide (0.13 g, 2.15 mmol). The reaction mixture was refluxed for 30 min and cooled to room temperature. To the reaction mixture was added 10 ml of brine and the reaction mixture was extracted with ethyl acetate (2x 15 ml). The water layer was acidified to pH 1-2 with concentrated aqueous hydrochloric acid to give a white precipitate. The solid was collected by

filtration, washed several times with water (3x 15 ml) and dried *in vacuo* to provide 4-(aminocarbonyl)-2-methylbenzoic acid (0.038 g, 49% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): 13.10 (br s, 1H), 8.07(s, 1H), 7.87 (d, 1H), 7.78-7.72 (m, 2H), 7.50 (s, 1H), 2.54 (s, 3H).

REAGENT PREPARATION 12: 4-[(aminocarbonyl)oxy]-2-methylbenzoic acid:



[00913] STEP 1: A solution of 4-hydroxy-2-methylbenzoic acid (550 mg, 3.60 mmol), benzyl chloride (458 mg, 3.60 mmol) and N,N-diisopropylethylamine (465 mg, 3.6 mmol) was stirred at 70° C for 22 h. A solution of saturated sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to afford phenylmethyl 4-hydroxy-2-methylbenzoate (687 mg, 79%). ^{1}H NMR (400 MHz, DMSO): 10.21-10.18 (br. s, 1H), 7.84-7.77 (d, 1H), 7.48-7.31 (m, 5H), 6.71-6.64 (br. s, 2H), 5.26 (s, 2H), 2.47 (s, 3H). MS (EI) for $C_{15}H_{14}O_3$: 243 (MH^+).

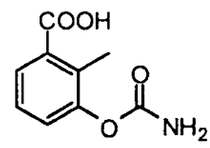
[00914] STEP 2: To a solution of phenylmethyl 4-hydroxy-2-methylbenzoate (687 mg, 2.82 mmol) in dichloromethane (8 ml) at 0° C, was added chlorosulfonyl isocyanate (1.20 g, 8.50 mmol). The reaction was allowed to warm to 25° C and stirred for 20 h. The reaction mixture was concentrated then taken into ethyl acetate and washed with water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to afford phenylmethyl 4-[(aminocarbonyl)oxy]-2-methylbenzoate (356 mg, 89%). ^{1}H NMR (400 MHz, DMSO): 7.91-7.87 (d, 1H), 7.49-7.29 (m, 5H), 7.11-7.00 (m, 4H), 5.31 (s, 2H), 2.52 (s, 3H). MS (EI) for $C_{16}H_{15}NO_4$: 286 (MH^+).

[00915] STEP 3: A mixture of phenylmethyl 4-[(aminocarbonyl)oxy]-2-methylbenzoate (356 mg, 1.25 mmol), 5% palladium on carbon (50 mg) and ethanol

(10 ml) was hydrogenated at 10 psi using a Parr apparatus. After completion of the hydrogenation, the mixture was filtered and the filtrate concentrated *in vacuo*. The resulting crude 4-[(aminocarbonyl)oxy]-2-methylbenzoic acid (14 mg, 6%) was used without further purification. ^{1}H NMR (400 MHz, DMSO): 12.86-12.69 (br. s, 1H), 7.87-7.81 (d, 1H), 7.34-7.27 (br. s, 1H), 7.07-6.98 (m, 3H), 2.52 (s, 3H). MS (EI) for $C_9H_9NO_4$: 196 (MH^+).

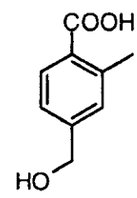
[00916] Using analogous synthetic techniques and substituting with alternative starting reagents, the following reagents were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00917] 3-[(aminocarbonyl)oxy]-2-methylbenzoic acid:



Synthesized according to the method of reagent preparation 12 starting with 3-hydroxy-2-methylbenzoic acid. ^{1}H NMR (400 MHz, DMSO): 12.87-12.70 (br. s, 1H), 7.65-7.60 (d, 1H), 7.35-7.19 (m, 3H), 7.00-6.93 (br. s, 1H), 2.30 (s, 3H). MS (EI) for $C_9H_9NO_4$: 196 (MH^+).

REAGENT PREPARATION 13: 4-(hydroxymethyl)-2-methylbenzoic acid:

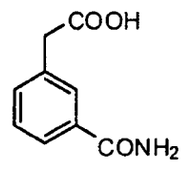


[00918] STEP 1: To 4-bromo-2-methyl benzoic acid (2.50 g, 11.6 mmol) suspended in anhydrous THF (90 ml) at -78° C was added n-butyl lithium (9.8 ml, 2.5 M in hexane) and dimethylformamide (2.0 ml). The reaction was stirred at -78° C for 1 h and then warmed to 25° C and allowed to react for an additional hour. The reaction was quenched with 1 N aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was extracted with 1 N aqueous sodium hydroxide and the aqueous layer was separated and the pH adjusted with 1 N aqueous hydrochloric acid.

The aqueous phase was extracted with ethyl acetate, then washed with brine, dried over sodium sulfate, filtered and concentrated. The resulting crude 4-formyl-2-methylbenzoic acid (900 mg, 47%) was obtained and was used without further purification. ^{1}H NMR (400 MHz, CD_3OD): 10.02-10.00 (s, 1H), 8.04-8.01 (d, 1H), 7.81-7.76 (m, 2H), 2.66-2.63 (s, 3H). MS (EI) for $C_9H_8O_3$: 163 (M^-).

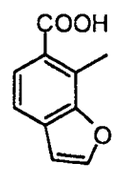
[00919] STEP 2: To 4-formyl-2-methylbenzoic acid (75 mg, 0.46 mmol), in methanol (5 ml), was added sodium borohydride (26 mg, 0.69 mmol). The solution was stirred at 25° C for 1 h. The reaction was quenched with saturated aqueous ammonium chloride and the pH adjusted to 2 with 2 N aqueous hydrochloric acid, then extracted with dichloromethane. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude 4-(hydroxymethyl)-2-methylbenzoic acid (37 mg, 76%) was obtained and was used without further purification. ^{1}H NMR (400 MHz, DMSO): 12.73-12.68 (s, 1H), 7.82-7.77 (d, 1H), 7.24-7.19 (m, 2H), 5.32-5.27 (m, 1H), 4.53-4.48 (d, 2H), 2.53-2.49 (s, 3H). MS (EI) for $C_9H_{10}O_3$: 167 (MH^+).

REAGENT PREPARATION 14: 2-[3-(aminocarbonyl)phenyl]acetic acid:



[00920] A solution of 3-cyanophenylacetic acid (0.2g, 1.24 mmol) in a mixture of trifluoroacetic acid (1 ml) and concentrated sulfuric acid (0.5 ml) was stirred at room temperature for 16h. The reaction mixture was then poured into ice-cold water and the resulting solid was filtered, washed with water and dried under vacuum to give 2-[3-(aminocarbonyl)phenyl]acetic acid (0.167g, 75% yield). MS (EI) for $C_9H_9NO_3$: 178 (M-H).

REAGENT PREPARATION 15: 7-methyl-1-benzofuran-6-carboxylic acid:



[00921] STEP 1: A solution of 3-hydroxy-2-methylbenzoic acid (5 g, 33 mmol) and sulfuric acid (500 µl) in methanol (20 mL) was stirred at reflux for 15 hours. The reaction mixture was allowed to cool to room temperature and partitioned between water and ethyl acetate. The aqueous portion was extracted with ethyl acetate and the combined organic portion was washed with saturated sodium bicarbonate, brine, and then was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford (5.46 g, 100%) of methyl 3-hydroxy-2-methylbenzoate. ^{1}H NMR (400 MHz, DMSO-d_6): 9.71 (s, 1H), 7.20-7.17 (m, 1H), 7.11-7.07 (m, 1H), 7.01-6.97 (m, 1H), 3.79 (s, 3H), 2.28 (s, 3H). MS (EI) for $C_9H_{10}O_3$: 166 (MH^+).

[00922] STEP 2: A mixture of 3-hydroxy-2-methylbenzoate (5.46 g, 33 mmol), allyl bromide (4.33 mL, 50 mmol) and cesium carbonate (21.5 g, 66 mmol) in dimethylformamide (60 mL) was stirred at 60°C for 2.5 hours. The reaction mixture was allowed to cool to room temperature and was then partitioned between water and ethyl acetate. The aqueous portion was extracted twice using ethyl acetate, and the combined organic portion was washed with 5% aqueous lithium chloride, 1N aqueous sodium hydroxide, brine, and then was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (6.85 g, 100%) of methyl 2-methyl-3-(prop-2-en-1-yloxy)benzoate as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): 7.33-7.30 (m, 1H), 7.27-7.23 (m, 1H), 7.18-7.15 (m, 1H), 6.13-6.02 (m, 1H), 5.35 (dd, 2H), 4.61 (d, 2H), 3.82 (s, 3H), 2.35 (s, 3H). MS (EI) for $C_{12}H_{14}O_3$: 207 (MH^+).

[00923] STEP 3: The above methyl 2-methyl-3-(prop-2-en-1-yloxy)benzoate was heated at 180°C for 1 hour. The reaction mixture was allowed to cool to room temperature then purified by column chromatography using 10-20% ethyl acetate in hexanes as eluent. Combined pure fractions were concentrated and dried *in vacuo* to afford (1.64 g, 24%) of methyl 3-hydroxy-2-methyl-4-prop-2-en-1-ylbenzoate. ^{1}H NMR (400 MHz, DMSO-d_6): 8.62 (br s, 1H), 7.22 (d, 1H), 6.99 (d, 1H), 6.00-5.89 (m, 1H), 5.07-5.02 (m, 2H), 3.79 (s, 3H), 3.40-3.35 (m, 2H), 2.35 (3H). MS (EI) for $C_{12}H_{14}O_3$: 207 (MH^+).

[00924] STEP 4: A solution of methyl 3-hydroxy-2-methyl-4-prop-2-en-1-ylbenzoate (1.64 g, 8.0 mmol) in methanol (20 mL) was cooled to -78°C. While maintaining the reaction temperature at -78°C, ozone was bubbled into the reaction mixture for 30 minutes, followed by the addition of dimethyl sulfide (5 mL). The

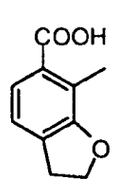
reaction mixture was allowed to warm to room temperature and was then stirred for an additional 15 hours. The reaction mixture was concentrated *in vacuo* and diluted with diethyl ether. The organic portion was washed with water, brine, dried over sodium sulfate and concentrated to afford (1.59 g, 90%) of methyl 7-methyl-2-(methyloxy)-2,3-dihydro-1-benzofuran-6-carboxylate as a yellow oil. MS (EI) for $C_{12}H_{14}O_4$: 223 (MH^+).

[00925] STEP 5: A solution of methyl 7-methyl-2-(methyloxy)-2,3-dihydro-1-benzofuran-6-carboxylate in phosphoric acid (3 mL) was stirred at room temperature for 10 minutes and then was stirred at 100°C for 15 minutes. The reaction mixture was cooled to room temperature and then was partitioned between water and diethyl ether. The aqueous portion was extracted three times with diethyl ether. The combined organic portion was washed three times with water and twice with 10% aqueous potassium carbonate. The basic portion was extracted three times with diethyl ether and the combined organic portions were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown residue which was purified by column chromatography eluting with 5% ethyl acetate in hexanes. Pure fractions were concentrated *in vacuo* to afford (371 mg, 54%) of methyl 7-methyl-1-benzofuran-6-carboxylate as a colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6): 8.21-8.18 (m, 1H), 7.80-7.77 (m, 1H), 7.60-7.56 (m, 1H), 7.07-7.04 (m, 1H), 3.86 (s, 3H), 2.72 (s, 3H). MS (EI) for $C_{11}H_{10}O_3$: 191 (MH^+).

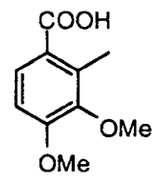
[00926] STEP 6: A solution of methyl 7-methyl-1-benzofuran-6-carboxylate (370 mg, 1.95 mmol) in 35% aqueous potassium hydroxide/methanol (1:3, 4mL) was stirred at reflux for 30 minutes. The methanol was removed under reduced pressure and resultant aqueous portion was brought to pH 2 using 6N aqueous hydrochloric acid. The precipitate which formed was collected by filtration and dried *in vacuo* to afford (258 mg, 75%) of 7-methyl-1-benzofuran-6-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6): 8.17 (d, 1H), 7.78 (d, 1H), 7.54 (d, 1H), 7.03 (d, 1H), 2.72 (s, 3H). MS (EI) for $C_{10}H_8O_3$: 177 (MH^+).

REAGENT PREPARATION 16: 7-methyl-2,3-dihydrobenzofuran-6-carboxylic acid:



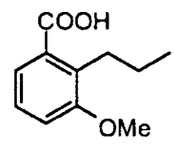
[00927] 7-Methyl-1-benzofuran-6-carboxylic acid (synthesized in reagent preparation 15) (0.050 g, 0.28 mmol) was solubilized in anhydrous ethanol (2.0 mL) and 0.050 g of palladium (II) hydroxide (20%) was added. This mixture was shaken for 3 hours under 35 psi hydrogen gas using a Parr hydrogenator apparatus. The mixture was filtered through celite and concentrated *in vacuo* to give crude 7-methyl-2,3-dihydro-1-benzofuran-6-carboxylic acid (0.049 g, 97% yield) which was used without further purification. ^{1}H NMR (400 MHz, d_6-DMSO): 12.67 (broad s, 1H), 7.33 (d, 1H), 7.11 (d, 1H), 4.55 (t, 2H), 3.23 (t, 2H), 2.32 (s, 3H).

REAGENT PREPARATION 17: 3,4-dimethoxy-2-methylbenzoic acid:



[00928] To a mixture of magnesium turnings (0.059 g, 2.40 mmol) in tetrahydrofuran (1 ml) was added a solution of 6-bromo-2,3-dimethoxy toluene (0.660 g, 2.3 mmol) in tetrahydrofuran (1 ml). The reaction was initiated by addition of methylmagnesium bromide and the solution was stirred at room temperature overnight under nitrogen. To the mixture was then added an excess of dry ice. When the addition was complete, water was added (2 ml) followed by 1.5 M hydrochloric acid to pH 2. The water phase was extracted with ethyl acetate (2x 5 ml) and the combined organic layers were dried over sodium sulfate, filtered and concentrated to give 3,4-dimethoxy-2-methylbenzoic acid (0.315 g, 70% yield). MS (EI) for $C_{10}H_{12}O_4$: 195 (M-H).

REAGENT PREPARATION 18: 3-(methyloxy)-2-propylbenzoic acid:

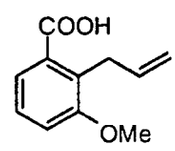


[00929] STEP 1: To methyl 3-hydroxy-2-prop-2-en-1-ylbenzoate (10.3 g, 53.6 mmol, M.A. Eissenstat et al., *J. Med. Chem.* **1995**, *38*, 3094-3105) and cesium

carbonate (26.2 g, 80.4 mmol) in DMF (100 ml) was added methyl iodide (15.2 g, 102.2 mmol). The reaction mixture was stirred at room temperature for 18 h, then filtered and concentrated. The residue was partitioned between ethyl acetate (250 mL) and water (100 mL). The layers were separated, the organic layer was washed with 5% lithium chloride (2 x 100 mL) and brine (100 mL), dried over sodium sulfate, and concentrated to provide methyl 3-(methyloxy)-2-prop-2-en-1-ylbenzoate (10.3 g, 93% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (m, 1H), 7.24 (m, 1H), 7.02 (m, 1H), 6.97 (m, 1H), 4.97 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.73 (m, 2H).

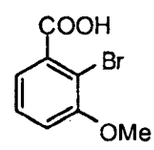
[00930] STEP 2: Methyl 3-(methyloxy)-2-prop-2-en-1-ylbenzoate (100 mg, 0.48 mmol) in methanol (2 mL) was hydrogenated over 5% palladium on carbon for 15 h under atmospheric pressure. The reaction mixture was filtered and 35% aqueous potassium hydroxide (1 mL) was added. The mixture was refluxed for 1 h and then concentrated. The pH was adjusted to 2 with 6N HCl. The precipitate was filtered, washed with water and dried to give 3-(methyloxy)-2-propylbenzoic acid (35 mg, 38% yield). MS (EI) for $C_{11}H_{14}O_3$: 193 (M-H)

REAGENT PREPARATION 19: 3-(methyloxy)-2- prop-2-en-1-ylbenzoic acid:



[00931] Proceeding as in reagent preparation 18 and omitting hydrogenation step 2, 3-(methyloxy)-2- prop-2-en-1-ylbenzoic acid was prepared.

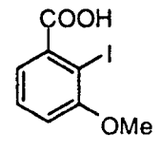
REAGENT PREPARATION 20: 2-bromo-3-(methyloxy)benzoic acid:



[00932] To 2-amino-3-(methyloxy)benzoic acid (4.00 g, 23.9 mmol) in 10% aqueous hydrobromic acid (54 ml) at 0°C was added sodium nitrite (1.65 g, 23.9 mmol) in water (17 ml). To this solution was added dropwise a solution of copper (I)

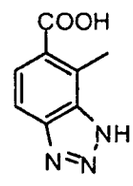
bromide (3.78 g, 26.3 mmol) in 48% hydrobromic acid (22 ml) and heated to 60°C for 2 h. The mixture was cooled to 0°C, and the resultant precipitate was collected by filtration, washed with cold water and recrystallized from water to give pure 2-bromo-3-(methyloxy)benzoic acid (4.07g, 74%). MS (EI) for $C_8H_7BrO_3$: 232 (MH^+).

REAGENT PREPARATION 21: 2-iodo-3-(methyloxy)benzoic acid:



[00933] To 2-amino-3-methoxybenzoic acid (1.00 g, 5.98 mmol) in 25% aqueous hydrochloric acid (8 ml) at 0°C was added sodium nitrite (0.45 g, 6.50 mmol) in water (3 ml). This solution was added drop-wise to a solution of potassium iodide (15.8 g, 59.3 mmol) in water (60 ml) and allowed to warm to 25°C then stirred for 16 h. The reaction mixture was quenched with 1 N aqueous sodium bicarbonate until the pH became basic. The solution was extracted with methylene chloride and the organic dried over sodium sulfate, filtered, and concentrated to give a purple oil. The residue was purified by column chromatography, eluting with 10% methanol in dichloromethane. Pure fractions were concentrated to afford (0.623 g, 38%) of 2-iodo-3-methoxybenzoic acid. MS (EI) for $C_8H_7IO_3$: 279 (MH^+).

REAGENT PREPARATION 22: 7-methyl-1H-benzotriazole-6-carboxylic acid:



[00934] Step 1: 4-(Acetylamino)-2-methylbenzoic acid (3.93 g, 20.3 mmol) was taken up in concentrated sulfuric acid (20 mL) and warmed to solubilize. The solution was then cooled with an ice bath. Fuming nitric acid (0.86 mL) in sulfuric acid (2.0 mL) was added dropwise and the resultant solution was stirred one hour. The solution was then diluted with water and a yellow solid was collected by filtration and discarded. Upon standing, an orange solid formed in the filtrate, which was collected by filtration to give (0.61 g) of 4-amino-2-methyl-3-nitrobenzoic acid. The

aqueous filtrate was then extracted (3 x 100 mL of 10% methanol in ethyl acetate), and the combined organic layers were dried (magnesium sulfate), filtered and concentrated to yield additional 4-amino-2-methyl-3-nitrobenzoic acid (0.90 g). ^{1}H NMR (400 MHz, d_6-DMSO): 7.75 (d, 1H), 6.75 (d, 1H), 2.41 (s, 3H). MS (EI) for $C_8H_8N_2O_4$: 195 (MH^+).

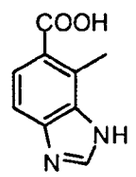
[00935] Step 2: 4-Amino-2-methyl-3-nitrobenzoic acid (1.87 g, 9.54 mmol) was solubilized in methanol (100 mL) and tetrahydrofuran (100 mL) and was treated with (trimethylsilyl)diazomethane solution (5.3 mL, 10.5 mmol, 2.0M in diethyl ether). After the reaction was shown to be complete, the mixture was concentrated and the residue was purified via column chromatography (silica gel, 5:1 hexanes/ethyl acetate) to give 1.10 g (55% yield) of methyl 4-amino-2-methyl-3-nitrobenzoate. ^{1}H NMR (400 MHz, d_6-DMSO): 7.73 (d, 1H), 6.75 (d, 1H), 6.51 (broad s, 2H), 3.75 (s, 3H), 2.37 (s, 3H). MS (EI) for $C_9H_{10}N_2O_4$: 210 (MH^+).

Step 3: To a solution of methyl 4-amino-2-methyl-3-nitrobenzoate (1.10 g, 5.22 mmol) in tetrahydrofuran (75 mL) and water (25 mL) was added ammonium formate (6.6 g, 104 mmol) and iron powder (2.92 g, 52.2 mmol). This mixture was refluxed for 12 hours then filtered and the filter cake rinsed with ethyl acetate. The filtrate layers were separated and the organic layer was dried (magnesium sulfate), filtered and concentrated to give 0.92 g (98% yield) of crude methyl 3,4-diamino-2-methylbenzoate, which was used without further purification. ^{1}H NMR (400 MHz, d_6-DMSO): 7.05 (d, 1H), 6.40 (d, 1H), 3.69 (s, 3H), 2.29 (s, 3H). MS (EI) for $C_9H_{12}N_2O_2$: 181 (MH^+).

[00936] Step 4: Methyl 3,4-diamino-2-methylbenzoate (0.27 g, 1.5 mmol) was taken up in concentrated sulfuric acid (30 mL) and heated to solubilize, then cooled with an ice bath. Concurrently, sodium nitrite (0.14 g, 2.1 mmol) was solubilized in concentrated sulfuric acid (8.4 mL) using heating. This sodium nitrite solution was then cooled and added dropwise to the cooled solution of diamine. The mixture was stirred at 0°C for 30 minutes then warmed to 60°C for 15 minutes. The solution was then poured onto ice and extracted with 10% methanol in ethyl acetate (2 x 100 mL). The combined organic layers were dried (magnesium sulfate), filtered and concentrated to give 0.3 g of crude methyl 7-methyl-1*H*-benzotriazole-6-carboxylate, which was taken up in methanol (5 mL) and tetrahydrofuran (10 mL) and treated with 2M aqueous lithium hydroxide (5 mL), then heated to 70°C for one hour. This

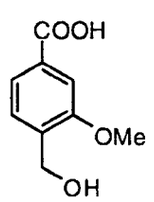
solution was made acidic using concentrated aqueous hydrochloric acid, then extracted with 10% methanol in ethyl acetate (2 x 50 mL). The combined organic layers were dried (magnesium sulfate), filtered and concentrated to give 0.26 g of 7-methyl-1H-benzotriazole-6-carboxylic acid. ^{1}H NMR (400 MHz, d_6-DMSO): 7.94 (d, 1H), 7.72 (m, 1H), 2.95 (s, 3H). MS (EI) for $C_8H_7N_3O_2$: 178 (MH^+).

REAGENT PREPARATION 23: 7-methyl-1H-benzimidazole-6-carboxylic acid:



[00937] Methyl 3,4-diamino-2-methylbenzoate (synthesized in reagent preparation 22) (0.18 g, 1.0 mmol) was taken up in formic acid (8.0 mL) and refluxed for 4 hours. The solution was then concentrated *in vacuo*. The material was taken up in methanol (2.5 mL) and tetrahydrofuran (5.0 mL) and treated with 2M aqueous lithium hydroxide (2.5 mL) and heated to 70°C for 12 hours. This solution was made acidic using concentrated aqueous hydrochloric acid, then extracted with 10% methanol in ethyl acetate (2 x 50 mL). The combined organic layers were dried (magnesium sulfate), filtered and concentrated to give 0.055 g of 7-methyl-1H-benzimidazole-6-carboxylic acid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.34 (s, 1H), 7.94 (d, 1H), 7.64 (d, 1H), 2.85 (s, 3H). MS (EI) for $C_9H_8N_2O_2$: 177 (MH^+).

REAGENT PREPARATION 24: 4-(hydroxymethyl)-3-(methyloxy)benzoic acid:

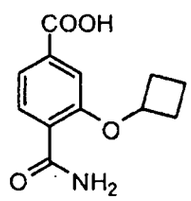


[00938] STEP 1: A mixture of methyl 4-methyl-3-(methyloxy)benzoate (1.00 g, 5.55 mmol), N-bromosuccinimide (1.09 g, 6.10 mmol) and a catalytic amount of 2,2'-azobis(isobutyronitrile) (AIBN) was refluxed in carbon tetrachloride (40 ml) for 16h. The reaction mixture was filtered and the solution was washed with brine (25 ml),

dried over sodium sulfate and concentrated to give methyl 4-(bromomethyl)-3-(methyloxy)benzoate (1.4g, 97% yield).

[00939] STEP 2: methyl 4-(bromomethyl)-3-(methyloxy)benzoate (300 mg, 1.15 mmol) was suspended in water (3 ml) and concentrated aqueous hydrochloric acid (380 μl) was added. The reaction mixture was refluxed for 16 h, then cooled to room temperature and partitioned with ethyl acetate (10 ml). The organic phase was separated, washed with brine, dried over sodium sulfate and concentrated. The residue was purified by flash chromatography on silica gel (dichloromethane:methanol 95:5) to provide 4-(hydroxymethyl)-3-(methyloxy)benzoic acid (74 mg, 35% yield). MS (EI) for $C_9H_{10}O_4$: 181(M-H).

REAGENT PREPARATION 25: 4-(aminocarbonyl)-3-(cyclobutyloxy)benzoic acid:



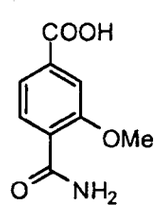
[00940] STEP 1: To a solution of methyl 4-bromo-3-hydroxybenzoate (1.01g, 4.4 mmol) in 7 ml of dimethylamine was added $Pd(OAc)_2$ (15 mg, 0.5 mol%), sodium carbonate (0.47 g, 4.4 mmol) and potassium ferricyanide (0.41 g, 0.97 mmol). The mixture was heated to 120°C and stirred at this temperature for 4 hours and at RT for 18 hours. The reaction mixture was diluted with 30 ml of ethyl acetate and the resulting slurry was filtered through Celite. The filtrate was washed with water (2x15 ml) and 5% aqueous ammonium hydroxide (1x15 ml). The organic layer was dried over sodium sulfate, filtered and concentrated to provide methyl 4-cyano-3-hydroxybenzoate (0.26g, 33.5% yield) (S.Weissman, D. Zewge, C. Chen; *J.Org. Chem.* **2005**, *70*, 1508-1510). ^{1}H NMR(400 MHz, CD_3OD): 7.65 (d, 1H), 7.56-7.54 (m, 2H), 3.91(s, 3H). MS (EI) for $C_9H_7NO_3$: 178 (MH^+).

[00941] STEP 2: To a solution of methyl 4-cyano-3-hydroxybenzoate (0.067 g, 0.38 mmol) in 2 ml of DMF was added cesium carbonate (0.2 g, 0.62 mmol), bromocyclobutane (0.051 g, 0.38 mmol), and the reaction mixture was heated at 60°C and stirred at this temperature for 3 hrs. The reaction mixture was cooled to RT, poured into ice water, and extracted several times with ethyl acetate (3x 20 ml). The

organic solution was dried over Na_2SO_4, filtered, rotary evaporated to dryness then dried *in vacuo* to provide methyl 4-cyano-3-(cyclobutyloxy)benzoate (0.055 g, 63%). ^{1}H NMR (400 MHz, CD_3OD): 7.74 (d, 1H), 7.67 (d, 1H), 7.54 (s, 1H), 3.93 (s, 3H), 2.57-2.52 (m, 2H), 2.26-2.21 (m, 2H), 1.94-1.90 (m, 1H), 1.94-1.78 (m, 2H). MS (EI) for $C_{13}H_{13}NO_3$: 232 (MH^+).

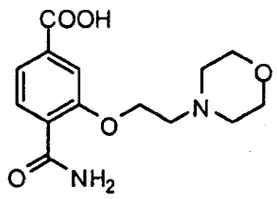
[00942] STEP 3: To a solution of methyl 4-cyano-3-(cyclobutyloxy)benzoate (0.051 g, 0.23 mmol) in 2 ml of ethanol was added 0.5 ml of DMSO, 1ml of 1N aqueous sodium hydroxide, 1 ml of 30% aqueous hydrogen peroxide, and the reaction mixture was stirred at RT for 18 hrs. The reaction mixture was diluted with 10 ml of water and the aqueous solution extracted three times with ethyl acetate (20 ml). The aqueous layer was acidified to pH 3-4 by portion-wise addition of aqueous hydrochloric acid, then extracted with ethyl acetate (3x 20 mL). The organic solution was rotary evaporated to dryness and dried *in vacuo* to provide 4-(aminocarbonyl)-3-(cyclobutyloxy)benzoic acid (0.026 g, 50%). ^{1}H NMR(400 MHz, DMSO-d_6): 13.25 (s, 1H), 7.80 (d, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.55 (d, 1H), 7.41 (s, 1H), 4.88-4.85 (m, 1H), 2.44-2.43 (m, 2H), 2.18-2.14 (m, 2H), 1.99-1.73 (m, 2H). MS (EI) for $C_{12}H_{13}NO_4$: 236 (MH^+).

REAGENT PREPARATION 26: 4-(aminocarbonyl)-3-(methoxy)benzoic acid:



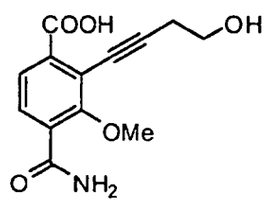
[00943] Synthesized according to the method of reagent preparation 25 using iodomethane in step 2. ^{1}HNMR (400 MHz, CD_3OD): 13.21 (s, 1H), 7.81 (d, 1H), 7.67 (d, 1H), 7.59 (d, 1H), 2.49 (s, 3H). MS(EI) for $C_9H_9NO_4$: 196(MH^+).

REAGENT PREPARATION 27: 4-(aminocarbonyl)-3-[(2-morpholin-4-ylethyl)oxy]benzoic acid:



[00944] Synthesized according to the method of reagent preparation 25 using 4-(2-chloroethyl)morpholine hydrochloride in step 2. MS(EI) for $C_{14}H_{18}N_2O_5$: 295(MH^+).

REAGENT PREPARATION 28: 4-(aminocarbonyl)-2-(4-hydroxybut-1-ynyl)-3-methoxybenzoic acid:



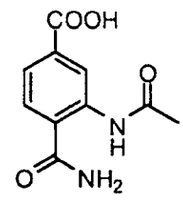
[00945] STEP 1: To a solution of 2-bromo-3-methoxybenzoic acid (718 mg, 3.11 mmol) in methanol (20 mL) was added a catalytic amount of concentrated sulfuric acid and the mixture was brought to reflux for 20 h. On cooling to room temperature, the solution was concentrated and the residue was taken into ethyl acetate and washed with water, saturated aqueous sodium bicarbonate (2x) and brine then dried over sodium sulfate. The solution was then filtered and concentrated to give methyl 2-bromo-3-methoxybenzoate (610 mg, 80%). MS (EI) for $C_9H_9BrO_3$: 245 (MH^+).

[00946] STEP 2: A mixture of methyl 2-bromo-3-methoxybenzoate (0.4 g, 1.63 mmol), $Pd(PPh_3)_2Cl_2$ (0.057 g, 0.082 mmol), copper (I) iodide (0.031 g, 0.16 mmol) and 3-butyn-1-ol (0.173 ml, 2.28 mmol) were stirred in trietylamine (5 ml) at 80 °C for 20h. The solvent was concentrated under vacuum, and the residue was partitioned between ethyl acetate (15 ml) and water (5 ml). The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography using hexanes:ethyl acetate 2:1 as eluent to afford methyl 2-(4-hydroxybut-1-yn-1-yl)-3-(methyloxy)benzoate (0.056 g; 15 % yield). MS (EI) for $C_{13}H_{14}O_4$: 235 (MH^+).

[00947] STEP 3: Methyl 2-(4-hydroxybut-1-yn-1-yl)-3-(methyloxy)benzoate (0.056 g, 0.24 mmol) was dissolved in methanol (2 ml), and a solution of potassium

hydroxide (0.027 g, 0.48 mmol) in water (0.5 ml) was added. The reaction mixture was stirred at 60 °C for 1h, cooled to room temperature, and 1.5M hydrochloric acid was added to pH 4. The aqueous mixture was extracted with ethyl acetate, and the organic layer was washed with brine then dried over sodium sulfate. The mixture was then filtered and concentrated to give 2-(4-hydroxybut-1-yn-1-yl)-3-(methyloxy)benzoic acid (0.052 g, 99% yield). MS (EI) for $C_{12}H_{12}O_4$: 219 (M-H).

REAGENT PREPARATION 29: 3-(acetylamino)-4-(aminocarbonyl)benzoic acid:



[00948] STEP 1: N,N-Diisopropylethylamine (0.41 mL, 2.30 mmol) was added to a mixture of O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (321 mg, 0.84 mmol) and 4-{[(1,1-dimethylethyl)oxy]carbonyl}-2-nitrobenzoic acid (prepared according to Gao, Y. et. al WO2001070737) (205 mg, 0.77 mmol) in N,N-dimethylformamide (2 mL), and the reaction mixture was stirred at room temperature for 30 minutes. Ammonia was bubbled into the reaction mixture and stirring was continued for 45 minutes. The reaction mixture was quenched with 0.5M aqueous hydrochloric acid solution (20 mL) and extracted with ethyl acetate (3 x 20 mL), and the combined extract was washed with water (20 mL), then brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel flash chromatography (25 to 75% ethyl acetate in hexanes) to give the 1,1-dimethylethyl 4-(aminocarbonyl)-3-nitrobenzoate (160 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.55 (s, 1H), 8.25 (d, 1H), 7.64 (d, 1H), 6.51 (br, 1H), 6.26 (br, 1H), 1.61 (s 9H); MS (EI) for $C_{12}H_{14}N_2O_5$: 267 (MH^+).

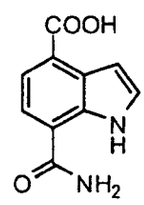
[00949] STEP 2: A mixture of 1,1-dimethylethyl 4-(aminocarbonyl)-3-nitrobenzoate (213 mg, 0.80 mmol), 10% palladium on charcoal (Degussa type, 200 mg) in ethyl acetate (20 mL) was shaken in a Parr hydrogenation apparatus at 35 psi for 4 hours. The reaction mixture was filtered and concentrated to give 1,1-

dimethylethyl 3-amino-4-(aminocarbonyl)benzoate (180 mg, 95% yield). MS (EI) for $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[00950] STEP 3: Acetyl chloride (50 uL, 0.32 mmol) was added to a solution of 1,1-dimethylethyl 3-amino-4-(aminocarbonyl)benzoate (126 mg, 0.53 mmol) and pyridine (52 uL, 0.64 mmol) in tetrahydrofuran (3 mL) at 0°C, and the resulting mixture was stirred at 0°C for one hour. The mixture was quenched with ice-water (10 mL) and extracted ethyl acetate (3x 10 mL). The combined extract was washed with 15 mL, each of 5% aqueous citric acid, saturated aqueous sodium bicarbonate, and brine solutions then dried over sodium sulfate, filtered and concentrated to give the 1,1-dimethylethyl 3-(acetylamino)-4-(aminocarbonyl)benzoate (140 mg, 94% yield). MS (EI) for $C_{14}H_{18}N_2O_4$: 279 (MH^+).

[00951] STEP 4: A solution of 1,1-dimethylethyl 3-(acetylamino)-4-(aminocarbonyl)benzoate (110 mg, 0.47 mmol) in trifluroacetic acid (2 mL) was stirred at room temperature for 15 minutes, concentrated, and the residue was rinsed with hexane (3 x 3 mL) and dried *in vacuo* to give 3-(acetylamino)-4-(aminocarbonyl)benzoic acid (100 mg, 97% yield), MS (EI) for $C_{10}H_{10}N_2O_4$: 223 (MH^+).

REAGENT PREPARATION 30: 7-(aminocarbonyl)-1H-indole-4-carboxylic acid:



[00952] STEP 1: To a solution of 4-tert-butyl 1-methyl 2-nitroterephthalate (prepared according to Gao, Y. et. al WO2001070737) (2.15 g, 7.64 mmol) in tetrahydrofuran (30 mL) was added a 1M solution of vinylmagnesium bromide in tetrahydrofuran (23.0 mL) at -40 °C, followed by stirring at room temperature for 18 hours. The reaction mixture was quenched by the addition of a solution of 1M aqueous ammonium chloride, and the organic portion of the solvent was evaporated. The resulting material was partitioned with ethyl acetate (300 mL), and the organic layer was separated then washed with 10% aqueous citric acid (100 mL) and brine,

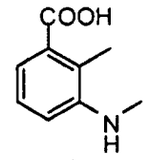
dried over sodium sulfate, filtered and the solvent was concentrated. The resulting crude material was purified by column chromatography (hexane:ethyl acetate 9:1 to 7:3 eluent) to give 4-tert-butyl 7-methyl 1H-indole-4,7-dicarboxylate (0.58 g, 27%). ^{1}H NMR (400 MHz, $CDCl_3$): 10.00 (bs, 1H), 7.88 (dd, 2H), 7.43 (m, 1H), 7.19 (m, 1H), 4.00 (s, 3H), 1.66 (s, 9H). MS (EI) for $C_{15}H_{17}NO_4$: 274 (M-H).

[00953] STEP 2: To a solution of 4-tert-butyl 7-methyl 1H-indole-4,7-dicarboxylate (0.58 g, 2.10 mmol) in a mixture of methanol (20 mL), terahydrofuran (10 mL) and water (10 mL) was added a 2M aqueous solution of lithium hydroxide (2.1 mL, 4.20 mmol), and the reaction mixture was stirred at 40 °C until full consumption of starting material. The organic portion of the solvent was evaporated and the pH of the aqueous solution was adjusted to 3-4 by the addition of 1M aqueous hydrochloric acid. The acidic aqueous phase was partitioned with ethyl acetate (150 mL), and the organic layer was separated and washed with brine, dried over sodium sulfate, filtered and concentrated to give 4-(tert-butoxycarbonyl)-1H-indole-7-carboxylic acid (0.36 g, 67%). MS (EI) for $C_{14}H_{15}NO_4$: 260 (M-H).

[00954] STEP 3: A solution of 4-(tert-butoxycarbonyl)-1H-indole-7-carboxylic acid (0.36 g, 1.38 mmol), HATU (0.30 g, 1.60 mmol), 4-methylmorpholine (0.75 mL, 6.89 mmol) and a 2M solution of ammonia in methanol (1.80 mL, 3.45 mmol) in dimethylformamide (5 mL) was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate (150 mL) and the organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography chloroform:(10% ammonium hydroxide in methanol) 9:1 as eluent afforded tert-butyl 7-carbamoyl-1H-indole-4-carboxylate (0.18 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): 10.50 (bs, 1H), 7.83 (d, 1H), 7.43 (m, 2H), 7.15 (m, 1H), 6.30 (bd, 2H), 1.62 (s, 9H). MS (EI) for $C_{14}H_{16}N_2O_3$: 259 (M-H).

[00955] STEP: 4: To a solution of tert-butyl 7-carbamoyl-1H-indole-4-carboxylate (0.15 g, 0.58 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL), and the mixture was heated to reflux until the starting material was fully consumed. The solvent was evaporated followed by rotary evaporation of the residue from a mixture of ethyl acetate (50 mL) and toluene (50 mL). The procedure was repeated three times and the residue dried *in vacuo* to obtain 7-(aminocarbonyl)-1H-indole-4-carboxylic acid (0.16 g, 89%). MS (EI) for $C_{10}H_8N_2O_3$: 205 (MH^+).

REAGENT PREPARATION 31: 2-methyl-3-(methylamino)benzoic acid:



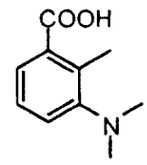
[00956] STEP 1: To 3-amino-2-methylbenzoic acid (500 mg, 3.3 mmol) in methanol (20 ml) was added sulfuric acid (500 µl) and heated to 70°C for 22 h, at which point the volume was reduced by rotary evaporation. The residue was diluted with saturated sodium bicarbonate and extracted with ethyl acetate. The resultant organic layer was dried over sodium sulfate, filtered, and then concentrated to afford a tan oil (125 mg, 23%) of methyl 3-amino-2-methylbenzoate, which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): 6.99-6.93 (m, 1H), 6.89-6.86 (d, 1H), 6.81-6.78 (d, 1H), 5.12-5.07 (br. s, 2H), 3.78 (s, 3H), 2.16 (s, 3H). MS (EI) for $C_9H_{11}NO_2$: 166 (MH^+).

[00957] STEP 2: To methyl 3-amino-2-methylbenzoate (125 mg, 0.758 mmol) in DMF (2 ml) was added DIPEA (291 µl, 1.67 mmol) and methyl iodide (104 µl, 1.67 mmol) and heated to 70°C for 6 h in a sealed vessel. The mixture was diluted with 1N aqueous potassium hydroxide (3 ml) and immediately extracted with ethyl acetate. The resultant organic layer was dried over sodium sulfate, filtered and concentrated to afford a brown residue which was purified by column chromatography eluting with 15% ethyl acetate in hexanes. Pure fractions were concentrated to afford (30 mg) of a faster eluting fraction consisting of methyl 3-(dimethylamino)-2-methylbenzoate and (125 mg) of a slower eluting fraction consisting of methyl 2-methyl-3-(methylamino)benzoate. ^{1}H NMR methyl 2-methyl-3-(methylamino)benzoate (400 MHz, DMSO-d_6): 7.14-7.08 (m, 1H), 6.91-6.87 (d, 1H), 6.67-6.62 (d, 1H), 5.34-5.27 (br. s, 1H), 3.78 (s, 3H), 2.76-2.71 (d, 3H), 2.17 (s, 3H). MS (EI) for $C_{10}H_{13}NO_2$: 180 (MH^+). ^{1}H NMR methyl 3-(dimethylamino)-2-methylbenzoate (400 MHz, DMSO-d_6): 7.40-7.36 (d, 1H), 7.28-7.22 (m, 2H), 3.81 (s, 3H), 2.63 (s, 6H), 2.39 (s, 3H). MS (EI) for $C_{11}H_{15}NO_2$: 194 (MH^+).

[00958] STEP 3: To methyl 2-methyl-3-(methylamino)benzoate (125 mg, 0.698 mmol) in methanol (7 ml) was added 2M aqueous lithium hydroxide (1.8 ml, 3.63 mmol), and the solution was stirred at 25°C for 3 h, at which point the volume was reduced by rotary evaporation. The aqueous mixture was diluted with water (3 ml)

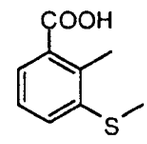
and the pH adjusted to 5 with 1 N hydrochloric acid. The resultant precipitate was collected by filtration and dried *in vacuo* to afford (50 mg, 42%) of 2-methyl-3-(methylamino)benzoic acid. MS (EI) for $C_9H_{11}NO_2$: 166 (MH^+).

REAGENT PREPARATION 32: 3-(dimethylamino)-2-methylbenzoic acid:



[00959] Synthesized according to the method of reagent preparation 31 by using methyl 3-(dimethylamino)-2-methylbenzoate (reagent preparation 31 step 2) in step 3. MS (EI) for $C_{10}H_{13}NO_2$: 180 (MH^+).

[00960] REAGENT PREPARATION 33: 2-methyl-3-(methylthio)benzoic acid:



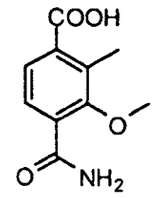
[00961] STEP 1: To a solution of 3-amino-2-methylbenzoic acid (500 mg, 3.3 mmol) in methanol (5 mL) cooled to 0 °C was added concentrated hydrochloric acid (1 mL), followed by a solution of sodium nitrite (275 mg, 4.0 mmol) in water (2 mL). The mixture was stirred at 0 °C for 30 minutes, then warmed to room temperature and stirred for an additional 30 minutes. The solution was diluted with diethyl ether to afford a solid residue that was collected by filtration, then washed with additional diethyl ether to afford 700 mg of the intermediate diazonium salt. The diazonium salt was then transferred to a warm (55 °C) solution of potassium ethylxanthogenate (635 mg, 4.0 mmol) in water (5 mL) while maintaining the pH at 8 by portion-wise addition of solid sodium carbonate. The solution was stirred at 55 °C for 30 minutes, then cooled to room temperature and poured into a 6N aqueous hydrochloric acid solution (30 mL). The precipitate which formed was collected by filtration, washed with water, then diethyl ether to afford 270 mg, 1.05 mmol (32%) of 3-{[(ethyloxy)carbonothioyl]thio}-2-methylbenzoic acid. MS (EI) for $C_{11}H_{12}S_2O_3$: 257 (MH^+).

[00962] STEP 2: 3-{[(ethyloxy)carbonothioyl]thio}-2-methylbenzoic acid (270 mg, 1.05 mmol) in a 1N aqueous sodium hydroxide solution (3 mL) was stirred at reflux for 15 hours. The mixture was cooled to room temperature and the pH was adjusted to 2 using concentrated aqueous hydrochloric acid. The aqueous mixture was extracted twice using dichloromethane and the combined organic solutions were washed with brine, then dried over anhydrous sodium sulfate. Filtration and concentration afforded 180 mg, 1.05 mmol (99%) of 3-mercapto-2-methylbenzoic acid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (d, 1H), 7.47 (d, 1H), 7.16-7.11 (m, 1H), 3.43 (s, 1H), 2.62 (s, 3H).

[00963] STEP 3: A mixture of 3-mercapto-2-methylbenzoic acid (180 mg, 1.05 mmol), cesium carbonate (690 mg, 2.1 mmol) and iodomethane (132 µl, 2.10 mmol) in dimethylformamide (3 mL) was stirred at room temperature for 2 hours. The mixture was diluted with ethyl acetate then washed with 5% aqueous lithium chloride, 1N aqueous sodium hydroxide, and brine then dried over anhydrous sodium sulfate. Filtration and concentration afforded 138 mg, 0.62 mmol (58%) of methyl 2-methyl-3-(methylthio)benzoate. ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (d, 1H), 7.41 (d, 1H), 7.21-7.16 (m, 1H), 4.09 (s, 3H), 2.83 (s, 3H), 2.58 (s, 3H). MS (EI) for $C_{10}H_{12}SO_2$: 197 (MH^+).

[00964] STEP 4: A solution of methyl 2-methyl-3-(methylthio)benzoate (138 mg, 0.62 mmol) in 35% aqueous potassium hydroxide:methanol (1:3, 4 mL) was stirred at 80 °C for 1 hour. After cooling to room temperature the methanol was evaporated. Water (4 mL) was added and the pH of the resulting mixture was adjusted to 2 using concentrated aqueous hydrochloric acid. The precipitate which formed was collected by filtration, washed with water, then diethyl ether to afford, 85 mg, 0.43 mmol (70%) of 2-methyl-3-(methylthio)benzoic acid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.76 (d, 1H), 7.37 (d, 1H), 7.29-7.25 (m, 1H), 2.65 (s, 3H), 2.49 (s, 3H). MS (EI) for $C_9H_{10}SO_2$: 181 (M-H).

[00965] REAGENT PREPARATION 34: 4-(aminocarbonyl)-2-methyl-3-(methyloxy)benzoic acid:



[00966] STEP 1: A solution of 3-hydroxy-2-methylbenzoic acid (5 g, 33 mmol) and concentrated sulfuric acid (3 mL) in methanol (300 mL) was stirrred at reflux for 48 hours. The mixture was cooled to room temperature and the pH was adjusted to 7 using solid sodium bicarbonate. Some methanol was evaporated and residue was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic portion was washed with brine then dried over anhydrous sodium sulfate. Filtration and concentration afforded 5.3 g, 32 mmol (97%) of methyl 3-hydroxy-2-methylbenzoate. ^{1}H NMR (400 MHz, $CDCl_3$): 7.41 (d, 1H), 7.13-7.09 (m, 1H), 6.94 (d, 1H), 3.89 (s, 3H), 2.46 (s, 3H). MS (EI) for $C_9H_{10}O_3$: 167 (MH^+).

[00967] STEP 2: To a solution of tert-butylamine (1.6 mL, 15 mmol) in dichloromethane (100 mL) at -78°C was added drop-wise over 30 minutes a solution of bromine (773 µl, 15 mmol in 15 mL of dichloromethane). The solution was stirred at -78°C for 30 minutes. While maintaining the temperature at -78°C, a solution of methyl 3-hydroxy-2-methylbenzoate (2.5 g, 15 mmol in 15 mL of dichloromethane) was added to the reaction mixture drop-wise over 30 minutes. The mixture was allowed to warm to room temperature and was stirred for 15 hours. The mixture was washed with 20% aqueous citric acid then brine and dried over anhydrous sodium sulfate. Filtration and concentration afforded a brown residue that was purified by silica gel column chromatography. Eluting with 10% diethyl ether in hexane, purified fractions were pooled and concentrated to afford 612 mg, 2.5 mmol (17%) of methyl 4-bromo-3-hydroxy-2-methylbenzoate as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.37-7.29 (m, 2H), 5.71 (s, 1H), 3.81 (s, 3H), 2.53 (s, 3H). MS (EI) for $C_9H_9BrO_3$: 245 (MH^+).

[00968] STEP 3: A solution of methyl 4-bromo-3-hydroxy-2-methylbenzoate (610 mg, 2.5 mmol), cesium carbonate (1.22 g, 3.7 mmol) and iodomethane (162 µl, 2.6 mmol) in dimethylformamide (5 mL) was stirred at room temperature for 15 hours. The mixture was diluted with ethyl acetate, then washed with 5% aqueous lithium chloride then brine and dried over anhydrous sodium sulfate. Filtration and

concentration affored an orange residue, which was purified by silica gel column chromatography. Eluting with 15% diethyl ether in hexane, purified fractions were pooled and concentrated to afford 455 mg, 1.76 mmol (71%) of methyl 4-bromo-2-methyl-3-(methyloxy)benzoate as a colorless residue. ^{1}H NMR (400 MHz, $CDCl_3$): 7.52 (d, 1H), 7.43 (d, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 2.55 (s, 3H). MS (EI) for $C_{10}H_{11}BrO_3$: 260 (MH^+).

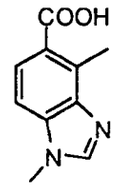
[00969] STEP 4: To a sealed tube vessel was added methyl 4-bromo-2-methyl-3-(methyloxy)benzoate (280 mg, 1.08 mmol), copper (I) cyanide (97 mg, 1.08 mmol) and dimethylformamide (2 mL). The mixture was heated at 150°C for 24 hours, then was cooled to room temperature and filtered through a pad of Celite. After washing the Celite with ethyl acetate, the combined filtrate was washed with 5% aqueous lithium chloride, and brine, then dried over anhydrous sodium sulfate. Filtration and concentration afforded a brown residue that was purified by silica gel column chromatography. Eluting with 10% ethyl acetate in hexane, purified fractions were pooled and concentrated to afford 150 mg, 0.73 mmol (68%) of methyl 4-cyano-2-methyl-3-(methyloxy)benzoate. ^{1}H NMR (400 MHz, $CDCl_3$): 7.61 (d, 1H), 7.47 (d, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 2.49 (s, 3H). MS (EI) for $C_{11}H_{11}NO_3$: 206 (MH^+).

[00970] STEP 5: Methyl 4-cyano-2-methyl-3-(methyloxy)benzoate (150 mg, 0.73 mmol) in a solution of 35% aqueous potassium hydroxide:methanol (1:3, 4 mL) was stirred at 60°C for 1 hour. The mixture was cooled to room temperature, and the methanol was removed by rotary evaporation. Water (4 mL) was added to the mixture and the pH was adjusted to 2 using concentrated aqueous hydrochloric acid. The precipitate which formed was collected by filtration and was washed with water, then hexanes to afford 86 mg, 0.45 mmol (62%) of 4-cyano-2-methyl-3-(methyloxy)benzoic acid. ^{1}H NMR (400 MHz, d_6-DMSO): 7.72 (d, 1H), 7.60 (d, 1H), 3.90 (s, 3H), 2.40 (s, 3H). MS (EI) for $C_{10}H_9NO_3$: 190 (M-H).

[00971] STEP 6: To a solution of 4-cyano-2-methyl-3-(methyloxy)benzoic acid (80 mg, 0.42 mmol) in DMSO:ethanol (1:4, 1 mL) was added 1N aqueous sodium hydroxide (1 mL), and hydrogen peroxide (30% wt. in water, 1 mL). The mixture was stirred at room temperature for 72 hours, then partitioned between 1N aqueous sodium hydroxide and ethyl acetate and the organic layer discarded. The pH of the aqueous portion was adjusted to 7 using 1N aqueous hydrochloric acid. The aqueous portion was extracted several times using ethyl acetate, and the combined organic

portion was washed with brine then dried over anhydrous sodium sulfate. Filtration and concentration afforded 55 mg, 0.26 mmol (63%) of 4-(aminocarbonyl)-2-methyl-3-(methyloxy)benzoic acid. ^{1}H NMR (400 MHz, d_6-DMSO): 7.77 (br s, 1H), 7.60 (br s, 1H), 7.54 (d, 1H), 7.41 (d, 1H), 3.72 (s, 3H), 2.41 (s, 3H). MS (EI) for $C_{10}H_9NO_3$: 190 (M-H).

REAGENT PREPARATION 35: 1,4-dimethyl-1H-benzoimidazole-5-carboxylic acid:



[00972] STEP 1: A mixture of 4-amino-2-methyl-3-nitrobenzoic acid (synthesized in reagent preparation 22, step 1) (500 mg, 2.6 mmol) methanol (25 mL) and concentrated sulfuric acid (1.25 mL) was stirred at 60°C for 18 hours. The reaction mixture was cooled concentrated, diluted with ethyl acetate (50 mL), washed with water (50 mL), saturated aqueous sodium bicarbonate solution (2x 30 mL), brine (30 mL), dried over sodium sulfate, filtered and concentrated to give the methyl 4-amino-2-methyl-3-nitrobenzoate (400 mg, 75% yield), MS (EI) for $C_9H_{10}N_2O_4$: 211 (MH^+).

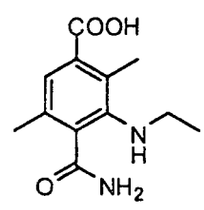
[00973] STEP 2: Iodomethane (125 uL, 2.0 mmol) was added to a mixture of the methyl 4-amino-2-methyl-3-nitrobenzoate (400 mg, 1.9 mmol) and sodium hydride (60% oil dispersion, 84 mg, 2.1 mmol) in tetrahydrofuran (10 mL) at 0°C . The reaction mixture was slowly warmed to room temperature and stirred for 18 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The combined extract was washed with water (2x 30 mL), brine (30 mL), dried over sodium sulfate, filtered and concentrated, then purified by flash chromatography (25% ethyl acetate in hexanes) to give methyl 2-methyl-4-(methylamino)-3-nitrobenzoate (308 mg, 72% yield). ^{1}H NMR (400MHz, $CDCl_3$): 7.94 (d, 1H), 6.63 (d, 1H), 5.68 (br, 1H), 3.86 (d, 2H), 2.58 (s, 3H); MS (EI) for $C_{10}H_{12}N_2O_4$: 225 (MH^+).

[00974] STEP 3: A mixture of methyl 2-methyl-4-(methylamino)-3-nitrobenzoate (90 mg, 0.4 mmol), 10% palladium on charcoal (Degussa type, 90 mg),

acetic acid (124 uL, 1.5 mmol), and ethyl acetate (20 mL) was shaken in a Parr hydrogenation apparatus at 40 psi for 18 hours. The reaction mixture was then filtered and concentrated. The residue was dissolved in formic acid was stirred at 100 °C for 1.5 hour. The reaction mixture was concentrated, quenched with ice-water (15 mL) and the pH was adjusted to basic by portion-wise sodium bicarbonate addition then extracted with ethyl acetate. The combined extract was washed with water (2x 30 mL), brine (30 mL), dried over sodium sulfate, filtered and concentrated to give methyl 1,4-dimethyl-1H-benzimidazole-5-carboxylate (78 mg, 95% yield). MS (EI) for $C_{11}H_{12}N_2O_2$: 205 (MH^+).

[00975] STEP 4: A mixture of the methyl 1,4-dimethyl-1H-benzimidazole-5-carboxylate (78 mg, 0.38 mmol) in methanol (2 mL) and 5% aqueous sodium hydroxide solution (2 mL) was stirred at 60°C for one hour. The reaction mixture was concentrated, diluted with water (10 mL) and the pH adjusted to 4 then saturated with solid sodium chloride. The aqueous mixture was extracted ethyl acetate (3x 10 mL) and the combined extract was washed with water (15 mL), brine (15 mL), dried over sodium sulfate, filtered and concentrated to give 1,4-dimethyl-1H-benzimidazole-5-carboxylic acid (46 mg, 63% yield), MS (EI) for $C_{10}H_{10}N_2O_2$: 191 (MH^+).

REAGENT PREPARATION 36: 4-(aminocarbonyl)-3-(ethylamino)-2,5-dimethylbenzoic acid:



[00976] STEP 1: 2,5-Dimethylterephthalic acid (3 g, 15.5 mmol) was suspended in ether (30 mL) and methanol (10 mL) and was cooled in an ice bath. (Trimethylsilyl)diazomethane (2 M solution in hexanes; 16 mL) was added drop-wise. The mixture was stirred at ambient temperature for 0.5 h and then was quenched with acetic acid (2 mL) and was concentrated. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic portion was washed with brine, dried over sodium sulfate, then filtered and was concentrated to afford dimethyl 2,5-dimethylterephthalate (3.18 g, 14.3 mmol, 93% yield). ^{1}H NMR (400

MHz, $CDCl_3$): δ 7.76 (s, 2H), 3.91 (s, 6H), 2.57 (s, 6H); MS (EI) for $C_{12}H_{14}O_4$: 223 (MH^+).

[00977] STEP 2: Dimethyl 2,5-dimethylterephthalate (3.14 g, 14.1 mmol) was dissolved in dichloromethane (30 mL) and was cooled in an ice bath. Fuming nitric acid (7.6 mL) and concentrated sulfuric acid (0.92 mL) were added carefully, and the mixture was stirred for 1.75 h. The mixture was then quenched with water and diluted with dichloromethane. The aqueous portion was extracted with dichloromethane. The combined organic portion was dried over sodium sulfate, then filtered and concentrated to afford a yellow oil which was purified by column chromatography (silica gel, 10-20% ethyl acetate in hexanes) to afford dimethyl 2,5-dimethyl-3-nitroterephthalate (2.78 g, 10.4 mmol, 74% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 2.49 (s, 3H), 2.46 (s, 3H); GCMS for $C_{12}H_{13}NO_6$: 267 (M^+).

[00978] STEP 3: Dimethyl 2,5-dimethyl-3-nitroterephthalate (2.27 g, 8.50 mmol) was dissolved in 1,4-dioxane (20 mL) and was cooled in an ice bath. 1N Sodium hydroxide (8.5 mL) was added dropwise, and the mixture was stirred at ambient temperature for 2.25 h. Additional 1N sodium hydroxide (0.5 mL) was added drop-wise and the mixture was stirred at ambient temperature for a further 1 h at which point another 0.5 mL aliquot of 1N aqueous sodium hydroxide was added and stirring was continued for an additional 1 h. The reaction mixture was diluted with water and was washed with ether. The aqueous portion was acidified with 1N hydrochloric acid to pH ~2 and then was extracted with ethyl acetate (2x). The combined ethyl acetate portion was dried over sodium sulfate, then filtered and concentrated to provide 4-(methoxycarbonyl)-2,5-dimethyl-3-nitrobenzoic acid (quantitative yield). ^1H NMR (400 MHz, d_6-DMSO): δ 13.8 (br s, 1H), 7.93 (d, 1H), 3.81 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H); MS (EI) for $C_{11}H_{11}NO_6$: 252 (M-H).

[00979] STEP 4: 4-(Methoxycarbonyl)-2,5-dimethyl-3-nitrobenzoic acid (9.5 mmol) was suspended in dichloromethane (30 mL) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.82 g, 9.5 mmol) and 4-dimethylaminopyridine (1.16 g, 9.5 mmol) were added. The mixture was stirred at ambient temperature for 0.5 h. tert-Butanol (6 mL, 64 mmol) was added and the mixture was stirred for 15.5 h. tert-Butanol (20 mL, 213 mmol) was added and the mixture was stirred at reflux for 1 h. The dichloromethane was removed and the mixture was stirred at 75 °C for

21 h. Triethylamine (1.3 mL, 9.3 mmol) and diphenylphosphoryl chloride (1.96 mL, 9.5 mmol) were added and the mixture was stirred at 75 °C for 6 h. The mixture was cooled to ambient temperature and then was concentrated. The residue was partitioned between ethyl acetate and 1N hydrochloric acid. The organic portion was washed with 1N sodium hydroxide, brine, dried over sodium sulfate, then filtered and concentrated to afford an orange semi-solid which was purified by column chromatography (silica gel, 5-15% ethyl acetate in hexanes) to afford crude 1-tert-butyl 4-methyl 2,5-dimethyl-3-nitroterephthalate (1.98 g, 6.4 mmol, 68% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 3.88 (s, 3H), 2.45 (s, 3H), 2.44 (s, 3H), 1.60 (s, 9H); GCMS for $C_{15}H_{19}NO_6$: 309 (M^+).

[00980] STEP 5: 1-tert-Butyl 4-methyl 2,5-dimethyl-3-nitroterephthalate (0.5 g, 1.62 mmol) was dissolved in tetrahyofuran (4 mL). 10 wt% Palladium on carbon (Degussa type, 50 mg) was added to the solution and the mixture was treated with hydrogen at ambient temperature for 3 h. 10 wt% Palladium on carbon (Degussa type, 50 mg) was added to the solution, and the mixture was treated with hydrogen at ambient temperature for a further 2 h. 10 wt% Palladium on carbon (Degussa type, 100 mg) was added to the solution, and the mixture was treated with hydrogen at ambient temperature for a further 5 h. The mixture was filtered and the filtrate was concentrated to afford 1-tert-butyl 4-methyl 3-amino-2,5-dimethylterephthalate (0.444 g, 1.59 mmol, 98% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (s, 1H), 5.20 (br s, 2H), 3.90 (s, 3H), 2.40 (s, 3H), 2.24 (s, 3H), 1.59 (s, 9H); MS (EI) for $C_{15}H_{21}NO_4$: 280 (MH^+).

[00981] STEP 6: 1-tert-Butyl 4-methyl 3-amino-2,5-dimethylterephthalate (0.444 g, 1.59 mmol) was dissolved in THF (10 mL), and the mixture was sparged with nitrogen for 10 minutes. Copper (I) iodide (302 mg, 1.59 mmol) and diiodomethane (0.64 mL, 7.93 mmol) were added followed by isoamyl nitrite (0.63 mL, 4.74 mmol), and the mixture was stirred at reflux for 20 h. The mixture was cooled to ambient temperature and then was partitioned between ethyl acetate and 1N hydrochloric acid. The aqueous portion was extracted with ethyl acetate (2x). The combined organic portion was washed with brine, dried over sodium sulfate, then filtered and concentrated to provide an oil which was purified by column chromatography (silica gel, 2-10% ethyl acetate in hexanes). The clean fractions were combined and concentrated, and the residue was partitioned between ethyl acetate and 1:1 saturated

sodium bicarbonate solution: 1M sodium thiosulfate. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, then filtered and concentrated to afford 1-tert-butyl 4-methyl 3-iodo-2,5-dimethylterephthalate (300 mg, 0.769 mmol, 48% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 1H), 3.96 (s, 3H), 2.60 (s, 3H), 2.31 (s, 3H), 1.59 (s, 9H); GCMS for $C_{15}H_{19}IO_4$: 359 ($[M-OCH_3]^+$).

[00982] STEP 7: 1-tert-Butyl 4-methyl 3-iodo-2,5-dimethylterephthalate (300 mg, 0.769 mmol) was dissolved in dioxane (3 mL) and sparged with nitrogen for 15 minutes. XANTPHOS (18 mg, 0.031 mmol), cesium carbonate (326 mg, 1.00 mmol), ethylamine (0.1 mL) and tris(dibenzylideneacetone)dipalladium (14 mg, 0.015 mmol) were added, and the mixture was stirred in a sealed tube at 95 °C for 19 h. XANTPHOS (36 mg, 0.062 mmol), ethylamine (0.1 mL) and tris(dibenzylideneacetone)dipalladium (28 mg, 0.030 mmol) were added and the mixture was stirred in a sealed tube at 95 °C for a further 20 h. The reaction mixture was cooled to ambient temperature and was filtered through celite. The filter cake was washed with ethyl acetate, and the filtrate was concentrated to afford an orange oil which was purified by column chromatography (silica gel, 2-10% ethyl acetate in hexanes) to afford 1-tert-butyl 4-methyl 3-(ethylamino)-2,5-dimethylterephthalate (158 mg, 0.515 mmol, 67% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 3.91 (s, 3H), 3.83 (br s, 1H), 3.00 (q, 2H), 2.36 (s, 3H), 2.29 (s, 3H), 1.59 (s, 9H), 1.14 (t, 3H); MS (EI) for $C_{17}H_{25}NO_4$: 308 (MH^+).

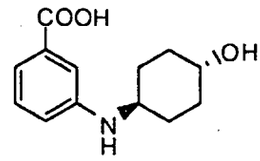
[00983] STEP 8: 1-tert-Butyl 4-methyl 3-(ethylamino)-2,5-dimethylterephthalate (142 mg, 0.463 mmol) was dissolved in dioxane (2 mL) and was cooled in an ice bath. 2N Lithium hydroxide (0.25 mL) was added and the mixture was stirred for 16 h and then methanol (0.5 mL) and 2N lithium hydroxide (0.25 mL) were added, and the mixture was stirred at ambient temperature for 1.5 h. The mixture was cooled in an ice bath and 1N sodium hydroxide (0.5 mL) was added and the mixture was stirred for 1 h and then was warmed to ambient temperature and was stirred for a further 1 h. The mixture was stirred at 50-55 °C for a further 16 h and then was cooled to ambient temperature and acidified with 1N hydrochloric acid to pH ~4.5. The mixture was diluted with water and extracted with ethyl acetate (2x). The organic portion was dried over sodium sulfate, then filtered and concentrated to provide 4-(tert-butoxycarbonyl)-2-(ethylamino)-3,6-dimethylbenzoic acid (115 mg, 0.392 mmol,

85% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 2.97 (q, 2H), 2.67 (s, 3H), 2.46 (s, 3H), 1.61 (s, 9H), 1.34 (t, 3H); MS (EI) for $C_{16}H_{23}NO_4$: 294 (MH^+).

[00984] STEP 9: 4-(tert-Butoxycarbonyl)-2-(ethylamino)-3,6-dimethylbenzoic acid (115 mg, 0.392 mmol) was dissolved in tetrahydrofuran (1 mL) and then cooled in an ice bath. N,N-Diisopropylethylamine (0.07 mL, 0.403 mmol) and triphosgene (40 mg, 0.135 mmol) were added, and the mixture was stirred at ambient temperature for 0.5 h. The mixture was quenched with water and extracted with dichloromethane (2x). The combined organic portion was dried over sodium sulfate, then filtered and concentrated to provide tert-butyl 1-ethyl-5,8-dimethyl-2,4-dioxo-2,4-dihydro-1H-benzo[d][1,3]oxazine-7-carboxylate (109 mg, 0.342 mmol, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 1H), 4.06 (q, 2H), 2.70 (s, 3H), 2.46 (s, 3H), 1.62 (s, 9H), 1.28 (t, 3H); MS (EI) for $C_{17}H_{21}NO_5$: 320 (MH^+).

[00985] STEP 10: tert-Butyl 1-ethyl-5,8-dimethyl-2,4-dioxo-2,4-dihydro-1H-benzo[d][1,3]oxazine-7-carboxylate (90 mg, 0.282 mmol) was dissolved in tetrahydrofuran (6 mL), treated with ammonia for 15 min and then stirred at ambient temperature for 1 h. The mixture was concentrated, and the residue was stirred for 15 min as a suspension in 20% citric acid (3 mL) and tetrahydrofuran (1 mL). The mixture was extracted with ethyl acetate. The aqueous portion was basified with sodium bicarbonate and then extracted with ethyl acetate. The combined organic portion was washed with water, brine, was dried over sodium sulfate, then filtered and concentrated to afford an orange film which was treated with trifluoroacetic acid (1 mL) at ambient temperature for 2 h. The mixture was concentrated and the residue was treated with 1N hydrochloric acid and concentrated. The residue was dissolved in a mixture of 1N hydrochloric acid and acetonitrile and then lyophilized to afford 4-aminocarbonyl-3-(ethylamino)-2,5-dimethylbenzoic acid hydrochloride salt (quantitative yield). MS (EI) for $C_{12}H_{16}N_2O_3$: 237 (MH^+).

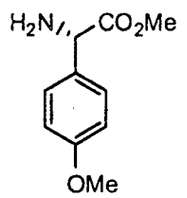
REAGENT PREPARATION 37: 3-[(trans-4-hydroxycyclohexyl)-amino]benzoic acid:



[00986] STEP 1: A suspension of methyl 3-bromobenzoate (0.43 g, 2.00 mmol), trans-4-aminocyclohexanol (0.35 g, 3.00 mmol), cesium carbonate (1.63 g, 5.00 mmol), Xantphos (0.024 g, 0.02 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.010 g, 0.01 mmol) in 1,4-dioxane (25 mL) was stirred at 80 °C under N_2 atmosphere for 18 hours. After cooling to room temperature the reaction mixture was filtered through a pad of Celite and was washed with ethyl acetate (200 mL), and the combined filtrate was partitioned with water. The organic layer was separated and washed with 1M aqueous hydrochloric acid and brine, dried over sodium sulfate, filtered, and the solution was concentrated. The residue was purified by column chromatography (hexane:ethyl acetate 4:1 to 3:2) to give methyl 3-[(trans-4-hydroxycyclohexyl)amino]benzoate. (0.28 g, 56%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.18 (m, 2H), 7.08 (m, 1H), 6.82 (m, 1H), 5.82 (d, 1H), 3.84 (s, 3H), 3.34 (m, 1H), 2.57 (m, 1H), 1.85 (m, 2H), 1.71 (m, 2H), 1.58 (m, 2H), 1.46 (m, 2H). MS (EI) for $C_{14}H_{19}NO_3$: 250 (MH^+).

[00987] STEP 2: To a solution of methyl 3-[(trans-4-hydroxycyclohexyl)amino]benzoate (0.25 g, 1.00 mmol) in a mixture of methanol (20 mL), terahydrofuran (10 mL) and water (10 mL) was added a 4M aqueous solution of potassium hydroxide (0.5 mL, 2.00 mmol), and the reaction mixture was heated to reflux for five minutes. The organic portion of the solvent was evaporated, and the pH of the aqueous solution was adjusted to 2 by the addition of 2M aqueous hydrochloric acid. The aqueous mixture was partitioned with ethyl acetate, the organic layer was separated and washed with brine, dried over sodium sulfate, filtered, and the solution was concentrated to give 3-[(trans-4-hydroxycyclohexyl)amino]benzoic acid (40 mg, 17%). MS (EI) for $C_{13}H_{17}NO_3$: 234 (M-H).

REAGENT PREPARATION 38: (S)-methyl 2-amino-2-(4-methoxyphenyl)-acetate:



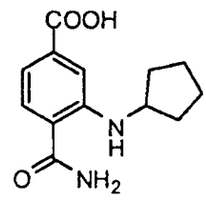
[00988] STEP 1: To a solution of L-4-hydroxyphenylglycine (1.00 g, 5.98 mmol) and sodium hydrogencarbonate (2.50 g, 29.11 mmol) in a mixture of 1,4-dioxane (20 mL) and water (20 mL) was added di-tert-butyl dicarbonate (1.40 g, 6.58 mmol) at 0 °C, followed by stirring at room temperature for 18 hours. The organic portion of the solvent was evaporated, and the reaction mixture was partitioned between ethyl acetate (300 mL) and 0.5M aqueous hydrochloric acid (50 mL). The organic layer was separated and washed with 0.5M aqueous hydrochloric acid, water and brine, dried over sodium sulfate, filtered and the solvent concentrated to give (S)-2-(tert-butoxycarbonylamino)-2-(4-hydroxyphenyl)acetic acid (1.6 g, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$): 8.80 (bs, 1H), 7.12 (d, 2H), 6.62 (d, 2H), 5.80 (d, 1H), 5.00 (d, 1H), 1.22 (s, 9H). MS (EI) for $C_{13}H_{17}NO_5$: 266 (M-H).

[00989] STEP 2: To a solution of (S)-2-(tert-butoxycarbonylamino)-2-(4-hydroxyphenyl)acetic acid (1.60 g, 5.98 mmol) in dimethylformamide (20 mL) was added potassium carbonate (1.85 g, 13.42 mmol), and the mixture was stirred at room temperature for thirty minutes, followed by the addition of methyl iodide (0.76 mL, 12.20 mmol). The reaction mixture was then stirred at room temperature for 18 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate (250 mL) and water (50 mL). The organic layer was separated and washed with saturated aqueous sodium hydrogencarbonate, water and brine, dried over sodium sulfate, filtered and the solvent was concentrated to give (S)-methyl 2-(tert-butoxycarbonylamino)-2-(4-methoxyphenyl)acetate (1.8 g, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$): 7.16 (d, 2H), 6.72 (d, 2H), 5.68 (d, 1H), 5.14 (d, 1H), 3.62 (s, 3H), 3.56 (s, 3H), 1.24 (s, 9H). MS (EI) for $C_{15}H_{21}NO_5$: 294 (MH^-).

[00990] STEP 3: To a solution of (S)-methyl 2-(tert-butoxycarbonylamino)-2-(4-methoxyphenyl)acetate (0.30 g, 1.00 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (2 mL) and the mixture was heated to 40 °C for thirty minutes. The solvent was evaporated followed by rotary evaporation of the residue from toluene and drying *in vacuo* to obtain (S)-methyl 2-amino-2-(4-

methoxyphenyl)acetate as the trifluoroacetate salt (0.30 g, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6): 7.18 (d, 2H), 6.82 (d, 2H), 5.68 (d, 1H), 4.82 (d, 1H), 3.78 (s, 3H), 3.64 (s, 3H). MS (EI) for $C_{10}H_{13}NO_3$: 196 (MH^+).

REAGENT PREPARATION 39: 4-(aminocarbonyl)-3-(cyclopentylamino)-benzoic acid:



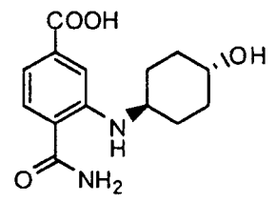
[00991] STEP 1: A mixture of ethyl 3-bromo-4-cyanobenzoate (500 mg, 1.97 mmol), XANTPHOS (228 mg, 0.39 mmol), cesium carbonate (1.282 g, 3.94 mmol), cyclopentylamine (233 mg, 2.75 mmol), and tris(dibenzylideneacetone)dipalladium (180 mg, 0.20 mmol) in dioxane (5 mL) was stirred at 100 °C for 17 h. The reaction mixture was partitioned between ethyl acetate (100 mL) and water (50 mL), the organic layer washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated. Column chromatography on silica (hexanes:ethyl acetate 9:1) afforded ethyl 4-cyano-3-(cyclopentylamino)benzoate (366 mg, 72% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.43 (m, 2H), 7.35 (m, 1H), 7.27 (m, 1H), 4.62 (d, 1H), 4.38 (q, 2H), 3.93 (m, 1H), 2.10 (m, 2H), 1.78 (m, 2H), 1.67 (m, 2H), 1.53 (m, 2H), 1.39 (t, 3H). MS (EI) for $C_{15}H_{18}N_2O_2$: 259 (MH^+).

[00992] STEP 2: A solution of ethyl 4-cyano-3-(cyclopentylamino)benzoate (363 mg, 1.41 mmol), potassium carbonate (50 mg, 0.36 mmol), and 30% aqueous hydrogen peroxide (0.25 mL) in DMSO (1.5 mL) was stirred at 60 °C for 1 h. After cooling to room temperature, water was added and the resulting mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over sodium sulfate, filtered and concentrated to give ethyl 4-(aminocarbonyl)-3-(cyclopentylamino)benzoate (333 mg, 86% yield). MS (EI) for $C_{15}H_{20}N_2O_3$: 277 (MH^+).

[00993] STEP 3: A suspension of ethyl 4-(aminocarbonyl)-3-(cyclopentylamino)-benzoate (333 mg, 1.21 mmol) and potassium hydroxide (135 mg, 2.41 mmol) in methanol (6 mL) and water (2 mL) was stirred at 55 °C for 1 h. After cooling to room temperature, water was added and the pH adjusted to 4 with 1N aqueous hydrochloric acid. The resulting precipitate was collected by filtration, washed with water and dried to provide 4-(aminocarbonyl)-3-(cyclopentylamino) benzoic acid (260 mg, 87% yield). ^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (br s, 1H), 8.17 (d, 1H), 7.97 (br s, 1H), 7.66 (d, 1H), 7.34 (br s, 1H), 7.21 (d, 1H), 7.04 (dd, 1H), 3.81 (m, 1H), 1.99 (m, 2H), 1.64 (m, 4H), 1.42 (m, 2H). MS (EI) for $C_{13}H_{16}N_2O_3$: 249 (MH^+).

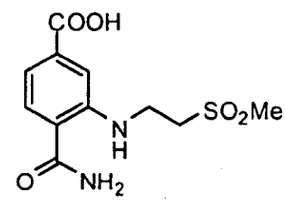
[00994] Using analogous synthetic techniques and substituting with alternative starting reagents, the following compounds were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00995] 4-(Aminocarbonyl)-3-[(trans-4-hydroxycyclohexyl)amino]benzoic acid:



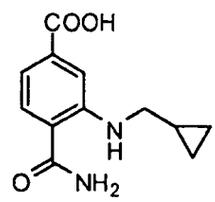
Prepared according to the method of reagent preparation 39 by using trans 4-aminocyclohexanol in step 1. MS (EI) for $C_{14}H_{18}N_2O_4$: 279 (MH^+).

[00996] 4-(Aminocarbonyl)-3-{[2-(methylsulfonyl)ethyl]amino}benzoic acid:



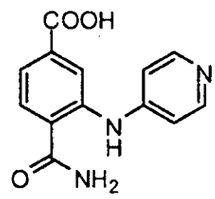
Prepared according to the method of reagent preparation 39 by using 2-aminoethylmethylsulfone hydrochloride in step 1. MS (EI) for $C_{11}H_{14}N_2O_5S$: 287 (MH^+).

[00997] 4-(Aminocarbonyl)-3-[(cyclopropylmethyl)amino]benzoic acid:



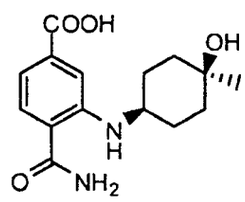
Prepared according to the method of reagent preparation 39 by using aminomethylcyclopropane in step 1. MS (EI) for $C_{12}H_{14}N_2O_3$: 235 (MH^+).

[00998] 4-(Aminocarbonyl)-3-(pyridin-4-ylamino)benzoic acid:



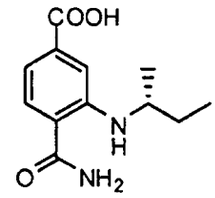
Prepared according to the method of reagent preparation 39 by using 4-aminopyridine in step 1. ^{1}H NMR (400 MHz, DMSO-d_6): 9.82 (s, 1H), 8.30 (d, 2H), 8.23 (s, 1H), 7.97 (d, 1H), 7.79 (d, 1H), 7.76 (s, 1H), 7.57 (dd, 1H), 7.03 (d, 2H). MS (EI) for $C_{13}H_{11}N_3O_3$: 258 (MH^+).

[00999] 4-(Aminocarbonyl)-3-[(cis-4-hydroxy-4-methylcyclohexyl)amino]benzoic acid:



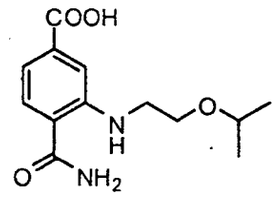
Prepared according to the method of reagent preparation 39 by using cis-4-hydroxy-4-methylcyclohexylamine (synthesized according to WO2005009966) in step 1. MS (EI) for $C_{15}H_{20}N_2O_4$: 293 (MH^+).

[001000] 4-(Aminocarbonyl)-3-{[(1R)-1-methylpropyl]amino}benzoic acid:



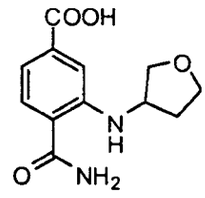
Prepared according to the method of reagent preparation 39 by using (R)-(-)-3-methyl-2-butylamine in step 1. ^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (br s, 1H), 8.26 (d, 1H), 7.97 (br s, 1H), 7.67 (d, 1H), 7.33 (br s, 1H), 7.20 (d, 1H), 7.00 (dd, 1H), 3.42 (m, 1H), 1.79 (m, 1H), 1.07 (d, 3H), 0.94 (d, 3H), 0.88 (d, 3H). MS (EI) for $C_{13}H_{18}N_2O_3$: 249 (M-H).

[001001] 4-(Aminocarbonyl)-3-({2-[(1-methylethyl)oxy]ethyl}amino)benzoic acid:



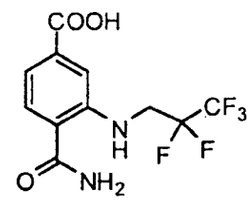
Prepared according to the method of reagent preparation 39 by using 2-{(1-methylethyl)oxy}ethanamine in step 1. MS (EI) for $C_{13}H_{18}N_2O_4$: 267 (MH^+).

[001002] 4-(Aminocarbonyl)-3-(tetrahydrofuran-3-ylamino)benzoic acid:



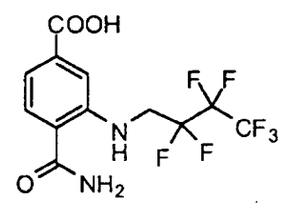
Prepared according to the method of reagent preparation 39 by using (±)-tetrahydrofuran-3-amine hydrochloride in step 1. MS (EI) for $C_{12}H_{14}N_2O_4$: 251 (MH^+).

[001003] 4-(Aminocarbonyl)-3-(2,2,3,3,3-pentafluoropropylamino)benzoic acid:



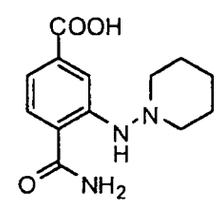
Prepared according to the method of reagent preparation 39 by using 2,2,3,3,3-pentafluoropropylamine in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.1 (br s, 1H), 8.54 (t, 1H), 8.11 (br s, 1H), 7.73 (d, 1H), 7.54 (br s, 1H), 7.42 (s, 1H), 7.19 (dd, 1H), 4.23 (td, 2H). MS (EI) for $C_{11}H_9F_5N_2O_3$: 311 (M-H).

[001004] 4-(Aminocarbonyl)-3-(2,2,3,3,4,4,4-heptafluorobutylamino)benzoic acid:



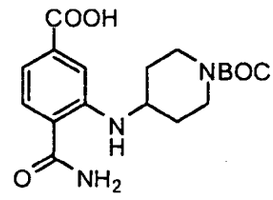
Prepared according to the method of reagent preparation 39 by using 2,2,3,3,4,4,4-heptafluorobutylamine in step 1. MS (EI) for $C_{12}H_9F_7N_2O_3$: 363 (MH^+).

[001005] 4-(Aminocarbonyl)-3-(piperidin-1-ylamino)benzoic acid:



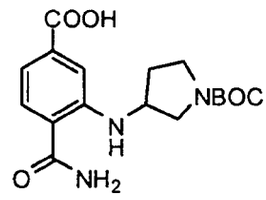
Prepared according to the method of reagent preparation 39 using piperidin-1-amine in step 1. ^{1}H NMR (400 MHz, CD_3OD): 8.00 (d, 1H), 7.58 (d, 1H), 724 (dd, 1H), 2.71 (br s, 4H), 1.75-1.69 (m, 4H), 1.47 (br s, 2H). MS (EI) for $C_{13}H_{17}N_3O_3$: 264 (MH^+).

[001006] 4-(Aminocarbonyl)-3-[(1-{[(1,1-dimethylethyl)oxy]carbonyl}piperidin-4-yl)amino]benzoic acid:



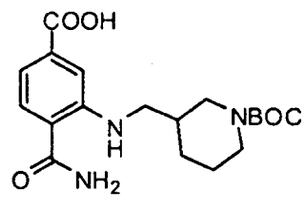
Prepared according to the method of reagent preparation 39 by using 1-tert-butoxycarbonyl-4-aminopiperidine in step 1. ^{1}HNMR (400 MHz, methanol-d_4): 7.63 (d, J = 8.0Hz, 1H), 7.40 (s, 1H), 7.20 (d, J = 8.0Hz, 1H), 3.93 (m, 2H), 3.67 (m, 1H), 3.05 (m, 2H), 2.03 (m, 2H), 1.46 (s, 9H), 1.40 (m, 2H). MS (EI) for $C_{18}H_{25}N_3O_5$: 364 (MH^+).

[001007] 4-(Aminocarbonyl)-3-[(1-{[(1,1-dimethylethyl)oxy]carbonyl}pyrrolidin-3-yl)amino]benzoic acid:



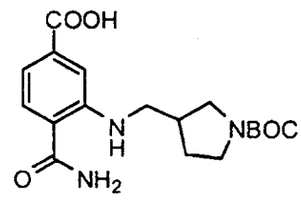
Prepared according to the method of reagent preparation 39 by using 1-tert-butoxy-carbonyl-3-aminopyrrolidine in step 1. ^{1}HNMR (400 MHz, methanol-d_4): 7.65 (d, J = 8.0Hz, 1H), 7.38 (s, 1H), 7.25 (d, J = 8.0Hz, 1H), 4.20 (m, 1H), 3.70 (m, 1H), 3.50 (m, 2H), 2.26 (m, 1H), 2.28 (m, 1H), 1.95 (m, 1H), 1.44 (s, 9H). MS (EI) for $C_{17}H_{23}N_3O_5$ 250 (MH^+-Boc).

[001008] 4-(Aminocarbonyl)-3-{(1-{[(1,1-dimethylethyl)oxy]carbonyl}piperidin-3-yl)methyl]amino}benzoic acid:



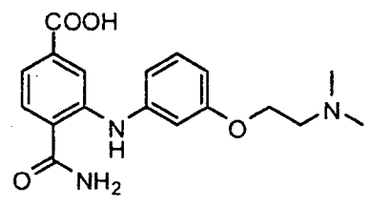
Prepared according to the method of reagent preparation 39 by using 4-aminomethyl-1-N-(tert-butoxycarbonyl)piperidine in step 1. ^{1}HNMR (400 MHz, methanol-d_4): 7.63 (d, J = 8.0Hz, 1H), 7.34 (s, 1H), 7.20 (d, J = 8.0Hz, 1H), 3.80 (br, s, 1H), 3.14 (m, 2H), 2.95 (m, 2H), 1.95-1.60 (m, 3H), 1.44 (m, 3H), 1.40 (s, 9H). MS(EI) for $C_{19}H_{27}N_3O_5$ 378 (MH^+).

[001009] 4-(Aminocarbonyl)-3-{(1-{[(1,1-dimethylethyl)oxy]carbonyl}pyrrolidin-3-yl)methyl]amino}benzoic acid:



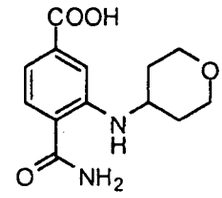
Prepared according to the method of reagent preparation 39 by using tert-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate in step 1. ^{1}HNMR (400 MHz, methanol-d_4): 7.63 (d, J = 8.0Hz, 1H), 7.36 (s, 1H), 7.21 (d, J = 8.0Hz, 1H), 3.56 (m, 1H), 3.47 (m, 1H), 3.30 (m, 1H), 3.12 (m, 1H), 3.09 (m,1H), 2.56 (m,1H), 2.11 (m,1H), 1.74 (m, 1H), 1.45 (s, 9H). MS(EI) for $C_{18}H_{25}N_3O_5$ 364 (MH^+).

[001010] 4-(Aminocarbonyl)-3-[(3-{[(2-dimethylamino)ethyl]oxy}phenyl)-amino]benzoic acid:



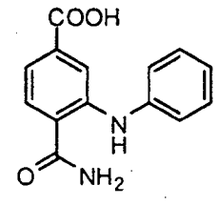
Prepared according to the method of reagent preparation 39 by using 3-[2-(dimethylamino)ethoxy]aniline (*Bioorg. & Med. Chem. Lett. 2005, 15(22)*, 4989-4993) in step 1. ^{1}HNMR (400 MHz, DMSO-d_6): 13.18 (br, s, 1H), 9.96 (s, 1H), 8.23 (s,1H), 7.83 (s, 1H), 7.79 (d, J = 8.0Hz, 1H), 7.69 (s, 1H), 7.31 (m, 2H), 6.82 (m, 2H), 6.69 (d, J = 8.0Hz, 1H), 4.34 (m, 2H), 3.50 (m, 2H), 2.84 (s, 6H). MS(EI) for $C_{18}H_{21}N_3O_4$ 344 (MH^+).

[001011] 4-(Aminocarbonyl)-3-(tetrahydro-2H-pyran-4-ylamino)benzoic acid:



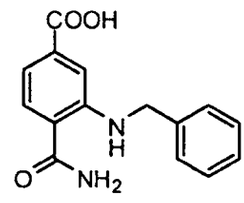
Prepared according to the method of reagent preparation 39 by using 4-aminotetrahydropyran in step 1. ^{1}H NMR (400 MHz, methanol-d_4): 7.64 (d, 1H), 7.41 (d, 1H), 7.21 (dd, 1H), 3.96 (dt, 2H), 3.73-3.65 (m, 1H), 3.60 (td, 2H), 2.08-2.00 (m, 2H), 1.58-1.48 (m, 2H). MS (EI) for $C_{13}H_{16}N_2O_4$: 265 (MH^+).

[001012] 4-(Aminocarbonyl)-3-(phenylamino)benzoic acid:



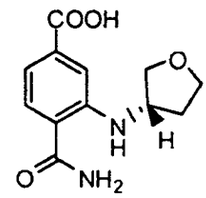
Prepared according to the method of reagent preparation 39 by using aniline in step 1. ^{1}H NMR (400 MHz, methanol-d_4): 7.91 (d, 1H), 7.71 (d, 1H), 7.39-7.32 (m, 3H), 3.19 (d, 2H), 7.04 (t, 1H). MS (EI) for $C_{14}H_{12}N_2O_3$: 257 (MH^+).

[001013] 4-(Aminocarbonyl)-3-(benzylamino)benzoic acid:



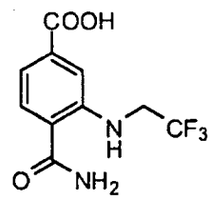
Prepared according to the method of reagent preparation 39 by using benzylamine in step 1. ^{1}H NMR (400 MHz, methanol-d_4): 7.63 (d, 1H), 7.40-7.36 (m, 2H), 7.34-7.30 (m, 3H), 7.24 (d, 1H), 7.21 (dd, 1H), 4.43 (s, 2H). MS (EI) for $C_{15}H_{14}N_2O_3$: 271 (MH^+).

[001014] (S)-4-(Aminocarbonyl)-3-(tetrahydrofuran-3-ylamino)benzoic acid:



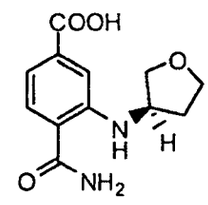
Prepared according to the method of reagent preparation 39 by using (S)-tetrahydrofuran-3-amine in step 1. ^{1}H NMR (400 MHz, methanol-d_4): 7.69-7.63 (m, 1H), 7.40-7.36 (m, 1H), 7.30-7.25 (m, 1H), 7.30-7.25 (m, 1H), 4.24-4.18 (m, 1H), 4.04-3.91 (m, 2H), 3.90-3.83 (m, 1H), 3.73-3.67 (m, 1H), 2.38-2.27 (m, 1H), 1.94-1.85 (m, 1H). MS (EI) for $C_{12}H_{14}N_2O_4$: 251 (MH^+).

[001015] 4-(Aminocarbonyl)-3-(2,2,2-trifluoroethylamino)benzoic acid:



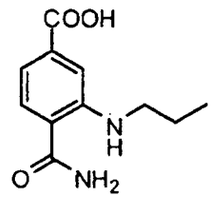
Prepared according to the method of reagent preparation 39 by using 2,2,2-trifluoroethylamine in step 1. MS (EI) for $C_{10}H_9F_3N_2O_3$: 261 (M-H).

[001016] (R)-4-(Aminocarbonyl)-3-(tetrahydrofuran-3-ylamino)benzoic acid:



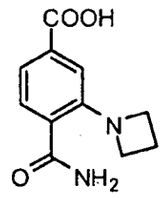
Prepared according to the method of reagent preparation 39 by using (R)-tetrahydrofuran-3-amine in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.04 (br s, 1H), 8.27 (br s, 1H), 8.02 (s, 1H), 7.69 (d, 1H), 7.41 (s, 1H), 7.19 (s, 1H), 7.09 (d, 1H), 4.16-4.09 (br s, 1H), 3.92-3.86 (m, 1H), 3.84-3.72 (m, 2H), 3.56-3.49 (m, 1H), 2.32-2.20 (m, 1H), 1.77-1.68 (m, 1H). MS (EI) for $C_{12}H_{14}N_2O_4$: 251 (MH^+).

[001017] 4-(Aminocarbonyl)-3-(propylamino)benzoic acid:



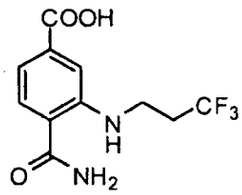
Prepared according to the method of reagent preparation 39 by using n-propylamine in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.01 (br s, 1H), 8.12 (t, 1H), 7.98 (br s, 1H), 7.67 (d, 1H), 7.36 (br s, 1H), 7.17 (s, 1H), 7.05 (dd, 1H), 3.12-3.07 (m, 2H), 1.64-1.56 (m, 2H), 0.96 (t, 3H). MS (EI) for $C_{11}H_{14}N_2O_3$: 221 (M-H).

[001018] 4-(Aminocarbonyl)-3-(azetidin-1-yl)benzoic acid:



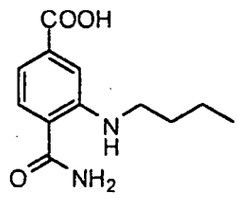
Prepared according to the method of reagent preparation 39 by using azetidine in step 1. MS (EI) for $C_{11}H_{12}N_2O_3$: 221 (MH+).

[001019] 4-(Aminocarbonyl)-3-(3,3,3-trifluoropropylamino)benzoic acid:



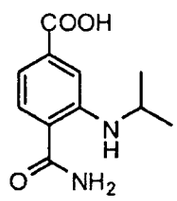
Prepared according to the method of reagent preparation 39 by using 3,3,3-trifluoropropylamine in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.06 (br s, 1H), 8.23 (t, 1H), 8.01 (br s, 1H), 7.69 (d, 1H), 7.41 (br s, 1H), 7.20 (dd, 1H), 3.46-3.41 (m, 2H), 2.66-2.54 (m, 3H). MS (EI) for $C_{11}H_{11}F_3N_2O_3$: 277 (MH^+).

[001020] 4-(Aminocarbonyl)-3-(butylamino)benzoic:



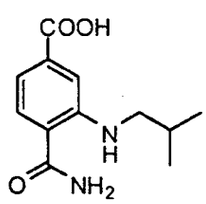
Prepared according to the method of reagent preparation 39 by using n-butylamine in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.02 (br s, 1H), 8.09 (t, 1H), 7.98 (br s, 1H), 7.67 (d, 1H), 7.35 (br s, 1H), 7.17 (d, 1H), 7.05 (dd, 1H), 3.15-3.10 (m, 2H), 1.059-1.54 (m, 2H), 1.42-1.37 (m, 2H), 0.95-0.91 (m, 3H). MS (EI) for $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[001021] 4-(aminocarbonyl)-3-[(1-methylethyl)amino]benzoic acid:



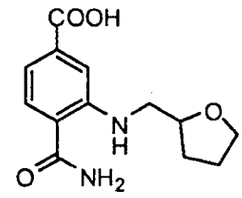
Prepared according to the method of reagent preparation 39 by using isopropylamine in step 1. MS (EI) for $C_{11}H_{14}N_2O_3$: 223 (MH^+).

[001022] 4-(aminocarbonyl)-3-[(2-methylpropyl)amino]benzoic acid:



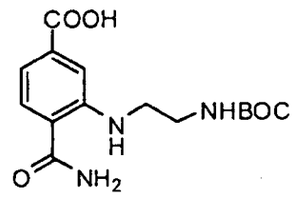
Prepared according to the method of reagent preparation 39 by using isobutylamine in step 1. MS (EI) for $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[001023] 4-(aminocarbonyl)-3-[(tetrahydrofuran-2-ylmethyl)amino]benzoic acid:



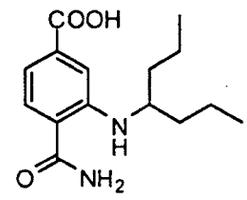
Prepared according to the method of reagent preparation 39 by using 2-tetrahydrofurfurylamine in step 1. MS (EI) for $C_{13}H_{16}N_2O_4$: 265 (MH^+)

[001024] 4-(aminocarbonyl)-3-{[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-ethyl]amino}benzoic acid:



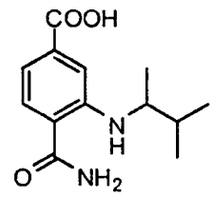
Prepared according to the method of reagent preparation 39 by using N-Boc-ethylenediamine in step 1. MS (EI) for $C_{15}H_{21}N_3O_5$: 324 (MH^+).

[001025] 4-(aminocarbonyl)-3-[(1-propylbutyl)amino]benzoic acid:



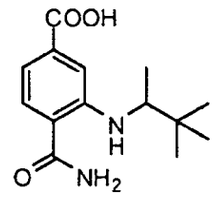
Prepared according to the method of reagent preparation 39 by using 4-heptylamine in step 1. MS (EI) for $C_{15}H_{22}N_2O_3$: 279 (MH^+).

[001026] 4-(aminocarbonyl)-3-[(1,2-dimethylpropyl)amino]benzoic acid:



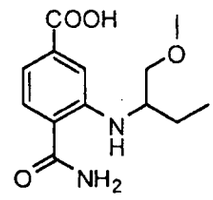
Prepared according to the method of reagent preparation 39 by using 1,2-dimethylpropylamine in step 1. MS (EI) for $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001027] 4-(aminocarbonyl)-3-[(1,2,2-trimethylpropyl)amino]benzoic acid:



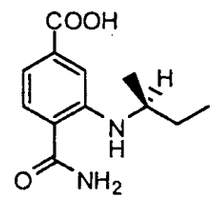
Prepared according to the method of reagent preparation 39 by using 1,2,2-trimethylpropylamine in step 1. MS (EI) for $C_{14}H_{20}N_2O_3$: 265 (MH^+).

[001028] 4-(aminocarbonyl)-3-({1-[(methyloxy)methyl]propyl}amino)benzoic acid:



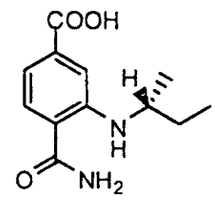
Prepared according to the method of reagent preparation 39 by using 2-amino-1-methyoxybutane in step 1. MS (EI) for $C_{13}H_{18}N_2O_4$: 267 (MH^+).

[001029] 4-(aminocarbonyl)-3-{[(1*S*)-1-methylpropyl]amino}benzoic acid:



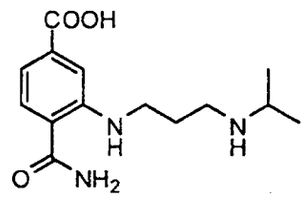
Prepared according to the method of reagent preparation 39 by using (*S*)-(+)-2-butylamine in step 1. MS (EI) for $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[001030] 4-(aminocarbonyl)-3-{[(1*R*)-1-methylpropyl]amino}benzoic acid:



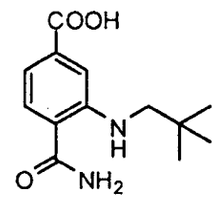
Prepared according to the method of reagent preparation 39 by using (*R*)-(-)-2-butylamine in step 1. MS (EI) for $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[001031] 4-(aminocarbonyl)-3-({3-[(1-methylethyl)amino]propyl}amino)benzoic acid:



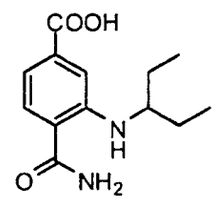
Prepared according to the method of reagent preparation 39 by using N-isopropyl-1,3-propanediamine in step 1. MS (EI) for $C_{14}H_{21}N_3O_3$: 507.2 (MH^+).

[001032] 4-(aminocarbonyl)-3-[(2,2-dimethylpropyl)amino]benzoic acid:



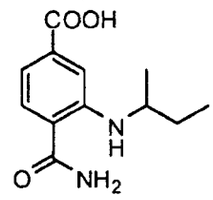
Prepared according to the method of reagent preparation 39 by using neopentylamine in step 1. MS (EI) for $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001033] 4-(aminocarbonyl)-3-[(1-ethylpropyl)amino]benzoic acid:



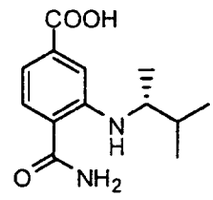
Prepared according to the method of reagent preparation 39 by using 3-aminopentane in step 1. MS (EI) for $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001034] 4-(aminocarbonyl)-3-[(1-methylpropyl)amino]benzoic acid:



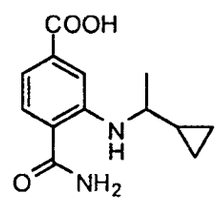
Prepared according to the method of reagent preparation 39 by using 2-aminobutane in step 1. MS (EI) for $C_{12}H_{16}N_2O_3$: 251 (MH^+).

[001035] 4-(aminocarbonyl)-3-{[(1R)-1,2-dimethylpropyl]amino}benzoic acid:



Prepared according to the method of reagent preparation 39 by using (2R)-3-methylbutan-2-amine in step 1. ^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (s, 1H), 8.30-8.24 (d, 1H), 7.98 (s, 1H), 7.69-7.64 (d, 1H), 7.33 (s, 1H), 7.20 (s, 1H), 7.03-6.98 (d, 1H), 3.46-3.39 (m, 1H), 1.85-1.75 (m, 1H), 1.09-1.04 (d, 3H), 0.97-0.93 (d, 3H), 0.91-0.87 (d, 3H). MS (EI) for $C_{13}H_{18}N_2O_3$: 251 (MH^+).

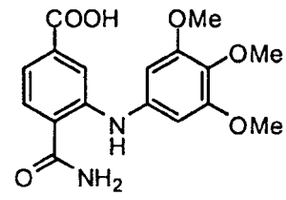
[001036] 4-(aminocarbonyl)-3-[(1-cyclopropylethyl)amino]benzoic acid:



Prepared according to the method of reagent preparation 39 by using 1-cyclopropylethanamine in step 1. ^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (br s, 1H), 8.14 (d, 1H), 7.96 (s, 1H), 7.65 (d, 1H), 7.33 (s, 1H), 7.18 (d, 1H), 7.01 (dd, 1H), 3.14

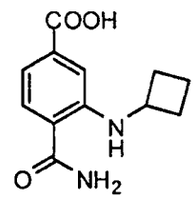
(m, 1H), 1.18 (d, 3H), 0.95 (m, 1H), 0.44 (m, 2H), 0.24 (m, 2H). MS (EI) for $C_{13}H_{16}N_2O_3$: 247 (M-H).

[001037] 4-(aminocarbonyl)-3-{[3,4,5-tris(methyloxy)phenyl]amino}benzoic acid:



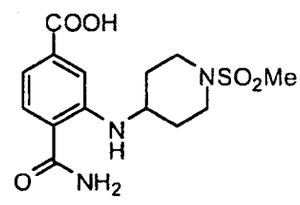
Prepared according to the method of reagent preparation 39 by using 3,4,5-trimethoxyaniline in step 1. MS (EI) for $C_{17}H_{18}N_2O_6$: 345 (M-H).

[001038] 4-(aminocarbonyl)-3-(cyclobutylamino) benzoic acid:



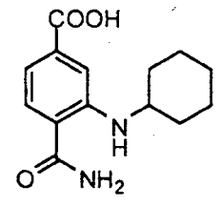
Prepared according to the method of reagent preparation 39 by using cyclobutylamine in step 1. MS (EI) for $C_{12}H_{14}N_2O_3$: 233 (M-H).

[001039] 4-(aminocarbonyl)-3-{[1-(methylsulfonyl)piperidin-4-yl]amino}benzoic acid:



Prepared according to the method of reagent preparation 39 by using methylsulfonyl-piperidin-4-ylamine hydrochloride in step 1. MS (EI) for $C_{14}H_{19}N_3O_5S$: 340 (M-H).

REAGENT PREPARATION 40: 4-(aminocarbonyl)-3-(cyclohexylamino)benzoic acid:



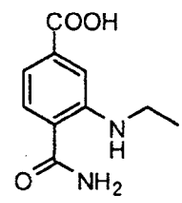
[001040] STEP 1: To a pressure vessel were added benzyl 3-bromo-4-cyanobenzoate (150 mg, 0.47 mmol) prepared as described in example 11 (steps 1, 2), cesium carbonate (310 mg, 0.95 mmol), cyclohexylamine (108 uL, 0.95 mmol), XANTPHOS (27 mg, 0.047 mmol), tris(dibenzylideneacetone)dipalladium(0) (21 mg, 0.023 mmol), and dioxane (3 mL). The vessel was sealed and heated to 95 °C for 4 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and was washed with water. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (10% ethyl acetate in hexanes) to provide benzyl 4-cyano-3-(cyclohexylamino)benzoate (118 mg, 0.35 mmol, 75% yield) as a yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): 7.45-7.30 (m, 7H), 7.27 (dd, 1H), 5.36 (s, 2H), 4.56 (d, 1H), 3.48-3.38 (m, 1H), 2.08-2.01 (m, 2H), 1.83-1.75 (m, 2H), 1.71-1.64 (m, 1H), 1.46-1.35 (m, 2H), 1.31-1.20 (m, 3H); MS (EI) for $C_{21}H_{22}N_2O_2$: 333 (M-H).

[001041] STEP 2: To a solution of benzyl 4-cyano-3-(cyclohexylamino)benzoate (66.2 mg, 0.198 mmol) in DMSO (2 mL) was added potassium carbonate (27.4 mg, 0.198 mmol) followed by 30% aqueous hydrogen peroxide (5 drops). The mixture was stirred at room temperature for 45 min, and was then diluted with ethyl acetate. Water was added and then the layers were separated. The aqueous phase was then extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (40% ethyl acetate in hexanes) to provide benzyl 4-(aminocarbonyl)-3-(cyclohexylamino)benzoate (45.0 mg, 0.128 mmol, 64% yield) as a yellow film. ^{1}H NMR (400 MHz, $CDCl_3$): 7.81 (d, 1H), 7.46-7.32 (m, 7H), 7.16 (dd, 1H), 5.77 (br s, 2H), 5.36 (s, 2H), 3.48-3.38 (m, 1H), 2.05-1.98 (m, 2H), 1.80-1.72(m, 2H), 1.66-1.59 (m, 1H), 1.45-1.23 (m, 4H); MS (EI) for $C_{21}H_{24}N_2O_3$: 353 (MH^+).

[001042] STEP 3: To a solution of benzyl 4-(aminocarbonyl)-3-(cyclohexylamino)benzoate (45 mg, 0.128 mmol) in methanol (2 mL) was added palladium on carbon (10W%, Degussa type, 45 mg). The mixture was vigorously stirred under 1 atm of hydrogen for 50 minutes. The catalyst was removed by filtration through celite, and the filtrate was concentrated to provide 4-(aminocarbonyl)-3-(cyclohexylamino)benzoic acid (25 mg, 0.095 mmol, 74% yield) as a yellow powder. ^{1}H NMR (400 MHz, CD_3OD): 7.59 (d, 1H), 7.35 (s, 1H), 7.14 (dd, 1H), 3.47-3.39 (m, 1H), 2.05-1.98 (m, 2H), 1.81-1.73 (m, 2H), 1.68-1.60 (m, 1H), 1.52-1.41 (m, 2H), 1.38-1.25 (m, 3H).

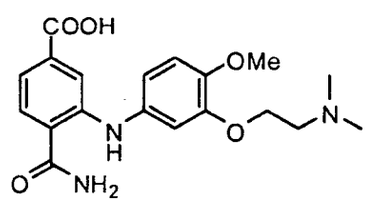
[001043] Using analogous synthetic techniques and substituting with alternative starting reagents, the following reagents were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[001044] 4-(aminocarbonyl)-3-(ethylamino)benzoic acid:



Prepared according to the method reagent preparation 40 using ethylamine in step 1. ^{1}H NMR (400 MHz, DMSO-d_6): 7.99-7.95 (m, 2H), 7.66 (d, 1H), 7.34 (br s, 1H), 7.17 (d, 1H), 7.06 (dd, 1H), 3.19-3.12 (m, 2H), 1.20 (t, 3H); MS (EI) for $C_{10}H_{12}N_2O_3$: 209 (MH^+).

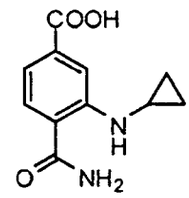
[001045] 4-(aminocarbonyl)-3-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}benzoic acid:



Prepared according to the method of reagent preparation 40 using 3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenylamine (Gaster et al. *J. Med. Chem.*

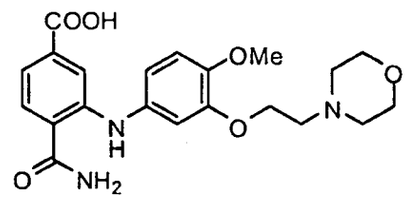
1998, *41(8)*, 1218-1235) in step 1. ^{1}H NMR (400 MHz, CD_3OD): 7.74 (s, 1H), 7.66 (d, 1H), 7.29 (d, 1H), 7.02-6.97 (m, 2H), 6.87 (dd, 1H), 4.34-4.30 (m, 2H), 3.86 (s, 3H), 3.55-3.51 (m, 2H), 2.99 (s, 6H).

[001046] 4-(aminocarbonyl)-3-(cyclopropylamino)benzoic acid:



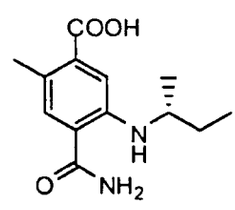
Prepared according to the method of reagent preparation 40 by using cyclopropylamine in step 1. MS (EI) for $C_{11}H_{12}N_2O_3$: 221 (MH^+).

[001047] 4-(aminocarbonyl-3-[4-methoxy-3-(2-morpholinoethoxy)phenylamino]-benzoic acid:



Prepared according to the method of reagent preparation 40 by using 4-methoxy-3-(2-morpholinoethoxy)aniline (Witty et al. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4865-4871) in step 1. MS (EI) for $C_{21}H_{25}N_3O_6$: 414 (M-H).

REAGENT PREPARATION 41: (R)-5-(sec-butylamino)-4-(aminocarbonyl)-2-methylbenzoic acid:



[001048] STEP 1: To a cooled (0°C) solution of 4-bromo-2-methylbenzoic acid (15.1 g, 0.070 mol) in tetrahydrofuran (180 mL) and methanol (45 mL) was slowly added (trimethylsilyl)diazomethane (2.0M in hexanes, 42 mL, 0.084 mol). The reaction mixture was allowed to warm to room temperature and stirred for 1h, at which time it was concentrated *in vacuo* to afford methyl 4-bromo-2-methylbenzoate (16 g, 100%) as a yellow oil. The residue was taken to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 7.78 (d, 1H), 7.42 (s, 1H), 7.38 (d, 1H), 3.88 (s, 3H), 2.58 (s, 3H). MS (EI) for $C_9H_9BrO_2$: 230 (MH^+).

[001049] STEP 2: To a solution of methyl 4-bromo-2-methylbenzoate (26.6 g, 0.116 mol) in DMF (300 mL) was added zinc cyanide (8.1 g, 0.07 mol) followed by tetrakis(triphenylphosphine)palladium(0) (6.7 g, 0.0058 mol). The reaction mixture was placed in a 100°C oil bath and stirred for 2 h, at which time it was filtered through a bed of celite and the filter cake rinsed with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (10% ethyl acetate in hexanes) to afford methyl 4-cyano-2-methylbenzoate (18.1 g, 89%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): 7.97 (d, 1H), 7.55 (s, 1H), 7.53 (br m, 1H), 3.93 (s, 3H), 2.62 (s, 3H).

[001050] STEP 3: A solution of methyl 4-cyano-2-methylbenzoate (18.1 g, 0.103 mol) in concentrated sulfuric acid (130 mL) was cooled to -10°C. While maintaining this internal temperature, fuming nitric acid (15.6 mL) was slowly added over a period of 30 min. The reaction mixture was stirred an additional 2.5 h at 0°C, at which time it was poured over 1.0 L of ice and then partitioned with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, and then concentrated *in vacuo*. The residue was triturated with 10% ethyl acetate/hexanes to afford methyl 4-cyano-2-methyl-5-nitrobenzoate (14.8 g, 65%) as a white powder. The title product was isolated as the major isomer in a 9:1 regioisomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$), Major: 8.85 (s, 1H), 7.81 (s, 1H), 4.00 (s, 3H), 2.77 (s, 3H); Minor: 8.07 (d, 1H), 7.72 (d, 1H), 3.98 (s, 3H), 2.57 (s, 3H). MS (EI) for $C_{10}H_8N_2O_4$: 238 ($M+H_2O$).

[001051] STEP 4: To a solution of methyl 4-cyano-2-methyl-5-nitrobenzoate (14.8 g, 0.0672 mol) in acetic acid (250 mL) was added iron powder (22.5 g, 0.40 mol). The reaction mixture was heated to 45°C and stirred for 1 h, at which time it was cooled to room temperature. The reaction mixture was filtered through a bed of

celite, and the filter cake rinsed with ethyl acetate. The volume of the filtrate was reduced by half and then partitioned between water and ethyl acetate. The organic layer was washed with 10% lithium chloride followed by saturated aqueous sodium bicarbonate. The organic layer was further washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was triturated with hexanes to afford methyl 5-amino-4-cyano-2-methylbenzoate (11.7 g, 91%) as a bright yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): 7.28 (s, 1H), 7.26 (s, 1H), 4.35 (br s, 2H), 3.89 (s, 3H), 2.43 (s, 3H). MS (EI) for $C_{10}H_{10}N_2O_2$: 191 (MH^+).

[001052] STEP 5: To a solution of methyl 5-amino-4-cyano-2-methylbenzoate (5.0 g, 0.0262 mol) in THF (100 mL) was added copper iodide (5.0 g, 0.0262 mol), diiodomethane (10.5 mL, 0.131 mol) and isoamyl nitrite (10.5 mL, 0.0786 mol). The reaction mixture was heated to 85°C and stirred for 3 h, at which time it was cooled to room temperature. The heterogeneous mixture was filtered through a bed of celite, and the filter cake rinsed with ethyl acetate. The filtrate was concentrated and the residue was purified by flash chromatography (100% hexanes to 2% diethyl ether in hexanes), then triturated with hexanes to afford methyl 4-cyano-5-iodo-2-methylbenzoate (3.7 g, 76%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): 8.39 (s, 1H), 7.50 (s, 1H), 3.94 (s, 3H), 2.56 (s, 3H).

[001053] STEP 6: To a solution of methyl 4-cyano-5-iodo-2-methylbenzoate (500 mg, 1.66 mmol) in 1,4-dioxane (25 mL) was added 9,9-dimethyl-4,5-(bis(diphenylphosphino)xanthene (96 mg, 0.166 mmol), tris(dibenzylideneacetone)-dipalladium (76 mg, 0.083 mmol), cesium carbonate (1.08 g, 3.32 mmol) and (R)-butan-2-amine (506 μL, 4.98 mmol). The reaction mixture was heated to 95°C and stirred for 16 h, at which time it was cooled to room temperature. The heterogeneous mixture was filtered through a bed of celite, and the filter cake rinsed with ethyl acetate. The filtrate was concentrated, and the residue was purified by flash chromatography (100% hexanes to 5% ethyl acetate in hexanes) to afford (R)-methyl 5-(sec-butylamino)-4-cyano-2-methylbenzoate (300 mg, 73%) as a bright yellow oil. MS (EI) for $C_{14}H_{18}N_2O_2$: 247 (MH^+).

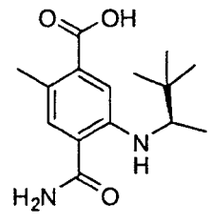
[001054] STEP 7: To a cooled (0°C) solution of (R)-methyl 5-(sec-butylamino)-4-cyano-2-methylbenzoate (300 mg, 1.22 mmol) in DMSO (1.5 mL) was added 30% hydrogen peroxide solution (258 μL, 8.96 mmol) and potassium carbonate (56 mg, 0.402 mmol). The reaction mixture was allowed to warm to room temperature and

stirred for 4 h, at which time it was concentrated *in vacuo*. The residue was purified by flash chromatography (100% hexanes to 10% ethyl acetate in hexanes) to afford (R)-methyl 5-(sec-butylamino)-4-(aminocarbonyl)-2-methylbenzoate (300 mg, 93%) as yellow crystals. MS (EI) for $C_{14}H_{20}N_2O_3$: 265 (MH^+).

[001055] STEP 8: To a solution of (R)-methyl 5-(sec-butylamino)-4-(aminocarbonyl)-2-methylbenzoate (300 mg, 1.13 mmol) in methanol (2.0 mL) and dichloromethane (1.0 mL) was added 2.0M aqueous sodium hydroxide solution (2.0 mL, 4.0 mmol). The reaction mixture was heated to 45°C and stirred for 2 h, at which time it was cooled to room temperature and all volatiles were removed by rotary evaporation. To the residual solution was slowly added 1.0M aqueous hydrochloric acid until pH<2. The yellow precipitate was collected by filtration and washed with water to afford (R)-5-(sec-butylamino)-4-(aminocarbonyl)-2-methylbenzoic acid (210 mg, 65%). MS (EI) for $C_{13}H_{18}N_2O_3$: 251 (MH^+).

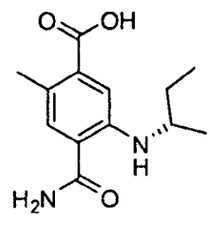
[001056] Using analogous synthetic techniques and substituting with alternative starting reagents, the following reagents were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[001057] (R)-4-(aminocarbonyl)-5-(3,3-dimethylbutan-2-ylamino)-2-methylbenzoic acid:



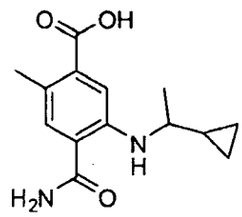
Synthesized according to the method of reagent preparation 41 using (R)-3,3-dimethylbutan-2-amine in step 6. MS (EI) for $C_{15}H_{22}N_2O_3$: 279 (MH^+).

[001058] (S)-5-(sec-butylamino)-4-(aminocarbonyl)-2-methylbenzoic acid:



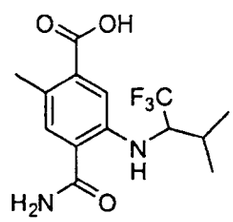
Synthesized according to the method of reagent preparation 41 using (S)-butan-2-amine in step 6. MS (EI) for $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001059] 4-(aminocarbonyl)-5-(1-cyclopropylethylamino)-2-methylbenzoic acid:



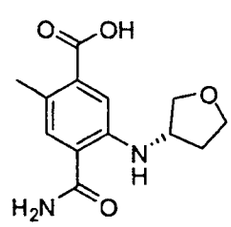
Synthesized according to the method of reagent preparation 41 using 1-cyclopropylethanamine in step 6. MS (EI) for $C_{14}H_{18}N_2O_3$: 263 (MH^+).

[001060] 4-(aminocarbonyl)-2-methyl-5-(1,1,1-trifluoro-3-methylbutan-2-ylamino)benzoic acid:



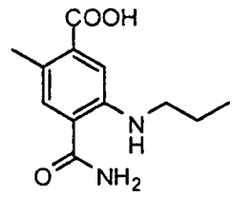
Synthesized according to the method of reagent preparation 41 using 1,1,1-trifluoro-3-methylbutan-2-amine in step 6. ^1H NMR (400 MHz, CD_3OD): 7.53 (s, 1H), 7.37 (s, 1H), 4.12-4.05 (m, 1H), 2.45 (s, 3H), 2.30-2.22 (m, 1H), 1.07 (d, 3H), 1.02 (d, 3H); MS (EI) for $C_{14}H_{17}F_3N_2O_3$: 319 (MH^+).

[001061] (S)-4-(aminocarbonyl)-2-methyl-5-(tetrahydrofuran-3-ylamino)benzoic acid:



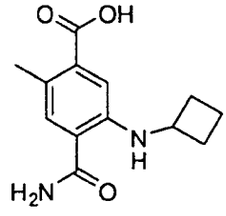
Synthesized according to the method of reagent preparation 41 using (S)-tetrahydrofuran-3-amine in step 6. ^{1}H NMR (400 MHz, d_6-DMSO): 12.95 (br s, 1H), 7.99 (d, 1H), 7.94 (br s, 1H), 7.53 (s, 1H), 7.36 (br s, 1H), 7.06 (br s, 1H), 4.11-4.04 (m, 1H), 3.90-3.70 (m, 1H), 3.50 (dd, 1H), 2.35 (s, 3H), 2.27-2.17 (m, 1H), 1.75-1.66 (m, 1H); MS (EI) for $C_{13}H_{16}N_2O_4$: 265 (MH^+).

[001062] 4-(aminocarbonyl)-2-methyl-5-(propylamino)benzoic acid:



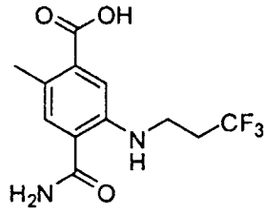
Synthesized according to the method of reagent preparation 41 using propan-1-amine in step 6. ^{1}HNMR (400 MHz, CD_3OD): 7.45 (s, 1H), 7.21 (s, 1H), 3.12 (t, 2H), 2.42 (s, 3H), 1.69 (q, 2H), 1.03 (t, 3H). MS (EI) for $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[001063] 4-(aminocarbonyl)-5-(cyclobutylamino)-2-methylbenzoic acid:



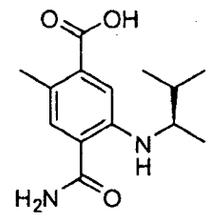
Synthesized according to the method of reagent preparation 41 using cyclobutanamine in step 6. ^{1}HNMR (400 MHz, CD_3OD): 7.43 (s, 1H), 7.04 (s, 1H), 3.95 (m, 1H), 2.46 (m, 2H), 2.40 (s, 3H), 1.85 (m, 4H). MS (EI) for $C_{13}H_{16}N_2O_3$: 249 (MH^+).

[001064] 4-(aminocarbonyl)-2-methyl-5-(3,3,3-trifluoropropylamino)benzoic acid:



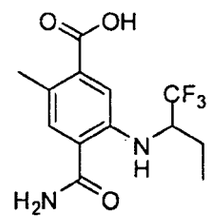
Synthesized according to the method of reagent preparation 41 using 3,3,3-trifluoropropan-1-amine in step 6. MS (EI) for $C_{12}H_{13}F_3N_2O_3$: 291 (MH^+).

[001065] (R)-4-(aminocarbonyl)-2-methyl-5-(3-methylbutan-2-ylamino)benzoic acid:



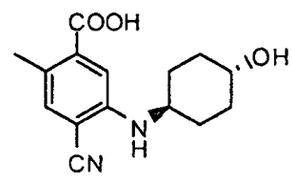
Synthesized according to the method of reagent preparation 41 using (R)-3-methylbutan-2-amine in step 6. MS (EI) for $C_{14}H_{20}N_2O_3$: 265 (MH^+).

[001066] 4-(aminocarbonyl)-2-methyl-5-(1,1,1-trifluorobutan-2-ylamino)benzoic acid:



Synthesized according to the method of reagent preparation 41 using 1,1,1 trifluorobutane-2-amine hydrochloride salt (synthesized in reagent preparation 53) in step 6. MS (EI) for $C_{13}H_{15}F_3N_2O_3$: 305 (MH^+).

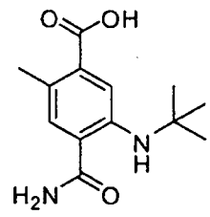
[001067] 4-cyano-5-(trans-4-hydroxycyclohexylamino)-2-methylbenzoic acid:



Synthesized according to the method of reagent preparation 41 using trans-4-(tert-butyldimethylsilyloxy)cyclohexanamine in step 6 followed by deprotection of the silyl protecting group as described by Greene, T.W. and Wuts, P.G.M, *Protective*

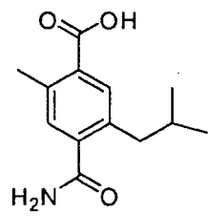
Groups in Organic Synthesis **1999**, John Wiley and Sons, Inc., New York, NY, then omission of step 7. MS (EI) for $C_{15}H_{18}N_2O_3$: 273 (M-H).

[001068] 4-(aminocarbonyl)-5-[(1,1-dimethylethyl)amino]-2-methylbenzoic acid:



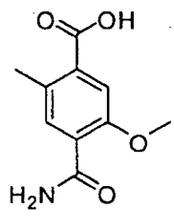
Synthesized according to the method of reagent preparation 41 using 1,1-dimethylethylamine in step 6. MS (EI) for $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001069] 4-(aminocarbonyl)-2-methyl-5-(2-methylpropyl)benzoic acid:



Synthesized according to the method of reagent preparation 41 using isobutylboronic acid in step 6. ^{1}H NMR (400 MHz, CD_3OD): 7.84 (s,1H), 7.39 (s,1H), 2.80-2.78 (d, 2H), 2.66 (s, 3H), 2.03-1.99 (m, 1H), 1.00-0.99 (d, 6H). MS (EI) for $C_{13}H_{17}NO_3$: 236 (M-H).

[001070] 4-(aminocarbonyl)-2-methyl-5-(methyloxy)benzoic acid:



Synthesized according to the method of reagent preparation 41 by replacement of step 6 with the conversion of methyl 4-cyano-5-iodo-2-methylbenzoate to methyl 4-cyano-5-hydroxy-2-methylbenzoate according to the method described in Chemical &

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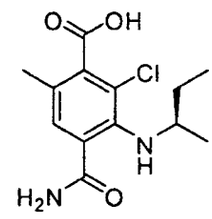
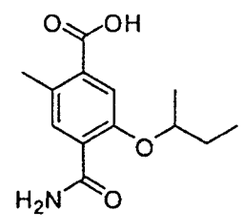
Pharmaceutical Bulletin (2007), 55(9), 1361-1364 followed by phenol alkylation with iodomethane then proceeding with steps 7 and 8. ^{1}H NMR (400 MHz, DMSO-d_6): 7.69 (b, 1H), 7.63 (b, 2H), 7.45 (s, 1H), 3.88 (s, 3H), 2.44 (s, 3H); MS (EI) for $C_{10}H_{11}NO_4$: 210 (MH^+).

[001071] 4-(aminocarbonyl)-2-chloro-6-methyl-3-{[(1R)-1-methylpropyl]amino}benzoic acid:



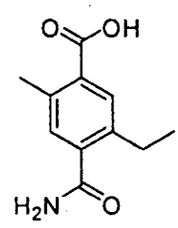
Synthesized according to the method of reagent preparation 41 using (R)-1-methylpropylamine in step 6 followed by chlorination of the resulting aniline using N-chlorosuccinimide then proceeding with steps 7 and 8. MS (EI) for $C_{13}H_{17}N_2O_3Cl$: 285 (MH^+).

[001072] 4-(aminocarbonyl)-2-methyl-5-[(1-methylpropyl)oxy]benzoic acid:



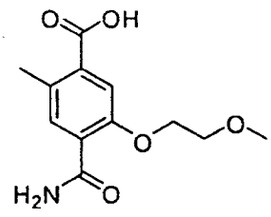
Synthesized according to the method of reagent preparation 41 by replacement of step 6 with the conversion of methyl 4-cyano-5-iodo-2-methylbenzoate to methyl 4-cyano-5-hydroxy-2-methylbenzoate according to the method described in Chemical & Pharmaceutical Bulletin (2007), 55(9), 1361-1364 followed by phenol alkylation with 2-bromobutane then proceeding with steps 7 and 8. MS (EI) for $C_{13}H_{17}NO_4$: 252 (MH^+).

[001073] 4-(aminocarbonyl)-5-ethyl-2-methylbenzoic acid:



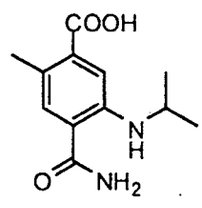
Synthesized according to the method of reagent preparation 41 by using ethylmagnesium chloride in step 6 according to the method described in Synlett 1996, 5, 473-474 then proceeding with steps 7 and 8. ^{1}H NMR (400 MHz, DMSO-d_6): 7.84 (s, 1H), 7.69 (s, 1H), 7.59 (s, 1H), 7.23 (s, 1H), 3.00 (s, 3H), 2.71 (q, 2H), 1.14 (t, 3H). MS (EI) for $C_{11}H_{13}NO_3$: 208 (MH^+).

[001074] 4-(aminocarbonyl)-2-methyl-5-{[2-(methyloxy)ethyl]oxy}benzoic acid:



Synthesized according to the method of reagent preparation 41 by replacement of step 6 with the conversion of methyl 4-cyano-5-iodo-2-methylbenzoate to methyl 4-cyano-5-hydroxy-2-methylbenzoate according to the method described in Chemical & Pharmaceutical Bulletin (2007), 55(9), 1361-1364 followed by phenol alkylation with 2-bromoethyl methyl ether then proceeding with steps 7 and 8. MS (EI) for $C_{12}H_{15}NO_5$: 254 (MH^+).

REAGENT PREPARATION 42: 4-(aminocarbonyl)-5-(isopropylamino)-2-methylbenzoic acid:



[001075] STEP 1: Methyl 5-amino-4-cyano-2-methylbenzoate (synthesized in reagent preparation 41, step 4) (240 mg, 1.26 mmol) was dissolved in 1,2-dichloroethane (7 mL) and was treated with trifluoroacetic acid (0.6 mL, 7.57 mmol), acetone (0.28 mL, 3.79 mmol), and sodium triacetoxyborohydride (802 mg, 3.78 mmol) at 45 °C for 20 min. The reaction mixture was cooled to ambient temperature and quenched with saturated aqueous sodium bicarbonate and was partitioned with dichloromethane. The aqueous portion was extracted with dichloromethane. The combined organic portion was washed with brine, dried over sodium sulfate, then filtered and concentrated to afford a yellow oil which was purified by column chromatography (silica gel, 10% dichloromethane in hexanes) to afford methyl 4-cyano-5-(isopropylamino)-2-methylbenzoate (224 mg, 0.96 mmol, 76% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.16 (s, 1H), 4.28 (d, 1H), 3.91 (s, 3H), 3.77-3.74 (m, 1H), 2.40 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H); MS (EI) for $C_{14}H_{16}N_2O_2$: 233 (MH^+).

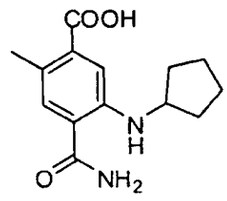
[001076] STEP 2: Methyl 4-cyano-5-(isopropylamino)-2-methylbenzoate (224 mg, 0.96 mmol) was dissolved in DMSO (2 mL) and cooled in a cold water bath. 30% Aqueous hydrogen peroxide (0.2 mL) and potassium carbonate (42.6 mg, 0.31 mmol) was added, and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was partitioned between ethyl acetate and 10% aqueous lithium chloride. The aqueous portion was extracted with ethyl acetate. The combined organic portion was dried over sodium sulfate, then filtered and concentrated to a yellow oil which was purified by column chromatography (silica gel, 15-30% ethyl acetate in hexanes to afford methyl 4-aminocarbonyl-5-(isopropylamino)-2-methylbenzoate (202 mg, 0.81 mmol, 83% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, 1H), 7.26 (d, 1H), 7.24-7.22 (m, 2H), 5.70 (br s, 1H), 3.90 (s, 3H), 3.75-3.68 (m, 1H), 2.42 (s, 3H), 1.26-1.24 (m, 6H); MS (EI) for $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001077] STEP 3: Methyl 4-aminocarbonyl-5-(isopropylamino)-2-methylbenzoate (202 mg, 0.81 mmol) was dissolved in methanol (3 mL) and was treated with 1M sodium hydroxide (3 mL, 3 mmol) at 45 °C for 1.5 h. The reaction mixture was cooled to ambient temperature and was concentrated to afford an aqueous residue that was acidified with 1N hydrochloric acid to pH ~3. The precipitate was collected by filtration, washed with water and dried to afford 4-aminocarbonyl-5-(isopropylamino)-2-methylbenzoic acid (99.5 mg, 0.42 mmol, 52% yield). ^{1}H NMR

(400 MHz, d_6-DMSO): δ 12.95 (br s, 1H), 7.90 (br s, 1H), 7.72 (d, 1H), 7.49 (s, 1H), 7.28 (br s, 1H), 7.06 (s, 1H), 3.64-3.54 (m, 1H), 2.33 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H); MS (EI) for $C_{12}H_{16}N_2O_3$: 237 (MH^+).

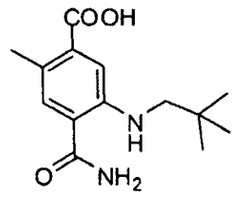
[001078] Using analogous synthetic techniques and substituting with alternative starting reagents, the following starting reagents were prepared. In cases where an aldehyde was used as the substrate for (step 1) acetic acid was generally used instead of trifluoroacetic acid. Alternative starting materials were obtained commercially unless otherwise indicated.

[001079] 4-(aminocarbonyl)-5-(cyclopentylamino)-2-methylbenzoic acid:



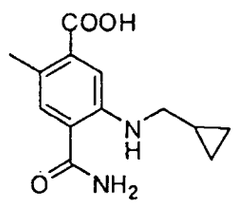
Synthesized according to the method of reagent preparation 42 using cyclopentanone in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.90 (br s, 1H), 7.92 (br s, 1H), 7.87 (d, 1H), 7.49 (s, 1H), 7.28 (br s, 1H), 7.08 (s, 1H), 3.78-3.73 (m, 1H), 2.34 (s, 3H), 2.02-1.90 (m, 2H), 1.70-1.53 (m, 4H), 1.43-1.33 (m, 2H); MS (EI) for $C_{14}H_{18}N_2O_3$: 263 (MH^+).

[001080] 4-(aminocarbonyl)-2-methyl-5-(neopentylamino)benzoic acid:



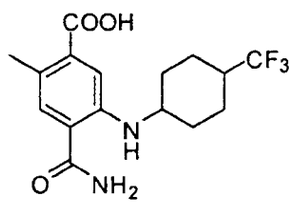
Synthesized according to the method of reagent preparation 42 using pivalaldehyde in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.94 (br s, 1H), 8.12 (t, 1H), 7.93 (br s, 1H), 7.51 (s, 1H), 7.28 (br s, 1H), 7.04 (s, 1H), 2.87 (d, 2H), 2.34 (s, 3H), 0.97 (m, 9H); MS (EI) for $C_{14}H_{20}N_2O_3$: 265 (MH^+).

[001081] 4-(aminocarbonyl)-5-(cyclopropylmethylamino)-2-methylbenzoic acid:



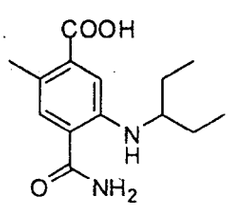
Synthesized according to the method of reagent preparation 42 using cyclopropanecarbaldehyde in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.89 (br s, 1H), 7.92 (br s, 1H), 7.85 (t, 1H), 7.50 (s, 1H), 7.29 (br s, 1H), 7.07 (s, 1H), 2.95 (t, 2H), 2.35 (t, 3H), 1.07-1.04 (m, 1H), 0.52-0.47 (m, 2H), 0.25-0.21 (m, 2H); MS (EI) for $C_{13}H_{16}N_2O_3$: 249 (MH^+).

[001082] 4-aminocarbonyl-2-methyl-5-[4-(trifluoromethyl)cyclohexylamino] benzoic acid:



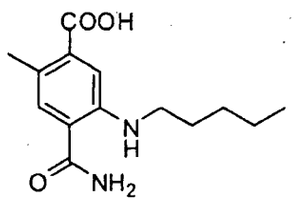
Synthesized according to the method of reagent preparation 42 using 4-(trifluoromethyl)cyclohexanone in step 1. MS (EI) for $C_{16}H_{19}F_3N_2O_3$: 345 (MH^+).

[001083] 4-aminocarbonyl-2-methyl-5-(pentan-3-ylamino)benzoic acid:



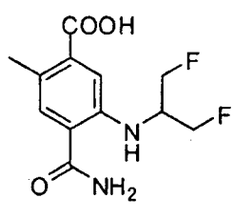
Synthesized according to the method of reagent preparation 42 using pentan-3-one in step 1. ^{1}H NMR (400 MHz, CD_3OD): 7.44 (s, 1H), 7.22 (s, 1H), 3.35-3.29 (m, 1H buried), 2.41 (s, 3H), 1.68-1.46 (m, 4H), 0.94 (t, 6H); MS (EI) for $C_{14}H_{20}N_2O_3$: 265 (MH^+).

[001084] 4-aminocarbonyl-2-methyl-5-(pentylamino)benzoic acid:



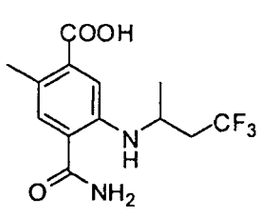
Synthesized according to the method of reagent preparation 42 using *n*-pentanal in step 1. ^{1}H NMR (400 MHz, CD_3OD): 7.45 (s, 1H), 7.20 (s, 1H), 3.15 (t, 2H), 2.42 (s, 3H), 1.70-1.62 (m, 2H), 1.47-1.34 (m, 4H), 0.94 (t, 6H).

[001085] 4-aminocarbonyl-5-(1,3-difluoropropan-2-ylamino)-2-methylbenzoic acid:



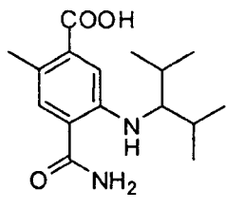
Synthesized according to the method of reagent preparation 42 using 1,3-difluoropropanone in step 1. ^{1}H NMR (400 MHz, CD_3OD): 7.50 (s, 1H), 7.34 (s, 1H), 4.67-4.58 (m, 2H), 4.56-4.46 (m, 2H), 4.11-3.97 (m, 1H), 2.42 (s, 3H); MS (EI) for $C_{12}H_{14}F_2N_2O_3$: 265 (MH^+).

[001086] 4-(aminocarbonyl)-2-methyl-5-[(3,3,3-trifluoro-1-methylpropyl)amino]-benzoic acid:



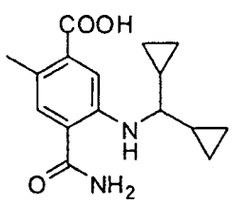
Synthesized according to the method of reagent preparation 42 using 4,4,4-trifluorobutan-2-one in step 1. MS (EI) for $C_{13}H_{15}F_3N_2O_3$: 305 (MH^+).

[001087] 4-(aminocarbonyl)-2-methyl-5-{[2-methyl-1-(1-methylethyl)propyl]amino}-benzoic acid:



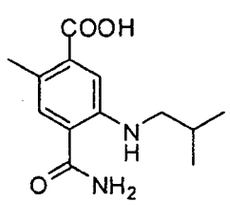
Synthesized according to the method of reagent preparation 42 using 2,4-dimethylpentan-3-one in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.85 (br s, 1H), 8.05-7.99 (d, 1H), 7.90 (br. s, 1H), 7.47 (s, 1H), 7.26 (br s, 1H), 7.18 (s, 1H), 3.09-3.00 (m, 1H), 2.31 (s, 3H), 1.89-1.77 (m, 2H), 0.91-0.79 (m, 12H); MS (EI) for $C_{16}H_{24}N_2O_3$: 293 (MH^+).

[001088] 4-(aminocarbonyl)-5-[(dicyclopropylmethyl)amino]-2-methylbenzoic acid:



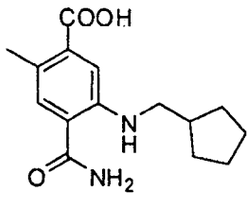
Synthesized according to the method of reagent preparation 42 using dicyclopropylmethanone in step 1. MS (EI) for $C_{16}H_{20}N_2O_3$: 293 (MH^+).

[001089] 4-(aminocarbonyl)-2-methyl-5-[(2-methylpropyl)amino]benzoic acid:



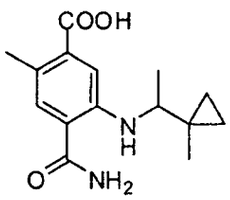
Synthesized according to the method of reagent preparation 42 using isobutyraldehyde in step 1. MS (EI) for $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001090] 4-(aminocarbonyl)-5-[(cyclopentylmethyl)amino]-2-methylbenzoic acid:



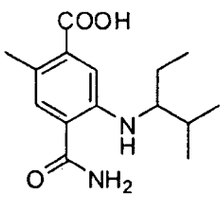
Synthesized according to the method of reagent preparation 42 using cyclopentanecarboxaldehyde in step 1. MS (EI) for $C_{15}H_{20}N_2O_3$: 277 (MH^+).

[001091] 4-(aminocarbonyl)-2-methyl-5-{[1-(1-methylcyclopropyl)-ethyl]amino}benzoic acid:



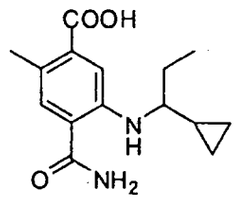
Synthesized according to the method of reagent preparation 42 using methyl 1-methylcyclopropyl ketone in step 1. MS (EI) for $C_{15}H_{20}N_2O_3$: 277 (MH^+).

[001092] 4-aminocarbonyl-2-methyl-5-(2-methylpentan-3-ylamino)benzoic acid:



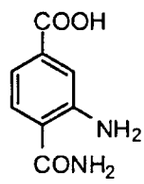
Prepared according to the method of reagent preparation 42 by using 2-methylpentan-3-one in step 1.

[001093] 4-aminocarbonyl-5-(1-cyclopropylpropylamino)-2-methylbenzoic acid:



Prepared according to the method of reagent preparation 42 by using 1-cyclopropylpropan-1-one in step 1.

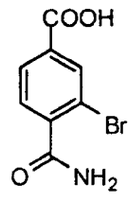
REAGENT PREPARATION 43: 3-amino-4-(aminocarbonyl)benzoic acid:



[001094] STEP 1: 4-(Methoxycarbonyl)-3-nitrobenzoic acid (100 g, 0.44 mol) was taken into concentrated aqueous ammonia (37w%, 500 mL), and the resulting yellow solution was allowed to stir at room temperature over 12 hours. The solution was then reduced in volume to approximately 300 mL by rotary evaporation, and the solution was acidified to pH 2 by portion-wise addition of concentrated aqueous hydrochloric acid. The thick precipitate was colleted by filtration and dried *in vacuo* to afford 4-(aminocarbonyl)-3-nitrobenzoic acid (51 g, 60% yield). ^{1}H-NMR (d_6-DMSO): 8.42 (d, 1H), 8.27 (dd, 1H), 8.26 (br s, 1H), 7.86 (br s, 1H), 7.76 (d, 1H).

[001095] STEP 2: 4-(aminocarbonyl)-3-nitrobenzoic acid (2.00 g, 9.52 mmol) was suspended in water (50 ml) and sodium bicarbonate (0.80 g, 9.52 mmol) was added. The resulting solution was hydrogenated in the presence of 10% palladium on carbon (300 mg) at 30 psi for 16 hours. The mixture was then filtered through Celite. The filtrate was acidified by addition of concentrated hydrochloric acid and the resulting solid was collected by filtration and dried *in vacuo* to afford 3-amino-4-(aminocarbonyl)benzoic acid (1.70 g, 99% yield). MS (EI) for $C_8H_8N_2O_3$: 179 (M-H).

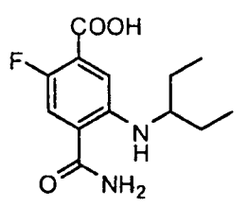
REAGENT PREPARATION 44: 3-bromo-4-(aminocarbonyl)benzoic acid:



[001096] STEP 1: Methyl 3-bromo-4-cyanobenzoate (prepared as described in Wang, G. T. *et al. Bioorg. Med. Chem. Lett.* **2005**, *15(1)*, 153) (130 mg, 0.54 mmol) was dissolved in DMSO (1.5 mL) and was cooled in a cold water bath. 30% aqueous hydrogen peroxide (0.1 mL) and potassium carbonate (23.9.0 mg, 0.17 mmol) were added and the mixture was stirred at room temperature for 18.5 h. The reaction mixture was partitioned between ethyl acetate and 10% aqueous lithium chloride. The aqueous portion was extracted with ethyl acetate. The combined organic portions were dried over sodium sulfate, filtered and concentrated to afford methyl 3-bromo-4-(aminocarbonyl)benzoate (quantitative yield) as a yellow oil. GCMS for $C_9H_8BrNO_3$: 257, 259 (M^+).

[001097] STEP 2: Methyl 3-bromo-4-(aminocarbonyl)benzoate (0.54 mmol) was dissolved in methanol (1 mL) and was treated with 1M aqueous sodium hydroxide (1 mL) at 45 °C for 3 h. The reaction mixture was cooled to room temperature and concentrated to afford an aqueous residue that was acidified with 1N aqueous hydrochloric acid to pH ~3. The precipitate was collected by filtration, washed with water, and dried to afford 3-bromo-4-(aminocarbonyl)benzoic acid (69.4 mg, 0.28 mmol, 53% overall). ^{1}H NMR (400 MHz, d_6-DMSO): 13.47 (br s, 1H), 8.08 (dd, 1H), 8.00 (br s, 1H), 7.94 (dd, 1H), 7.73 (br s, 1H), 7.51 (d, 1H); MS (EI) for $C_8H_6BrNO_3$: 242, 244(M-H).

REAGENT PREPARATION 45: 4-(aminocarbonyl)-2-fluoro-5-(pentan-3-ylamino)benzoic acid:



[001098] STEP 1: To a solution of 4-bromo-2-fluorobenzoic acid (2.0 g, 9.1 mmol) in THF (24 mL) and methanol (6 mL) at 0 °C was added a solution of (trimethylsilyl)diazomethane in hexanes (2.0 M, 5.46 mL, 10.9 mmol). The yellow solution was allowed to gradually warm to room temperature over 1 h. The volatile materials were removed and the residue was treated with aqueous hydrochloric acid (1 M). The aqueous mixture was extracted with ethyl acetate. The organic extract was dried over magnesium sulfate, filtered, and concentrated to provide crude methyl 4-bromo-2-fluorobenzoate (2.7 g, quantitative yield). This material was used in the subsequent step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 7.85-7.81 (m, 1H), 7.38-7.33 (m, 2H), 3.93 (s, 3H); MS (EI) for $C_8H_6BrFO_2$: 232, 234 (MH^+).

[001099] STEP 2: To a solution of methyl 4-bromo-2-fluorobenzoate (9.1 mmol) in DMF (50 mL) was added zinc cyanide (641 mg, 5.5 mmol) followed by tetrakis(triphenyphosphine)palladium(0) (1.05 g, 0.91 mmol). The mixture was heated to 100 °C and stirred for 3 h. At that point, additional tetrakis(triphenyphosphine)- palladium(0) (500 mg, 0.43 mmol) was added. The mixture was stirred a further 30 min and was then cooled to room temperature. Water and ethyl acetate were added, and insoluble solids were removed by filtration through celite. The layers were then separated. The aqueous phase was extracted with ethyl acetate. The organic extracts were combined, washed with 10% aqueous lithium chloride, dried over magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography (10% ethyl acetate in hexanes) to provide methyl 4-cyano-2-fluorobenzoate (1.36 g, 7.6 mmol, 84% yield).
^{1}H NMR (400 MHz, $CDCl_3$): 8.06 (dd, 1H), 7.53 (dd, 1H), 7.47 (dd, 1H), 3.98 (s, 3H); MS (EI) for $C_9H_6FNO_2$: 179 (M^+).

[001100] STEP 3: To a flask containing methyl 4-cyano-2-fluorobenzoate (1.61 g, 9.0 mmol) was added fuming nitric acid (15 mL) followed by concentrated sulfuric acid (4 mL). The mixture was heated to 45 °C for 15 h before cooling to room temperature. The solution was then poured into ice water and the resulting mixture was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered, and concentrated to provide methyl 4-cyano-2-fluoro-5-nitrobenzoate (859 mg, 3.83 mmol, 43% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 8.95 (d, 1H), 7.72 (d, 1H), 4.04 (s, 3H); MS (EI) for $C_9H_5FN_2O_4$: 224 (M^+).

[001101] STEP 4: To a solution of methyl 4-cyano-2-fluoro-5-nitrobenzoate (785 mg, 3.5 mmol) in acetic acid (15 mL) was added iron powder (1.17 g, 21.0 mmol). The mixture was stirred vigorously at room temperature for 2 h. Insoluble solids were then removed by filtration through celite. Water was added to the filtrate and the aqueous mixture was extracted with ethyl acetate. The organic extract was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (30% ethyl acetate in hexanes) to provide methyl 5-amino-4-cyano-2-fluorobenzoate (463 mg, 2.38 mmol, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.30 (d, 1H), 7.19 (d, 1H), 4.41 (br s, 2H), 3.94 (s, 3H); MS (EI) for $C_9H_7FN_2O_2$: 193 (M-H).

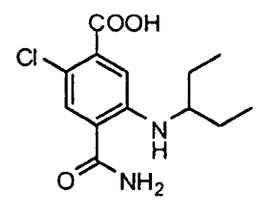
[001102] STEP 5: To a solution of methyl 5-amino-4-cyano-2-fluorobenzoate (437 mg, 2.2 mmol) in THF (13 mL) was added copper(I) iodide (419 mg, 2.2 mmol), diiodomethane (890 uL, 11 mmol), and isoamyl nitrite (890 uL, 6.6 mmol). The solution was heated to reflux for 4 h and was then allowed to cool to room temperature. After dilution with ethyl acetate, water was added and the mixture was filtered through celite. The biphasic filtrate was partitioned. The organic phase was dried over magnesium sulfate, filtered, and concentrated. The residue was then subject to column chromatography to provide impure methyl 4-cyano-2-fluoro-5-iodobenzoate (452 mg, ~ 63% purity, ~ 0.93 mmol). The remainder of the material consisted primarily of methyl 4-cyano-2-fluorobenzoate and was carried forward into the subsequent reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 8.44 (d, 1H), 7.43 (d, 1H), 3.97 (s, 3H); MS (EI) for $C_9H_5FINO_2$: 305 (M^+).

[001103] STEP 6: To a pressure vessel were added the above methyl 4-cyano-2-fluoro-5-iodobenzoate (~ 0.93 mmol), cesium carbonate (606 mg, 1.86 mmol), pentan-3-amine (325 uL, 2.79 mmol), XANTPHOS (54 mg, 0.093 mmol), tris(dibenzylideneacetone)dipalladium(0) (43 mg, 0.047 mmol), and dioxane (4 mL). The vessel was sealed and heated to 95 °C for ~17 h. After cooling to room temperature, the mixture was filtered through celite, and the filter cake rinsed with ethyl acetate. The filtrate was then concentrated. The residue was subject to column chromatography (10% ethyl acetate in hexanes). Eluent containing the desired project was collected and concentrated to afford an impure residue. This residue was

dissolved in DMSO (6 mL) and was treated with potassium carbonate (111 mg, 0.8 mmol) and 30% aqueous hydrogen peroxide (150 uL). After stirring at room temperature for 30 min, the mixture was diluted with ethyl acetate. The organic solution was washed with a mixture of water and 10% aqueous lithium chloride. The aqueous wash was extracted with ethyl acetate. The combined organic extracts were washed with 10% aqueous lithium chloride, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by gradient column chromatography (30% ethyl acetate in hexanes to 50% ethyl acetate in hexanes) to provide methyl 4-(aminocarbonyl)-2-fluoro-5-(pentan-3-ylamino)benzoate (73.7 mg, 0.26 mmol, 28% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (d, 1H), 7.18-7.15 (m, 2H), 5.86 (br s, 2H), 3.94 (s, 3H), 3.37-3.29 (m, 1H), 1.67-1.47 (m, 4H), 0.93 (t, 6H).

[001104] STEP 7: To a solution of methyl 4-(aminocarbonyl)-2-fluoro-5-(pentan-3-ylamino)benzoate (73.7 mg, 0.26 mmol) in methanol (1 mL) at 0 °C was added 1 N sodium hydroxide (520 uL, 0.52 mmol). The mixture was stirred 30 min at 0 °C, and was then warmed to room temperature. Dichloromethane (500 uL) was added to improve solubility, and the homogeneous solution was stirred 3.5 h at room temperature. After acidification with 1 N hydrochloric acid (500 uL), the volatile solvents were removed by rotary evaporation. An insoluble solid material was then isolated from the aqueous residue by filtration. The solid was dried to give 4-(aminocarbonyl)-2-fluoro-5-(pentan-3-ylamino)benzoic acid (61.7 mg, 0.23 mmol, 88% yield). ^{1}H NMR (400 MHz, CD_3OD): 7.41 (d, 1H), 7.16 (d, 1H), 3.43-3.28 (m, 1H buried), 1.68-1.46 (m, 4H), 0.95 (t, 6H).

REAGENT PREPARATION 46: 4-(aminocarbonyl)-2-chloro-5-(pentan-3-ylamino)benzoic acid



[001105] STEP 1: To a pressure vessel were added ethyl 3-bromo-4-cyanobenzoate (500 mg, 1.97 mmol), cesium carbonate (1.28 g, 3.94 mmol), pentan-3-amine (688

uL, 5.90 mmol), XANTPHOS (114 mg, 0.20 mmol), tris(dibenzylideneacetone)dipalladium(0) (90 mg, 0.10 mmol), and dioxane (3 mL). The vessel was sealed and heated to 95 °C for 15 h. After cooling to room temperature, the mixture was filtered through celite and the filter cake rinsed with ethyl acetate. The filtrate was then concentrated and the residue was purified by column chromatography (10% ethyl acetate in hexanes) to provide ethyl 4-cyano-3-(pentan-3-ylamino)benzoate (315 mg, 1.21 mmol, 61% yield) as a yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): 7.43 (d, 1H), 7.33 (s, 1H), 7.25 (dd, 1H), 4.44-4.35 (m, 3H), 3.48-3.40 (m ,1H), 1..72-1.48 (m ,4H), 1.40 (t, 3H), 0.96 (t, 6H); MS (EI) for $C_{15}H_{20}N_2O_2$: 261 (MH^+).

[001106] STEP 2: To a solution of ethyl 4-cyano-3-(pentan-3-ylamino)benzoate (315 mg, 1.21 mmol) in DMF was added *N*-chlorosuccinimide (162 mg, 1.21 mmol), and the solution was heated to 45 °C for 24 h. After cooling to room temperature, the mixture was diluted with ethyl acetate. The organic solution was then washed with a mixture of water and 10% aqueous lithium chloride. The aqueous wash was extracted with ethyl acetate and the organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated.

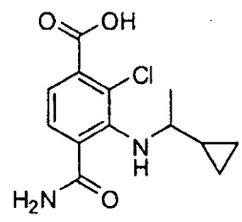
[001107] STEP 3: The above residue was then dissolved in DMSO (6 mL) and was treated with potassium carbonate (167 mg, 1.21 mmol) and 30% aqueous hydrogen peroxide (150 uL) at room temperature for 5.5 h. After dilution with ethyl acetate, water was added to the reaction mixture. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with 10% aqueous lithium chloride, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (30% ethyl acetate in hexanes) to provide ethyl 4-(aminocarbonyl)-2-chloro-5-(pentan-3-ylamino)benzoate (126.5 mg, 0.40 mmol, 33% yield) as a yellow film. ^{1}H NMR (400 MHz, $CDCl_3$): 7.73 (d, 1H), 7.41 (s, 1H), 7.04 (s, 1H), 5.86 (br s, 2H), 4.40 (q, 2H), 3.34-3.26 (m, 1H), 1.68-1.47 (m, 4H), 1.41 (t, 3H), 0.93 (t, 6H); MS (EI) for $C_{15}H_{21}ClN_2O_3$: 313 (MH^+).

[001108] STEP 4: To a solution of ethyl 4-(aminocarbonyl)-2-chloro-5-(pentan-3-ylamino)benzoate (126.5 mg, 0.40 mmol) in methanol (2 mL) was added 2 N aqueous sodium hydroxide (400 uL, 0.80 mmol). The mixture was stirred 4.5 h at room temperature. After acidification with 1 N hydrochloric acid (800 uL), the volatile

solvent were removed. An insoluble solid material was then isolated from the aqueous residue by filtration. The solid was dried to give 4-(aminocarbonyl)-2-chloro-5-(pentan-3-ylamino)benzoic acid (73 mg, 0.26 mmol, 64% yield). ^{1}H NMR (400 MHz, CD_3OD): 7.65 (s, 1H), 7.07 (s, 1H), 3.35-3.29 (m, 1H buried), 1.69-1.47 (m, 4H), 0.94 (t, 6H).

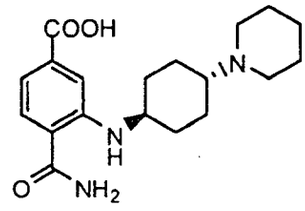
[001109] Using analogous synthetic techniques and substituting with alternative starting reagents the following reagents were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[001110] 4-(aminocarbonyl)-2-chloro-3-[(1-cyclopropylethyl)amino]benzoic acid:



Synthesized according to the method of reagent preparation 46 by first conducting step 2 to give a mixture of ethyl 3-bromo-2-chloro-4-cyanobenzoate and ethyl 5-bromo-2-chloro-4-cyanobenzoate then proceeding with step 1 using 1-cyclopropylethylamine followed by steps 3 and 4. ^{1}HNMR (400 MHz, CD_3OD): 7.49(d, 1H), 7.22 (d, 1H), 2.84 (q, 2H), 1.17(d, 3H), 0.9-0.76(m, 1H), 0.3-0.26(m, 2H), 0.04-0.00 (m, 2H). MS (EI) for $C_{13}H_{15}ClN_2O_3$: 284 (MH^+).

REAGENT PREPARATION 47: 4-(aminocarbonyl)-3-[trans-4-(piperidin-1-yl)cyclohexylamino]benzoic acid:



[001111] STEP 1: A mixture of ethyl 3-bromo-4-cyanobenzoate (0.82 g, 3.24 mmol), 1,1-dimethylethyl (trans-4-aminocyclohexyl)carbamate (0.69g, 3.24 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.148 g, 0.16 mmol), XANTPHOS (0.19 g, 0.32 mmol) and cesium carbonate (1.48 g, 4.54 mmol) in dioxane (13 mL) was refluxed for 15 hours. On cooling to room temperature, the mixture was filtered through Celite, concentrated, and purified by silica gel column chromatography using hexanes:ethyl acetate from 5:1 to 4:1 to afford ethyl 4-cyano-3-{[trans-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]amino}benzoate (0.370 g, 30% yield). ^{1}H NMR (400 MHz, d_6-DMSO): 7.59 (d, 1H), 7.28 (s, 1H), 7.13 (dd, 1H), 6.82 (d, 1H), 6.05 (d, 1H), 4.31 (q, 2H), 3.46-3.37 (m, 1H), 3.28-3.17 (m, 1H), 1.95-1.85 (m, 2H), 1.84-1.76 (m, 2H), 1.46, 1.22 (m, 16H).

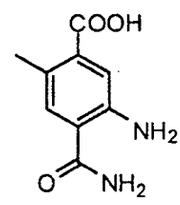
[001112] STEP 2: ethyl 4-cyano-3-{[trans-4-({[(1,1-dimethylethyl)oxy]carbonyl}-amino)cyclohexyl]amino}benzoate (0.37 g, 0.97 mmol) was stirred in a mixture of dichloromethane (2 mL) and trifluoroacetic acid (2 mL) at room temperature for 1 hour. The solvent was rotary evaporated, and the residue was dried *in vacuo* to give ethyl 3-[(trans-4-aminocyclohexyl)amino]-4-cyanobenzoate (0.490 g, 99% yield) as trifluoroacetic acid salt. MS (EI) for $C_{16}H_{21}N_3O_2$: 288 (MH^+).

[001113] STEP 3: A mixture of ethyl 3-[(trans-4-aminocyclohexyl)amino]-4-cyanobenzoate (0.490 g, 0.96 mmol), potassium carbonate (0.66g, 4.78 mmol) and 1,5 dibromopentane (0.130 mL, 0.96 mmol) was stirred in dimethylformamide (10 mL) at room temperature for 48 h. Water (20 mL) was then added to the mixture, and the water phase was extracted with dichloromethane (2x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography using methanol in dichloromethane (5%

to 10%) to afford ethyl 4-cyano-3-[(trans-4-piperidin-1-ylcyclohexyl)amino]benzoate (0.145 g, 43% yield). MS (EI) for $C_{21}H_{29}N_3O_2$: 356 (MH^+).

[001114] STEP 4: To a solution of ethyl 4-cyano-3-[(trans-4-piperidin-1-ylcyclohexyl)amino]benzoate (0.145 g, 0.41 mmol) in DMSO (0.5 mL) was added a 30% hydrogen peroxide solution (0.078 mL, 0.81 mmol) and potassium carbonate (0.014 g, 0.10 mmol). The reaction mixture was stirred at 50 °C for 3 h. A mixture of methanol (1.5 mL) and water (0.5mL) was then added followed by potassium hydroxide (0.046 g, 0.81 mmol), and the solution was stirred at 55 °C for 2 h. The mixture was acidified to pH 5 by addition of 1N aqueous hydrochloric acid and lyophilized to afford crude 4-(aminocarbonyl)-3-(trans-4-(piperidin-1-yl)cyclohexylamino]benzoic acid which was used without further purification. MS (EI) for $C_{19}H_{27}N_3O_3$: 346 (MH^+).

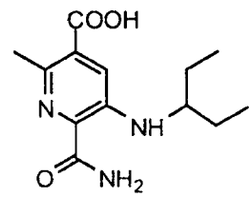
REAGENT PREPARATION 48: 5-amino-4-(aminocarbonyl)-2-methylbenzoic acid:



[001115] STEP 1: Methyl 5-amino-4-cyano-2-methylbenzoate (151 mg, 0.79 mmol) (synthesized according to reagent preparation 41) was dissolved in DMSO (1.5 mL). 30% Aqueous hydrogen peroxide (0.3 mL) and potassium carbonate (35 mg, 0.25 mmol) were added, and the mixture was stirred at ambient temperature for 1.5 h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous portion was extracted (2x) with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated to a yellow oil which was purified by preparative reverse phase HPLC to afford methyl 5-amino-4-(aminocarbonyl)-2-methylbenzoate (108 mg, 0.52 mmol, 66% yield). NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.45 (br s, 1H), 7.26 (s, 1H), 7.19 (br s, 1H), 6.48 (s, 2H), 3.80 (s, 3H), 2.32 (s, 3H); MS (EI) for $C_{10}H_{12}N_2O_3$: 209 (MH^+).

[001116] STEP 2: Methyl 5-amino-4-(aminocarbonyl)-2-methylbenzoate (108 mg, 0.52 mmol) was dissolved in methanol (1.5 mL) and was treated with 1M sodium hydroxide (1.5 mL, 1.5 mmol) for 1 h. The reaction mixture was concentrated to afford an aqueous residue that was acidified with 1N hydrochloric acid to pH ~3. The precipitate was collected by filtration, washed with water, and dried *in vacuo* to afford 5-amino-4-carbamoyl-2-methylbenzoic acid (60.8 mg, 0.31 mmol, 61% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.95 (br s, 1H), 7.99 (br s, 1H), 7.52 (s, 1H), 7.42 (br s, 1H), 7.35 (s, 1H), 4.75 (br s, 2H), 2.33 (s, 3H).

REAGENT PREPARATION 49: 6-(aminocarbonyl)-2-methyl-5-(pentan-3-ylamino)nicotinic acid:



[001117] STEP 1: To a solution of ethyl 5-amino-2-methylnicotinate (Fanta, P. E. *J. Am. Chem Soc.* **1953**, *75*, 737) (4.1 g, 22.78 mmol) in DMF (50 ml) was added NBS (4.46 g, 25.06 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (100 ml) and then extracted with ethyl acetate (3x 100 ml). The organic layer was washed with saturated aqueous sodium bicarbonate and brine. After evaporation of solvent, the residue was triturated with ethanol to give ethyl 5-amino-6-bromo-2-methylnicotinate (5.2 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.56 (s, 1H), 4.40 (q, J = 6.8 Hz, 2H), 4.05 (br, s, 2H), 2.75 (s, 3H), 1.39(t, J = 6.8Hz, 3H). MS (EI) for $C_9H_{11}BrN_2O_2$: 259.1 (MH^+).

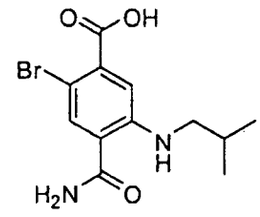
[001118] STEP 2: To a solution of ethyl 5-amino-6-bromo-2-methylnicotinate (1.267 g, 4.89 mmol) in ethyl acetate (30 ml) were added 3-pentanone (0.463 g, 5.38 mmol), sodium triacetoxyborohydride (1.244 g, 5.868 mmol) and trifluoroacetic acid (1.15 g, 9.78 mmol) at room temperature. After stirring overnight at room temperature, another portion of sodium triacetoxyborohydride (0.6 g, 2.83 mmol) was added. The reaction mixture was stirred for another 6 hours. The reaction mixture was quenched with water (20ml). The organic layer was washed with saturated sodium

bicarbonate and brine. After evaporation of solvent, ethyl 6-bromo-2-methyl-5-(pentan-3-ylamino)nicotinate (1.20g, 74.6% yield) was purified by column chromatography with 7% ethyl acetate/Hexane as eluent. ^{1}H NMR (400 MHz, $CDCl_3$): 7.35(s, 1H), 4.40 (q, J = 6.8 Hz, 2H), 4.10 (br, s, 1H), 3.30 (m, 1H), 2.68 (s, 3H), 1.8-1.5 (m, 4H), 1.42(t, J = 6.8Hz, 3H), 1.0 (t, J = 7.2 Hz, 6H). MS (EI) for $C_{14}H_{21}BrN_2O_2$: 329.1 (MH^+).

[001119] STEP 3: To a solution of ethyl 6-bromo-2-methyl-5-(pentan-3-ylamino)nicotinate (1.202 g,3.65 mmol) in acetonitrile (30 ml) was added sodium cyanide (0.357 g, 7.3 mmol) , tributyltin chloride (1.306 g, 4.015 mmol) and $Pd(dpppf)_3$ (0.298 g, 0.365 mmol). The reaction mixture was stirred at 88°C overnight. The reaction mixture was diluted with water (100 ml), then extracted with ethyl acetate (3 x 100 ml). The organic layer was washed with saturated aqueous sodium bicarbonate and brine. After evaporation of solvent, ethyl 6-cyano-2-methyl-5-(pentan-3-ylamino)nicotinate (0.59 g, 59% yield) was obtained by column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 7.56(s, 1H), 4.50 (q, J = 6.8 Hz, 2H), 4.35 (br, s, 1H), 3.40 a9m, 1H), 2.64 (s, 3H), 1.80-1.50 (m, 4H), 1.42(t, J = 6.8Hz, 3H), 1.0 (t, 6H). MS (EI) for $C_{15}H_{21}N_3O_2$: 276.2 (MH^+).

[001120] STEP 4: To a solution of 6-cyano-2-methyl-5-(pentan-3-ylamino)nicotinate (0.543 g, 1.97 mmol) in DMSO (10 ml) were added 50% aqueous hydrogen peroxide (0.2441 g, 3.55 mmol) and potassium carbonate (0.068 g, 0.49 mmol) at 10 °C. The reaction mixture was stirred at room temperature for two hours then a solution of potassium hydroxide (0.22 g, 3.94 mmol) in water (2 ml) and methanol (10 ml) were added to above reaction mixture. After being stirred for another two hours at 45°C, the reaction mixture was cooled to room temperature and neutralized to PH 7. 6-(Aminocarbonyl)-2-methyl-5-(pentan-3-ylamino)nicotinic acid (0.453 g, 87%) was obtained by filtration and drying. ^{1}HNMR (400 MHz, MeOH-D_4): 7.62(s, 1H), 3.35 (m, 1H), 2.60 (s, 3H), 1.65 (m, 2H), 1.52(m, 2H), 0.95(t, J = 7.20Hz, 6H). MS (EI) for $C_{13}H_{20}N_3O_3$: 267.2 (MH^+).

REAGENT PREPARATION 50: 1: 4-(aminocarbonyl)-2-bromo-5-[(2-methylpropyl)amino]benzoic acid:



[001121] STEP 1: A mixture of ethyl 3-bromo-4-cyanobenzoate (500 mg, 2.08 mmol), 2-methylpropan-1-amine (250 µL, 4.16 mmol), $Pd_2(dba)_3$ (96 mg, 5 mol%), Xantphos (120 mg, 10 mol%) and potassium phosphate (959 mg, 4.16 mmol) in dioxane (10 mL) was stirred for overnight at 95 °C. After cooling to room temperature the mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated followed by column chromatography (10 % ethyl acetate in hexanes) to give ethyl 4-cyano-3-[(2-methylpropylamino)]benzoate (393 mg, 76.7 %) as a yellow solid. [1] MS (EI) for $C_{14}H_{18}N_2O_2$: 247.1 (MH^+).

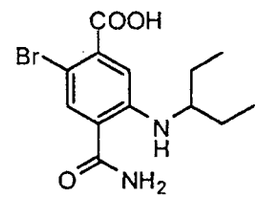
[001122] STEP 2: To a solution of ethyl 4-cyano-3-[(2-methylpropylamino)]benzoate (393 mg, 1.60 mmol) in DMF (10 mL) was added N-bromsuccinimide (284 mg, 1.60 mmol). The mixture was stirred overnight at 45 °C then cooled to room temperature and diluted with water then extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (10 % ethyl acetate in hexanes) to give ethyl 2-bromo-4-cyano-5-[(2-methylpropyl)amino]benzoate (374 mg, 72.0 %) as a yellow solid. MS (EI) for $C_{14}H_{17}BrN_2O_2$: 324 (M^+).

[001123] STEP 3: To a solution of ethyl 2-bromo 4-cyano-5[(2-methylpropyl)amino]benzoate (374 mg, 1.15 mmol) in DMSO (10 mL), potassium carbonate (51 mg, 0.37 mmol) and aqueous hydrogen peroxide (645 µl, 6.31 mmol) were added successively. The mixture was stirred for 3hr at room temperature then diluted with water, extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to give ethyl 4-(amino)-2-bromo-5-[(2-methylpropyl)amino]benzoate (315 mg, 85.0 %) as a crystalline solid. MS (EI) for $C_{14}H_{19}BrN_2O_3$: 342.1 (M^+).

[001124] STEP 4: To a solution of ethyl 2-bromo-4-(aminocarbonyl)-5-[(2-methylpropyl)amino]benzoate (315 mg, 0.91 mmol) in methanol (20 mL) was added 1N aqueous sodium hydroxide (15 mL) and the mixture was stirred for 2hr at 45 °C. The mixture was then concentrated by rotary evaporation and diluted with water then adjusted to pH 2 by 1N aqueous hydrochloric acid addition and the mixture was allowed to stand for 1hr at room temperature. The crystalline solid was collected by filtration and washed with water then dried to give 4-(aminocarbonyl)-2-bromo-5-[(2-methylpropyl)amino]benzoic acid (250 mg, 87.1 %). MS (EI) for $C_{12}H_{15}BrN_2O_3$: 315.1 (MH^+)

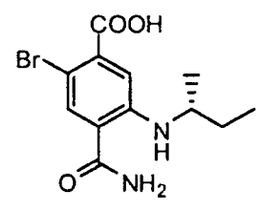
[001125] Using analogous synthetic techniques and substituting with alternative starting reagents the following reagents were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[001126] 4-(Aminocarbonyl)-2-bromo-5-[(1-ethylpropyl)amino]benzoic acid.



Prepared according to the method of reagent preparation 50 by using pentan-3-amine in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.40 (broad s, 1H), 8.20 (d, 1H), 8.06 (broad s, 1H), 7.85 (s, 1H), 7.40 (broad s, 1H), 6.94 (s, 1H), 1.55 (m, 2H), 1.44 (m, 2H), 0.86 (t, 3H). MS (EI) for $C_{13}H_{17}BrN_2O_3$: 330 (MH^+).

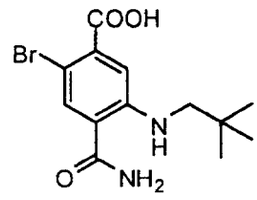
[001127] 4-(Aminocarbonyl)-2-bromo-5-{[(1*R*)-1-methylpropyl]amino}benzoic acid.



Prepared according to the method of reagent preparation 50 by using (2*R*)-butan-2-amine in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.42 (broad s, 1H), 8.16 (d, 1H),

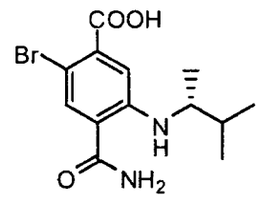
8.06 (broad s, 1H), 7.84 (s, 1H), 7.40 (broad s, 1H), 6.92 (s, 1H), 3.47 (m, 1H), 1.49 (m, 2H), 1.10 (d, 3H), 0.87 (t, 3H). MS (EI) for $C_{12}H_{15}BrN_2O_3$: 317 (MH^+).

[001128] 4-(Aminocarbonyl)-2-bromo-5-[(2,2-dimethylpropyl)amino]benzoic acid.



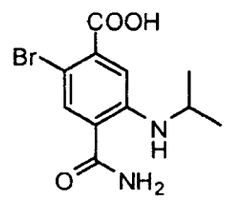
Prepared according to the method of reagent preparation 50 by using 2,2-dimethylpropan-1-amine in step 1. ^{1}H NMR (400 MHz, CD_3OD): 7.83 (s, 1H), 7.04 (s, 1H), 2.94 (s, 2H), 1.03 (s, 9H); MS (EI) for $C_{13}H_{17}BrN_2O_3$: 329, 331 (MH^+, Br isotopes).

[001129] 4-(Aminocarbonyl)-2-bromo-5-{[(1R)-1,2-dimethylpropyl]amino}benzoic acid.



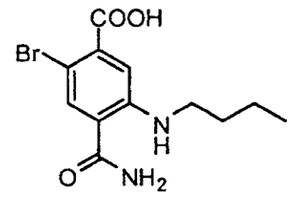
Prepared according to the method reagent preparation 50 by using (2R)-3-methylbutane-2-amine in step 1. ^{1}H NMR (400 MHz, DMSO- d_6): 13.36 (s, 1H), 8.32 (d, 1H), 8.04 (bs, 1H), 7.84 (s, 1H), 7.38 (bs, 1H), 7.73 (s, 1H), 3.43 (m, 1H), 1.76 (m, 1H), 1.05 (d, 3H), 0.92 (d, 3H), 0.87 (d, 3H). MS (EI) for $C_{13}H_{17}BrN_2O_3$: 330 (MH^+).

[001130] 4-(Aminocarbonyl)-2-bromo-5-[(1-methylethyl)amino]benzoic acid.



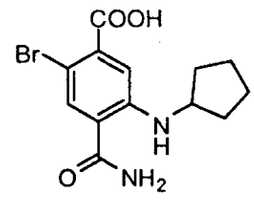
Prepared according to the method of reagent preparation 50 by using propan-2-amine in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): 8.07 (d, 2H), 7.85 (s, 1H), 7.40 (s, 1H), 6.93 (s, 1H), 3.61-3.69 (m, 1H), 1.15 (d, 6H). MS (EI) for $C_{11}H_{13}BrN_2O_3$: 303 (MH^+).

[001131] 4-(Aminocarbonyl)-2-bromo-5-(butylamino)benzoic acid.



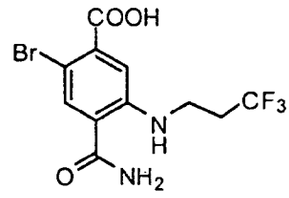
Prepared according to the method of reagent preparation 50 by using propan-1-amine in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): δ 13.43 (br s, 1H), 8.18 (m, 1H), 8.07 (br s, 1H), 7.86 (s, 1H), 7.42 (br s, 1H), 6.90 (s, 1H), 3.09-3.05 (m, 2H), 1.60-1.54 (m, 3H), 0.94 (t, 2H); MS (EI) for $C_{11}H_{13}BrN_2O_3$: 299, 301 (MH^+) (bromine isotope pattern).

[001132] 4-(Aminocarbonyl)-2-bromo-5-(cyclopentylamino)benzoic acid.



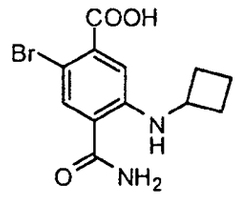
Prepared according to the method of reagent preparation 50 by using cyclopentanamine in step1. ^{1}H NMR (400 MHz, CD_3OD): 7.81(s, 1H), 7.06(s, 1H), 3.83-3.82(m, 1H), 2.06-2.01(m, 2H), 1.77-1.65(m, 4H), 1.54-1.50(m, 2H). MS(EI) for $C_{13}H_{15}BrN_2O_3$: 328(MH^+).

[001133] 4-(Aminocarbonyl)-2-bromo-5-[(3,3,3-trifluoropropyl)amino]benzoic acid.



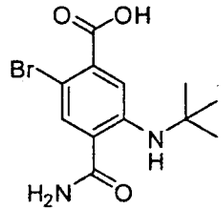
Prepared according to the method of reagent preparation 50 by using 3,3,3-trifluoropropan-1-amine in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.47 (br. s, 1H), 8.28 (s, 1H), 8.10 (s, 1H), 7.88 (d, 1H), 7.47 (d, 1H), 6.97 (s, 1H), 3.47-3.39 (m, 2H), 2.66-2.53 (m, 2H). MS (EI) for $C_{11}H_{10}BrF_3N_2O_3$: 356 (MH^+).

[001134] 4-(Aminocarbonyl)-2-bromo-5-(cyclobutylamino)benzoic acid.



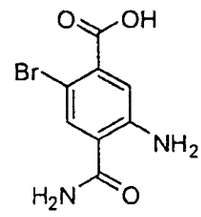
Prepared according to the method of reagent preparation 50 by using cyclobutanamine in step 1. ^{1}H NMR (400 MHz, CD_3OD): 7.82 (s, 1H), 6.92 (s, 1H), 4.00-3.89 (m, 1H), 2.50-2.41 (m, 2H), 1.95-1.80 (m, 4H). MS (EI) for $C_{12}H_{13}BrN_2O_3$: 314 (MH^+).

[001135] 4-(aminocarbonyl)-2-bromo-5-[(1,1-dimethylethyl)amino]benzoic acid:



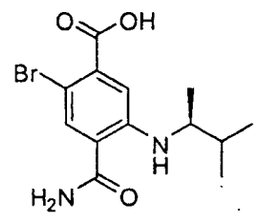
Synthesized according to the method of reagent preparation 50 by using 1,1-dimethylethylamine in step 1. MS (EI) for $C_{12}H_{15}BrN_2O_3$: 315 (MH^+).

[001136] 5-amino-4-(aminocarbonyl)-2-bromobenzoic acid:



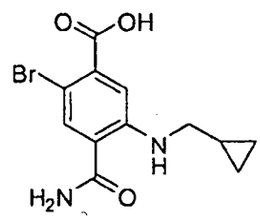
Synthesized according to the method of reagent preparation 50 by conducting only step 2 using 1,1-dimethylethyl 3-amino-4-(aminocarbonyl)benzoate (reagent preparation 29 step 2) followed by acid catalyzed tert-butyl ester hydrolysis under standard conditions, see Green and Wutts in Protective Groups in Organic Synthesis, Wiley-Interscience Ed. ^{1}H NMR (400 MHz, DMSO-d_6): 13.14 (s, 1H), 8.28 (s, 1H), 8.00 (bs, 2H), 7.80 (s, 1H), 7.28 (bs, 2H). MS (EI) for $C_8H_7BrN_2O_3$: 260 (MH^+).

[001137] 4-(aminocarbonyl)-2-bromo-5-{[(1S)-1,2-dimethylpropyl]amino}benzoic acid:



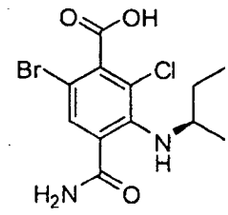
Synthesized according to the method of reagent preparation 50 by using (1S)-1,2-dimethylpropylamine in step 1. ^{1}H NMR (400 MHz, DMSO-d_6): 13.36 (s, 1H), 8.33 (d, 1H), 8.04 (bs, 1H), 7.82 (s, 1H), 7.38 (bs, 1H), 7.72 (s, 1H), 3.42 (m, 1H), 1.74 (m, 1H), 1.05 (d, 3H), 0.93 (d, 3H), 0.88 (d, 3H). MS (EI) for $C_{13}H_{17}BrN_2O_3$: 330 (MH^+).

[001138] 4-(aminocarbonyl)-2-bromo-5-[(cyclopropylmethyl)amino]benzoic acid:



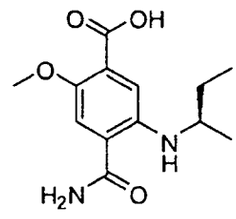
Synthesized according to the method of reagent preparation 50 by using cyclopropylmethylamine in step 1. MS (EI) for $C_{12}H_{13}BrN_2O_3$: 314 (MH^+).

[001139] 4-(aminocarbonyl)-6-bromo-2-chloro-3-{[(1R)-1-methylpropyl]amino}benzoic acid:



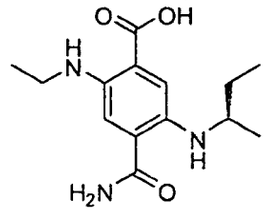
Synthesized according to the method of reagent preparation 50 by using (1R)-1-methylpropylamine in step 1 then repetition of step 2 first using N-bromosuccinimide then using N-chlorosuccinimide and proceeding with steps 3 and 4.. MS (EI) for $C_{12}H_{14}BrClN_2O_3$: 350 (MH^+).

[001140] 4-(aminocarbonyl)-2-(methyloxy)-5-{[(1R)-1-methylpropyl]amino}benzoic acid:



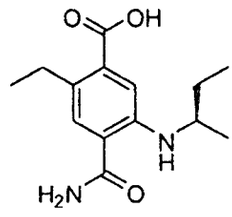
Synthesized according to the method of reagent preparation 50 by using (1R)-1-methylpropylamine in step 1 then following step 2 with the conversion of ethyl 2-bromo-4-cyano-5-{[(1R)-1-methylpropyl]amino}benzoate to ethyl 4-cyano-2-hydroxy-5-{[(1R)-1-methylpropyl]amino}benzoate according to the method described in Chemical & Pharmaceutical Bulletin (2007), 55(9), 1361-1364 and subsequent methylation using iodomethane under standard conditions then proceeding through steps 3 and 4. ^{1}H NMR (400 MHz, d6-DMSO): 12.79-12.74 (s,1H), 8.03-7.95 (s,1H), 7.60-7.52 (d, 1H), 7.35-7.28 (s, 1H), 7.26-7.24 (s, 1H), 6.85-6.81 (s, 1H), 3.72-3.70 (s, 3H), 3.31-3.29 (s, 1H), 1.49-1.40 (m, 2H), 1.08-1.05 (d, 3H), 0.89-0.83 (m, 3H). MS (EI) for $C_{13}H_{18}N_2O_4$: 267 (MH^+).

[001141] 4-(aminocarbonyl)-2-(ethylamino)-5-{[(1R)-1-methylpropyl]amino}benzoic acid:



Synthesized according to the method of reagent preparation 50 by using (1R)-1-methylpropylamine in step 1 then following step 2 with the conversion of ethyl 2-bromo-4-cyano-5-{[(1R)-1-methylpropyl]amino}benzoate to ethyl 4-cyano-2-(ethylamino)-5-{[(1R)-1-methylpropyl]amino}benzoate according to the method described in step 1 then proceeding through steps 3 and 4. MS (EI) for $C_{14}H_{21}N_3O_3$: 280 (MH^+).

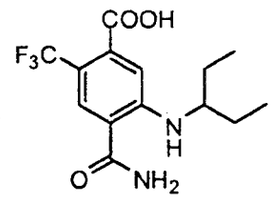
[001142] 4-(aminocarbonyl)-2-ethyl-5-{[(1R)-1-methylpropyl]amino}benzoic acid:



Synthesized according to the method of reagent preparation 50 by using (1R)-1-methylpropylamine in step 1 then following step 2 with the conversion of ethyl 2-bromo-4-cyano-5-{[(1R)-1-methylpropyl]amino}benzoate to ethyl 4-cyano-2-ethyl-5-{[(1R)-1-methylpropyl]amino}benzoate by treatment with ethylmagnesium chloride according to the method described in Synlett 1996, 5, 473-474 then proceeding through steps 3 and 4. ^{1}H NMR (400 MHz, DMSO-d_6): 7.94 (s, 1H), 7.81 (d, 1H), 7.49 (s, 1H), 7.27 (s, 1H), 6.98 (s, 1H), 2.67-2.75 (m, 2H), 1.44-1.53 (m, 2H), 1.06-1.15 (m, 6H), 0.89 (t, 3H).

MS (EI) for $C_{14}H_{20}N_2O_3$: 265 (MH^+).

REAGENT PREPARATION 51: 4-(aminocarbonyl)-5-[(1-ethylpropyl)amino]-2-(trifluoromethyl)benzoic acid:



[001143] STEP 1: 4-Amino-2-(trifluoromethyl)benzoic acid (10 g, 48.8 mmol) was suspended in THF (100 mL) and methanol (30 mL) and was cooled in an ice bath. (Trimethylsilyl)diazomethane (2 M solution in hexanes; 32 mL) was added drop-wise. The mixture was stirred for 5 minutes and then concentrated to afford methyl 4-amino-2-(trifluoromethyl)benzoate (quantitative yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, 1H), 6.99 (d, 1H), 6.77 (d, 1H), 4.18 (br s, 2H), 3.88 (s, 3H); GCMS for $C_9H_8F_3NO_2$: 219 (M^+).

[001144] STEP 2: Methyl 4-amino-2-(trifluoromethyl)benzoate (~22 mmol), was dissolved in THF (100 mL) and the mixture was sparged with nitrogen for 15 minutes. Copper (I) iodide (4.14 g, 21.8 mmol) and diiodomethane (8.8 mL, 109 mmol) were added followed by isoamyl nitrite (8.8 mL, 66.2 mmol) and the mixture was stirred at reflux for 4 h. The mixture was cooled to ambient temperature and then was partitioned between ethyl acetate and 1N hydrochloric acid. The aqueous portion was extracted with ethyl acetate (2x). The combined organic portion was washed sequentially with 1:1 saturated sodium bicarbonate solution: 1M sodium thiosulfate (2x) and brine, dried over sodium sulfate, then filtered and concentrated to provide a brown oil which was purified by column chromatography (silica gel, 2-40% dichloromethane in hexanes) to afford methyl 4-iodo-2-(trifluoromethyl)benzoate (5.42 g, 16.4 mmol, ~75% yield over 2 steps) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.97 (dd, 1H), 7.52 (d, 1H), 3.93 (s, 3H); GCMS for $C_9H_6F_3IO_2$: 330 (M^+).

[001145] STEP 3: Methyl 4-iodo-2-(trifluoromethyl)benzoate (1.65 g, 5.0 mmol) was dissolved in concentrated sulfuric acid (6 mL) and was cooled in an ice bath. Fuming nitric acid (4 mL) was added drop-wise and the mixture was stirred at 70 °C for 1.5 h. The mixture was cooled to ambient temperature and then poured into ice

(~100 mL). The aqueous mixture was extracted with ethyl acetate (2x). The combined organic portion was washed with saturated sodium bicarbonate (2x), brine, dried over sodium sulfate then filtered and concentrated to afford (1.7 g, 4.53 mmol, 91% yield) composed of the two regioisomers methyl 4-iodo-5-nitro-2-(trifluoromethyl)benzoate (major) and methyl 4-iodo-3-nitro-2-(trifluoromethyl)benzoate (minor) in a 4:1 ratio. ^{1}H NMR for desired (major) isomer (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.26 (s, 1H), 3.98 (s, 3H); GCMS for $C_9H_5F_3INO_4$: 375 (M^+).

[001146] STEP 4: A mixture of methyl 4-iodo-5-nitro-2-(trifluoromethyl)benzoate (desired) and methyl 4-iodo-3-nitro-2-(trifluoromethyl)benzoate as obtained in step 3 (1.7 g, 4.53 mmol) in acetic acid (20 mL) was treated with iron powder (1.5 g, 26.8 mmol) at 45 °C for 2 h. The reaction mixture was cooled to ambient temperature and was filtered through celite. The filter cake was washed with ethyl acetate and the filtrate was concentrated. The residue was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, then filtered and concentrated to afford a brown oil which was purified by column chromatography (silica gel, 10-30% ethyl acetate in hexanes) to afford the two regioisomers methyl 5-amino-4-iodo-2-(trifluoromethyl)benzoate (major) and methyl 3-amino-4-iodo-2-(trifluoromethyl)benzoate (minor) in a 4:1 ratio (1.484 g, 4.30 mmol, 95% yield). ^{1}H NMR for desired (major) isomer (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.06 (s, 1H), 4.55 (br s, 2H), 3.90 (s, 3H); GCMS for $C_9H_7F_3INO_2$: 345 ($M^{+\cdot}$).

[001147] STEP 5: A mixture of methyl 5-amino-4-iodo-2-(trifluoromethyl)benzoate (desired) and methyl 3-amino-4-iodo-2-(trifluoromethyl)benzoate as obtained in step 4 (392 mg, 1.14 mmol) was dissolved in 1,2-dichloroethane (12 mL) and was treated with trifluoroacetic acid (0.5 mL, 6.73 mmol), 3-pentanone (0.36 mL, 3.40 mmol) and sodium triacetoxyborohydride (724 mg, 3.42 mmol) at 45 °C for 0.5 h. GCMS indicated complete conversion of desired isomer to required product. After a further 0.5 h at 45 °C, the reaction mixture was cooled to ambient temperature and was quenched with 1N sodium hydroxide (5 mL) and saturated sodium bicarbonate and was partitioned with dichloromethane. The aqueous portion was extracted with dichloromethane. The combined organic portion was washed with brine, dried over magnesium sulfate, then filtered and concentrated to afford a yellow oil which was purified by column chromatography (silica gel, 10-40% dichloromethane in hexanes)

to afford pure methyl 4-iodo-5-(pentan-3-ylamino)-2-(trifluoromethyl)benzoate (330 mg, 0.795 mmol, 70% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 6.79 (s, 1H), 4.44 (d, 1H), 3.92 (s, 3H), 3.44-3.34 (m, 1H), 1.73-1.48 (m, 4H), 0.95 (t, 6H); GCMS for $C_{14}H_{17}F_3INO_2$: 415 (M^+).

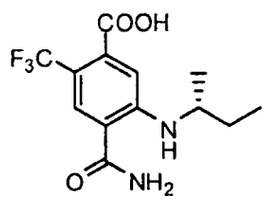
[001148] STEP 6: Methyl 4-iodo-5-(pentan-3-ylamino)-2-(trifluoromethyl)benzoate (401 mg, 0.966 mmol) was dissolved in DMF (9 mL) and the mixture was sparged with nitrogen for 15 minutes. Zinc cyanide (79 mg, 0.673 mmol) and tetrakis(triphenylphosphine)palladium(0) (100 mg, 0.086 mmol) were added and the mixture was stirred at 100 °C for 15 h. The reaction mixture was cooled to ambient temperature and was filtered through celite. The filter cake was washed with ethyl acetate and the filtrate was washed with 5% lithium chloride (2x). The combined aqueous wash was back-extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, then filtered and concentrated to afford a brown semi-solid which was purified by column chromatography (silica gel, 30-50% dichloromethane in hexanes) to afford methyl 4-cyano-5-(pentan-3-ylamino)-2-(trifluoromethyl)benzoate (262 mg, 0.834 mmol, 86% yield) as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 6.96 (s, 1H), 4.76 (d, 1H), 3.94 (s, 3H), 3.49-3.38 (m, 1H), 1.75-1.63 (m, 2H), 1.61-1.49 (m, 2H), 0.96 (t, 6H); GCMS for $C_{15}H_{17}F_3N_2O_2$: 314 ($M^{+\cdot}$).

[001149] STEP 7: Methyl 4-cyano-5-(pentan-3-ylamino)-2-(trifluoromethyl)benzoate (257 mg, 0.818 mmol) was dissolved in DMSO (2 mL) and was cooled in a cold water bath. 30% Aqueous hydrogen peroxide (0.2 mL) and potassium carbonate (38 mg, 0.275 mmol) was added and the mixture was stirred at ambient temperature for 1.5 h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was dried over sodium sulfate then filtered and concentrated to afford methyl 4-aminocarbonyl-5-(pentan-3-ylamino)-2-(trifluoromethyl)benzoate (quantitative yield) as a yellow oil. MS (EI) for $C_{15}H_{19}F_3N_2O_3$: 333 (MH^+).

[001150] STEP 8: Methyl 4-aminocarbonyl-5-(pentan-3-ylamino)-2-(trifluoromethyl)benzoate (0.818 mmol) was dissolved in methanol (2 mL) and was treated with 2M sodium hydroxide (1 mL, 2 mmol) at 45 °C for 1.5 h. The reaction mixture was cooled to ambient temperature and was concentrated to afford an

aqueous residue that was washed with ether, then cooled in an ice bath and acidified with 1N hydrochloric acid to pH ~3. The precipitate was collected by filtration, washed with water, then dried to afford 4-aminocarbonyl-5-(pentan-3-ylamino)-2-(trifluoromethyl)benzoic acid (233 mg, 0.733 mmol, 90% yield over 2 steps). ^{1}H NMR (400 MHz, d_6-DMSO): δ 13.5 (br s, 1H), 8.74 (d, 1H), 8.21 (br s, 1H), 7.95 (s, 1H), 7.46 (br s, 1H), 6.94 (s, 1H), 3.51-3.43 (m, 1H), 1.63-1.51 (m, 2H), 1.51-1.39 (m, 2H), 0.87 (t, 6H); MS (EI) for $C_{14}H_{17}F_3N_2O_3$: 319 (MH^+).

REAGENT PREPARATION 52: 4-(aminocarbonyl)-5-{[(1R)-1-methylpropyl]amino}-2-(trifluoromethyl)benzoic acid:



[001151] STEP 1: A mixture of methyl 5-amino-4-iodo-2-(trifluoromethyl)benzoate (major) and methyl 3-amino-4-iodo-2-(trifluoromethyl)benzoate (minor) in a 4:1 ratio (prepared in Example 51 Step 4) (1.08 g, 3.13 mmol) was dissolved in DMF (17 mL), and the mixture was sparged with nitrogen for 15 minutes. Zinc cyanide (257 mg, 2.19 mmol) and tetrakis(triphenylphosphine)palladium(0) (362 mg, 0.313 mmol) were added and the mixture was stirred at 100 °C for 15 h. The reaction mixture was cooled to ambient temperature and was filtered through celite. The filter cake was washed with ethyl acetate and the filtrate was washed with 5% lithium chloride. The aqueous wash was back-extracted with ethyl acetate (2x). The combined organic portion was washed with 10% lithium chloride and brine, was dried over sodium sulfate then filtered and concentrated to afford a residue which was purified by column chromatography (silica gel, 30-50% ethyl acetate in hexanes) to afford pure methyl 5-amino-4-cyano-2-(trifluoromethyl)benzoate (556 mg, 2.28 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.10 (s, 1H), 4.88 (br s, 2H), 3.93 (s, 3H); GCMS for $C_{10}H_7F_3N_2O_2$: 244 (M^+).

[001152] STEP 2: Methyl 5-amino-4-cyano-2-(trifluoromethyl)benzoate (250 mg, 1.02 mmol) was dissolved in THF (6 mL), and the mixture was sparged with nitrogen

for 15 minutes. Copper (I) iodide (195 mg, 1.02 mmol) and diiodomethane (0.4 mL, 4.95 mmol) were added followed by isoamyl nitrite (0.4 mL, 3.01 mmol), and the mixture was stirred at reflux for 2.5 h. The mixture was cooled to ambient temperature and then was partitioned between ethyl acetate and 1N hydrochloric acid. The aqueous portion was extracted with ethyl acetate (2x). The combined organic portion was washed sequentially with 1:1 saturated sodium bicarbonate solution: 1M sodium thiosulfate (2x) and brine, was dried over sodium sulfate, then filtered and concentrated to provide a semi-solid which was purified by column chromatography (silica gel, 20-50% dichloromethane in hexanes) to afford methyl 4-cyano-5-iodo-2-(trifluoromethyl)benzoate (174 mg, 0.49 mmol, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.93 (s, 1H), 3.98 (s, 3H); GCMS for $C_{10}H_5F_3INO_2$: 355 (M^+).

[001153] STEP 3: Methyl 4-cyano-5-iodo-2-(trifluoromethyl)benzoate (174 mg, 0.49 mmol) was dissolved in dioxane (2 mL) and was sparged with nitrogen for 15 minutes. XANTPHOS (57 mg, 0.098 mmol), cesium carbonate (350 mg, 1.07 mmol), (R)-sec-butylamine (0.1 mL, 0.986 mmol), and tris(dibenzylideneacetone)dipalladium (45 mg, 0.049 mmol) were added, and the mixture was stirred in a sealed tube at 95 °C for 20 h. The reaction mixture was cooled to ambient temperature and was filtered through celite. The filter cake was washed with ethyl acetate and the filtrate was concentrated to afford an orange oil which was purified by column chromatography (silica gel, 5-15% ethyl acetate in hexanes) to afford (R)-methyl 5-(sec-butylamino)-4-cyano-2-(trifluoromethyl)benzoate (45 mg, 0.150 mmol, 31% yield) as a yellow oil. GCMS for $C_{14}H_{15}F_3N_2O_2$: 300 (M^+).

[001154] STEP 4: (R)-Methyl 5-(sec-butylamino)-4-cyano-2-(trifluoromethyl)benzoate (45 mg, 0.150 mmol) was dissolved in DMSO (1 mL) and was treated with 30% aqueous hydrogen peroxide (0.05 mL) and potassium carbonate (6 mg, 0.043 mmol) at ambient temperature for 2 h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was dried over sodium sulfate, then filtered and concentrated to afford a yellow oil which was purified by column chromatography (silica gel, 10-40% ethyl acetate in hexanes) to afford (R)-methyl 5-(sec-butylamino)-4-aminocarbonyl-2-(trifluoromethyl)benzoate (27 mg, 0.085 mmol, 57% yield). (R)-Methyl 5-(sec-butylamino)-4-aminocarbonyl-2-(trifluoromethyl)benzoate (27 mg, 0.085 mmol) was suspended in methanol (1 mL)

and was treated with 1M sodium hydroxide (0.2 mL, 0.2 mmol) at 45 °C for 1 h. Dichloromethane (0.5 mL) and 1M sodium hydroxide (0.2 mL, 0.2 mmol) was added and the mixture was stirred at 45 °C for a further 1.5 h. Dichloromethane (0.5 mL) and 1M sodium hydroxide (0.2 mL, 0.2 mmol) were added, and the mixture was stirred at 45 °C for a further 1 h and then at ambient temperature for 15 h. The reaction mixture was concentrated to afford an aqueous residue that was cooled in an ice bath, was acidified with 1N hydrochloric acid to pH ~2, then extracted with ethyl acetate (2x). The organic portion was dried over sodium sulfate, then filtered and concentrated to provide 4-(aminocarbonyl)-5-{[(1R)-1-methylpropyl]amino}-2-(trifluoromethyl)benzoic acid

(23 mg, 0.076 mmol, 89% yield). MS (EI) for $C_{13}H_{15}F_3N_2O_3$: 305 (MH^+).

REAGENT PREPARATION 53: 1,1,1-trifluorobutan-2-amine:

[001155] STEP1: To a solution of 1,1,1-trifluorobutan-2-one (5.0 g, 39.9 mmol) and hydroxylamine hydrochloride (3.22 g, 46.3 mmol) in water (28 mL) was added a solution of sodium hydroxide (1.84 g, 46.0 mmol) in water (14 mL), then the mixture was brought to reflux for 4hr. After cooling to room temperature, the mixture was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were washed with water, brine, then dried over anhydrous sodium sulfate. Filtration and concentration then distillation using a 10 cm Vigreux column (b.p. 123-124 °C) afforded (*E*)-1,1,1-trifluorobutan-2-one oxime (2.50 g, 44.5 % yield) as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$): 9.18 (br s, 1H), 2.52 (q, 2H), 1.21 (t, 3H).

[001156] STEP 2: To a solution of 1M lithium aluminum hydride in ethyl ether (40 ml) was added (*E*)-1,1,1-trifluorobutan-2-one oxime (2.50 g, 17.7 mmol) dissolved in ethyl ether (25 mL) at room temperature. The reaction mixture was stirred for 3hr, then carefully quenched by addition of water and the aqueous solution was extracted with ethyl acetate (3x 50 mL) and dried over anhydrous sodium sulfate. After filtration, 4.0 M hydrogen chloride in dioxane was added (10 mL). The solution was then rotary evaporated nearly 80 % in volume, and ethyl ether (30 mL) was added to give a precipitate. The solid was collected by filtration and dried to give 1,1,1-trifluorobutan-2-amine hydrochloride salt (2.46 g, 85.6 % yield). ^{1}H NMR (400 MHz, d6-DMSO): 9.30 (br s, 2H), 4.18 (m, 1H), 1.81 (q, 2H), 1.02 (t, 3H).

HSP90 ASSAYS:

Hsp90 Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) Assay Protocol

[001157] The determination of IC50 values of HSP90 inhibitors was conducted using a time-resolved fluorescence resonance energy transfer (TR-FRET) displacement binding assay. The assay employs a biotinylated geldanamycin probe (biotin-GM) and His6-tagged human Hsp90 N-terminal ATP-binding domain (Hsp90N). Test compounds are serially diluted in DMSO and 0.5 μL aliquots are transferred to 384-well black, medium binding microtiter assay plates (Greiner). Reagent 1 is prepared by mixing 80 nM biotin-GM, 1 nM anti-His-Eu chelate, and 100 nM streptavidin allophycocyanin (SA-APC) in binding buffer (50 mM Tris-HCl, pH 7.5, 1 mM EDTA, 150 mM NaCl, 0.1% Triton X-100, 0.05% BSA, and 1 mM DTT) and 10 μL is transferred to the assay plate. Reagent 2 is prepared by mixing 80 nM HSP90N in binding buffer and 10 μL is transferred to columns 3-24 of the assay plate. Binding buffer (10 μL) is added to columns 1-2 as 100% inhibition control. The plate is incubated for 180 minutes at room temperature. TR-FRET signals are measured on an Envision plate reader (Perkin Elemer) using the LANCE® assay detection protocol. IC(50) values are calculated as a percentage of the displacement of biotin-GM from HSP90N by compounds at variable molar concentrations.

[001158] The compounds in both Table I and II have been tested for their HSP90 inhibitory activity (IC_{50} values), and these compounds have HSP90 IC_{50} values of less than 10,000 nM. A preferred group of compounds of Table I have HSP90 IC_{50} values of less than 5,000 nM. Another preferred group of compounds of Table I have HSP90 IC_{50} values of less than 2,000 nM. Another preferred group of compounds of Table I have HSP90 IC_{50} values of less than 1,000 nM. Another preferred group of compounds of Table I have HSP90 IC_{50} values of less than 500 nM. Another preferred group of compounds of Table I have HSP90 IC_{50} values of less than 200 nM. Another preferred group of compounds of Table I have HSP90 IC_{50} values of less than 100 nM. Another preferred group of compounds of Table I have HSP90

IC_{50} values of less than 50 nM. Another preferred group of compounds of Table I have HSP90 IC_{50} values of less than 25 nM.

Pharmaceutical Composition Examples

[001159] The following are representative pharmaceutical formulations containing a compound of Formula I, II or III.

Tablet Formulation

[001160] The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
Formula I, II or III	400
Cornstarch	50
croscarmellose sodium	25
Lactose	120
magnesium stearate	5

Capsule Formulation

[001161] The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per tablet, mg
Formula I, II or III	200
lactose, spray-dried	148
magnesium stearate	2

Suspension Formulation

[001162] The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
Formula I, II or III	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 mL

Ingredient	Amount
Colorings	0.5 mg
distilled water	q.s. to 100 mL

Injectable Formulation

[001163] The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
Formula I, II or III	1.2 g
sodium acetate buffer solution	0.4 M 2.0 mL
HCl (1 N) or NaOH (1 M)	q.s. to suitable pH
water (distilled, sterile)	q.s.to 20 mL

[001164] All of the above ingredients, except water, are combined and heated to 60° - 70° with stirring. A sufficient quantity of water at 60° C. is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository Formulation

[001165] A suppository of total weight 2.5 g is prepared by mixing the compound of disclosed herein (compounds of Fomula I, II or III) with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

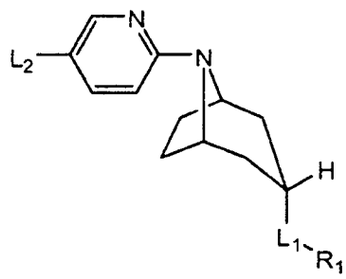
Ingredient	Quantity per tablet, mg
Formula I, II or III	500
Witepsol® H-15	Balance

[001166] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. 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 can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the

invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

We Claim:

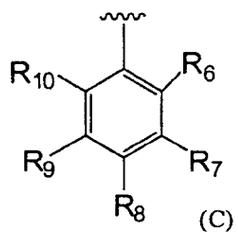
1. A compound according to Formula I:



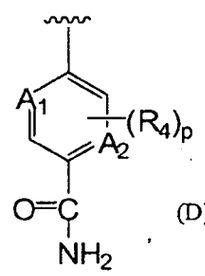
I

or a pharmaceutically acceptable salt thereof, wherein:

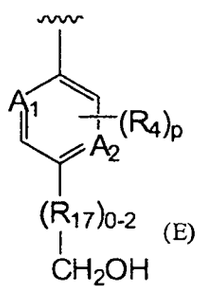
R_1 is selected from



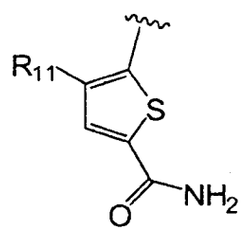
(C) ,



(D) ,



(E) and



(Q) ;

R_3 is selected from hydrogen, $-CF_3$, $-NH_2$, -OH, alkyl optionally substituted with 1, 2 or 3 R_5, alkoxy, dialkylaminoalkyl, cycloalkyl optionally substituted with arylalkoxy, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy and heterocycloalkyl optionally substituted with alkyl or aryl, alkenyl, alkynyl, heterocycloalkyl optionally substituted with a group selected from alkyl, -C(O)O-alkyl and arylalkyl, arylalkyl optionally substituted with alkylheterocycloalkyl at any ring position of the aryl group, and heteroaryl;

R_4, R_7, R_8, R_9 and R_{11} are each independently selected from hydrogen, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hydroxy, alkenyl, alkynyl, hydroxyalkynyl, halogen, hydroxyalkyl, dihydroxyalkyl, $-O-C(O)-NH_2$, amino(imino)alkyl, $-C(O)-NH_2$, -N(H)C(O)alkyl,

alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkyl optionally substituted with 1-8 halogen, dialkylamino, -N(H)alkylheterocycloalkyl, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkoxy, $-NH_2$, -O-alkyl-heterocycloalkyl, dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl optionally substituted with 1, 2 or 3 groups selected from alkyl, alkoxy and halogen;

R_5 is selected from halogen, cycloalkyl, cycloalkylalkylamino, heteroaryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl and alkoxy, alkylthio, heterocycloalkyl optionally substituted with 1, 2, or 3 groups selected from alkyl, halogen, phenyl and oxo, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy, and heterocycloalkyl optionally substituted with alkyl, alkoxy, dialkylamino, -OH, $-C(O)-NH_2$, $-C(O)-O-CH_3$, $-C(O)-N(H)(C_1-C_3)$alkyl, heteroarylamino optionally substituted with halogen, and $-OCF_3$;

R_6 and R_{10} are each selected from hydrogen, alkyl optionally substituted with 1-8 halogens, alkylthio, alkenyl, alkynyl, hydroxyalkynyl, halogen, hydroxyalkyl, dihydroxyalkyl, amino(imino)alkyl, $-C(O)-NH_2$, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkylamino optionally substituted with 1-8 halogens, dialkylamino, alkoxyalkylamino, -N(H)alkylheterocycloalkyl, cycloalkylalkylamino, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkylamino optionally substituted with a group selected form -OH, alkyl, $-CF_3$ and heterocycloalkyl, -N(H)cycloalkyl optionally substituted with -OH or $-NH_2$, $-NH_2$, -N(H)-heteroaryl, -N(H)-aryl optionally substituted with 1, 2 or 3 groups selected from alkoxy, heterocycloalkylalkoxy and dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl;

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, alkyl, heterocycloalkyl, and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkyl, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl;

R_{17}, when present, is $-CH_2-$ or -CH(OH)-;

each of A_1 or A_2 is N or C(H), wherein A_1 and A_2 can be the same or different, provided that A_1 can be substituted with R_4 only when A_1 is C(H), and provided that A_2 can be substituted with R_4 only when A_2 is C(H);

L_1 is selected from -C(O)O-, -C(O)NH-, -C(O)NHSO$_2$-, -(CH$_2$)$_n$C(O)NH-, -(CH$_2$)$_n$NHC(O)-, -(CH$_2$)$_m$NH-, -(CH$_2$)$_n$SO$_2$NH-, -(CH$_2$)$_n$NHSO$_2$-, -(CH$_2$)$_m$C(O)-, -(CH$_2$)$_m$O-, and -(CH$_2$)$_m$NH-(CH$_2$)$_n$-;

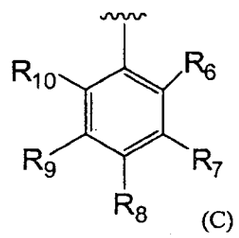
L_2 is -C(O)-NH-R_3, -CN, -C(O)-N(CH$_3$)-OCH$_3$, or -C(O)-R_3;

n is 0 or 1;

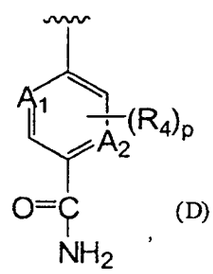
m is 0, 1 or 2; and

each p is independently 0, 1, 2, 3 or 4.

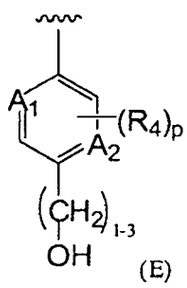
2. The compound according to claim 1, wherein R_1 is selected from



(C)

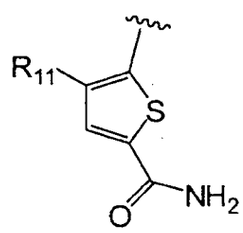


(D)



(E)

and



(Q) ;

R_3 is selected from hydrogen, -CF$_3$, -NH$_2$, -OH, alkyl optionally substituted with 1, 2 or 3 R_5, alkoxy, dialkylaminoalkyl, cycloalkyl optionally substituted with arylalkoxy, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy and heterocycloalkyl optionally substituted with alkyl or aryl, alkenyl, alkynyl, heterocycloalkyl optionally substituted with a group selected from alkyl, -C(O)O-alkyl and arylalkyl, arylalkyl optionally substituted with alkylheterocycloalkyl at any ring position of the aryl group, and heteroaryl;

R_4, R_7, R_8 , R_9 and R_{11} are each independently selected from hydrogen, -OR$_{16}$, -SR$_{16}$, -N(H)R$_{16}$, hydroxy, alkenyl, alkynyl, hydroxyalkynyl, alkoxy, halogen, hydroxyalkyl, dihydroxyalkyl, -O-C(O)-NH$_2$, amino(imino)alkyl, -C(O)-NH$_2$,

-N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkyl optionally substituted with 1-8 halogen, dialkylamino, -N(H)alkylheterocycloalkyl, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkoxy, $-NH_2$, -O-alkyl-heterocycloalkyl, dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl optionally substituted with 1, 2 or 3 groups selected from alkyl, alkoxy and halogen;

R_5 is selected from halogen, cycloalkyl, cycloalkylalkylamino, heteroaryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl and alkoxy, alkylthio, heterocycloalkyl optionally substituted with 1, 2, or 3 groups selected from alkyl, halogen, phenyl and oxo, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy, and heterocycloalkyl (optionally substituted with alkyl), alkoxy, dialkylamino, -OH, $-C(O)-NH_2$, $-C(O)-O-CH_3$, $-C(O)-N(H)(C_1-C_3)$alkyl, heteroarylamino optionally substituted with halogen, and $-OCF_3$;

R_6 and R_{10} are each selected from hydrogen, alkyl optionally substituted with 1-8 halogens, alkylthio, alkenyl, alkynyl, hydroxyalkynyl, halogen, hydroxyalkyl, dihydroxyalkyl, amino(imino)alkyl, $-C(O)-NH_2$, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkylamino optionally substituted with 1-8 halogens, dialkylamino, alkoxyalkylamino, -N(H)alkylheterocycloalkyl, cycloalkylalkylamino, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkylamino optionally substituted with a group selected form -OH, alkyl, $-CF_3$ and heterocycloalkyl, -N(H)cycloalkyl optionally substituted with -OH or $-NH_2$), $-NH_2$, -N(H)-heteroaryl, -N(H)-aryl optionally substituted with 1, 2 or 3 groups selected from alkoxy, heterocycloalkylalkoxy and dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl;

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, alkyl, heterocycloalkyl, and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkoxy, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkoxy;

each of A_1 or A_2 is –N= or –CH=, wherein A_1 and A_2 can be the same or different;

L_1 is selected from -NHC(O)-, -$NHSO_2$-, -NHC(O)O-, -C(O)O-, -C(O)NH-, -C(O)$NHSO_2$-, -C(O)-, -$(CH_2)_n$C(O)NH-, -$(CH_2)_n$NHC(O)-, -$(CH_2)_m$NH-, -$(CH_2)_n SO_2$NH-, -$(CH_2)_n NHSO_2$-, -$(CH_2)_m$C(O)-, -$(CH_2)_m$O-, and -$(CH_2)_m$NH-;

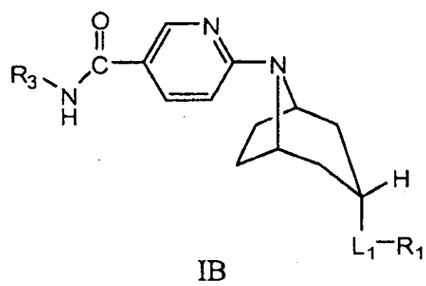
L_2 is -C(O)-NH-R_3 , -CN or -C(O)-R_3;

n is 0 or 1;

m is 0, 1 or 2; and

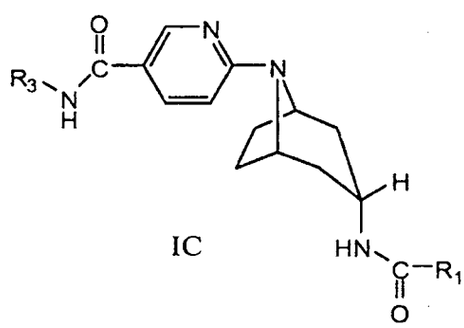
each p is independently 0, 1, 2, 3 or 4.

3. The compound according to claim 1 selected from:



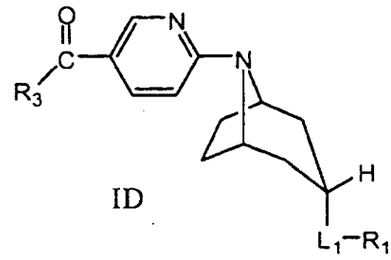
IB

or a pharmaceutically acceptable salt thereof, wherein L_1, R_1 and R_3 are as defined in claim 1,



IC

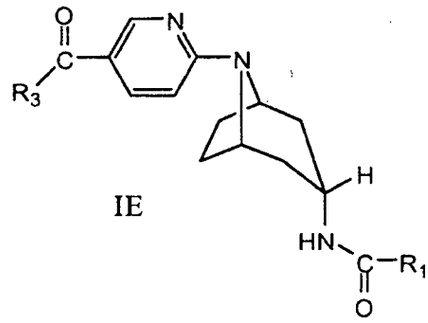
or a pharmaceutically acceptable salt thereof, wherein R_1 and R_3 are as defined in claim 1,



ID

or a pharmaceutically acceptable salt thereof,

wherein R_1, R_3 and L_1 are as defined in claim 1, and



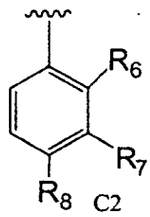
IE

or a pharmaceutically acceptable salt thereof,

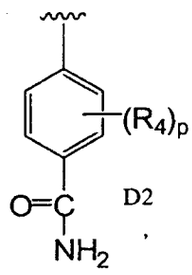
wherein R_1 and R_3 are as defined in claim 1.

4. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from

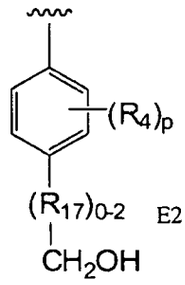


C2 ,



D2 ,

and



E2 ;

R_3 is selected from CF_3, cyclopropyl, cyclobutyl, cyclohexyl optionally substituted with hydroxyl, cyclopropylmethyl, N-propyl, 3-methylbutyl, (1S)-2-hydroxy-1-methylethyl, (2S)-2-hydroxypropyl, methoxyethyl, ethoxyethyl, methylphenyl, phenyl, dimethylphenyl, methoxyphenyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminoethyl, diethylaminopropyl, cyclopentyl, halophenyl, phenylmethyl, phenylethyl optionally substituted with hydroxyl at the ethyl position of phenylethyl, phenylpropyl, phenylpiperidinyl, diethylaminoethyloxyphenylmethyl, diethylaminoethyloxyphenylethyl, pyrrolidinylphenylmethyl, diethylaminoethyloxy-2-fluorophenylethyl, phenyl(C_1-C_3)alkyl optionally substituted at the phenyl position of phenyl(C_1-C_3)alkyl with 1-3 groups selected from methoxy, halo and methyl, methylphenyl(C_1-C_4)alkyl wherein the (C_1-C_4)alkyl portion of methylphenyl(C_1-C_4)alkyl is optionally substituted with -C(O)NH_2, -C(O)$NHCH_3$ or -C(O)$NHCH_2CH_3$, thienylmethyl, furanylmethyl, pyridinylethyl, pyridinylmethyl, methylpyrazinylmethyl, methyl, ethyl, methylpropyl, 2-methylpropyl, 2,3-dihydroxypropyl, (1S)-1-methylpropyl, (1S)-1,2-dimethylpropyl, (1R)-1,2-dimethylpropyl, methyloxypropyl, ethyloxypropyl, (1S)-1-methyl-2-(methyloxy)ethyl, 1,3-benzodioxolyl, 1,3-benzodioxolylmethyl, N-prop-2-yn-1-yl, N-[3-(4-methylpiperazin-1-yl)propyl, N-[2-(ethylthio)ethyl], (1S,2S)-2-[(phenylmethyl)oxy]cyclopentyl, 6-chloropyridinylmethyl, 2-chloro-6-fluorophenylmethyl, methylthioethyl, N-butyl, 1-methylethyloxyethyl, 1-methylethyloxypropyl, 4,4-bismethyloxybutyl, methylpyrazinylmethyl, propyloxypropyl, trifluoromethyloxyphenylmethyl, methyloxyphenylethyl, (2,2-dimethyl-1,3-dioxolan-4-yl)methyl, phenylmethylpyrrolidinyl, oxopyrrolidinylpropyl, pyrrolidinylethyl, methylpyrrolidinylethyl, ethylpyrrolidinylmethyl, N-(1R,2R,4S)-bicyclo[2.2.1]hept-2-yl, 3,3-dimethylbutyl, ethyloxyphenylmethyl, phenylmethylpiperidinyl, ethoxycarbonylpiperidinyl, trifluoromethylphenylmethyl, imidazolylpropyl, (3R)-pyrrolidin-3-yl, morpholinylethyl, morpholinylpropyl, piperidinylethyl, pyrrolidinyl, piperidinyl, pyrrolidinylmethyl, 1-methylethylpyrrolidinyl, ethylpyrrolidinyl, methylpyrrolidinyl, methylethylpiperidinyl, methylpiperidinyl, ethylpiperidinyl, ethylazetidinyl, azetidinyl, methylazetidinyl, 1-methylethylazetidinyl, methylpiperazinylphenylmethyl, piperazinylphenylmethyl, methylpiperazinylphenyl, methylpiperidinylphenyl, piperidinylphenyl(C_1-C_3)alkyl optionally substituted with 1-

4 halo, methylpiperazinylphenyl(halo)methyl, methylpiperidinylphenylmethyl, methylpiperazinylphenylethyl, 2-methylpropylpiperazinylphenylmethyl, morpholinylphenylmethyl, piperazinylpyridinylethyl, $-CH(CH_3)C(O)-NH_2$, dimethylaminoethyloxyphenyl, isopropyl, (C_1-C_5)alkyl optionally substituted with 1-7 halo,-OH, $-NH_2$, cylcohexyl(C_1-C_5)alkyl optionally substituted with 1-2 hydroxyl groups, phenylaminoethyl optionally substituted with halo, morpholinylethyl, phenylpiperazinylethyl, and methylpiperazinylethyl;

each R_4, when present, is independently selected from halo, 1-ethylpropylamino, methyl, ethyl, cyclohexylamino optionally substituted with hydroxyl, cyclobutylamino, 1-methylpropyloxy, methoxyethoxy, $-CF_3$, piperidinyl or amino, mopholinylamino, dimethylaminobutyl, methylethylaminopropyl, methylethylaminopropylamino, cyclopentylamino, piperidinylamino, methylethylamino, ethylamino, 2-methylpropylamino, tetrahydraopyranylamino, ethylpiperidinylamino, 2,2-dimethylpropylamino, pyrrolidinylamino, 1-methylpropylamino, 2-methylpropylamino, amino, 1,1 dimethylethylamino, tetrahydropyranylmethylamino, piperidinylamino optionally substituted with methylsulfonyl, phenylamino optionally substituted with 1-3 groups selected from methoxy and dimethylaminoethyloxy, methylsulfonylethylamino, methoxyethylamino, morpholinylethyloxy, $-N(H)C(O)CH_3$, cyclobutylamino, methoxy, cyclobutyloxy, cyclobutylamino, pyridinylamino, ethylamino, 1-methylcyclopropylethylamino, methylethyloxyethylamino, butylamino, piperidinyl, pentylamino, azetinyl, 1,2-dimethylpropylamino, 1-methylethylpropylamino, propylamino, 1-cyclopropylpropylamino, 1-propylbutylamino, 1-cyclopropylethylamino, dicyclopropylmethylamino, 1,2,2-trimethylpropylamino, tetrahydrofuranylamino, (C_1-C_5)alkylamino substituted with 1-7 halo, morpholinylethyloxy and cyclopropylmethylamino;

R_6 is selected from hydrogen, (C_1-C_4)alkyl optionally substituted with hydroxy, (C_1-C_3)alkylamino or dimethylamino, (C_1-C_4)alkynyl optionally substituted with hydroxyl, and halo;

R_7 is selected from hydrogen, -OH, $-O(C_1-C_3)$alkyl, $-S(C_1-C_3)$alkyl, $-N(H)(C_1-C_3)$alkyl, (C_5-C_6)cycloalkylamino optionally substituted with hydroxyl, (C_1-C_3)alkylamino or dimethylamino, $-C(O)NH_2$, and $-O-C(O)NH_2$;

R_8 is selected from hydrogen, -O(C_1-C_3)alkyl, -O-C(O)NH_2, and -C(=NH)-NH_2;

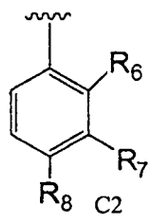
L_1 is -N(H)C(O)-;

L_2 is -C(O)-NH-R_3 or -C(O)-R_3; and

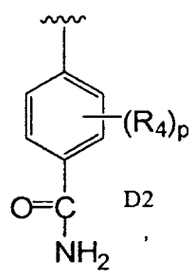
each p is independently 0, 1, 2 or 3.

5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from

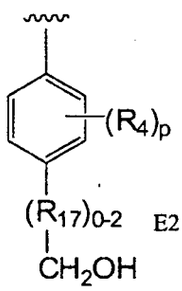


C2 ,



D2 ,

and



E2 ;

R_3 is selected from hydrogen, -CF_3, -NH_2, -OH, alkyl optionally substituted with 1, 2 or 3 R_5, alkoxy, diethylaminoethoxy, ethylmethylaminoethoxy, dimethylaminoethoxy, cylcopentyl optionally substituted with arylalkoxy, cyclobutyl optionally substituted with arylalkoxy, cyclopropyl optionally substituted with arylalkoxy, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy, piperazinyl optionally substituted with alkyl or phenyl, morpholinyl optionally substituted with alkyl or phenyl, azetidinyl and piperidinyl optionally substituted with alkyl or phenyl, alkenyl, alkynyl, heterocycloalkyl selected from piperidinyl, pyrrolidinyl, morpholinyl and piperizinyl, wherein the heterocycloalkyl is optionally substituted with a group selected from alkyl, -C(O)O-alkyl and arylalkyl, arylalkyl optionally substituted with alkylheterocycloalkyl at any ring position of the aryl group, and heteroaryl;

each R_4, when present, is independently selected from methyl, 1-methylethylamino, ethylamino, 1-ethylpropylamino, 2-methylpropylamino, (2,2-

dimethylpropyl)amino, (2-aminoethyl)amino, (2,2,3,3,3-pentafluoropropyl)amino, 1-methylpropylamino, (1S)-1-methylpropylamino, (2,2,2-trifluoroethyl)amino, 1-propylbutylamino, propylamino, 1,2-dimethylpropylamino, (3,3,3-trifluoropropyl)amino, (2,2,3,3,4,4,4-heptafluorobutyl)amino, butylamino, 1,2,2-trimethylpropylamino, 1-[(methyloxy)methyl]propylamino, 1-methylethyloxyethylamino, 1-methylpropylamino, pentylamino, (2,2,3,3,3-pentafluoropropyl)amino, butylamino, 2-[(1-methylethyl)oxy]ethylamino, (1S)-1-methylpropylamino, (1R)-1-methylpropylamino, (1S)-1,2-dimethylpropylamino, 1-cyclopropylethylamino, (1R)-1,2-dimethylpropylamino, 1-ethyl-2-methylpropylamino, and 3-[(1-methylethyl)amino]propylamino;

R_6 is selected from hydrogen, $(C_1\text{-}C_4)$alkyl optionally substituted with hydroxy, $(C_1\text{-}C_3)$alkylamino or dimethylamino, $(C_1\text{-}C_4)$alkynyl optionally substituted with hydroxyl, and halo;

R_7 is selected from hydrogen, -OH, $-O(C_1\text{-}C_3)$alkyl, $-S(C_1\text{-}C_3)$alkyl, $-N(H)(C_1\text{-}C_3)$alkyl, $(C_5\text{-}C_6)$cycloalkylamino optionally substituted with hydroxyl, $(C_1\text{-}C_3)$alkylamino or dimethylamino, $-C(O)NH_2$, and $-O\text{-}C(O)NH_2$;

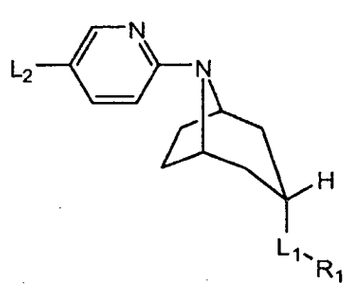
R_8 is selected from hydrogen, $-O(C_1\text{-}C_3)$alkyl, $-O\text{-}C(O)NH_2$, and $-C(=NH)\text{-}NH_2$;

L_1 is -N(H)C(O)-;

L_2 is $-C(O)\text{-}NH\text{-}R_3$ or $-C(O)\text{-}R_3$; and

each p is independently 0, 1, 2 or 3.

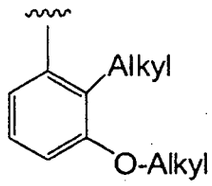
6. The compound according to claim 1 having Formula I:



I

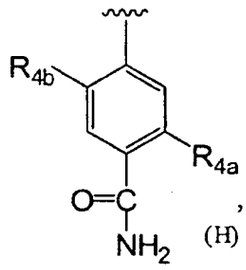
or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from:



(G)

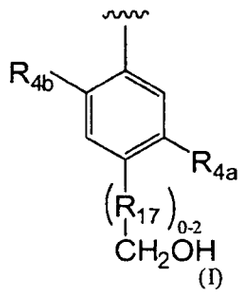
,



,

(H)

and



(I)

wherein R_{4a} is selected from hydrogen, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hydroxy, alkenyl, alkynyl, hydroxyalkynyl, alkoxy, halogen, hydroxyalkyl, dihydroxyalkyl, -O-C(O)-NH_2, amino(imino)alkyl, -C(O)-NH_2, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkyl optionally substituted with 1-8 halogens, dialkylamino, -N(H)alkylheterocycloalkyl, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkoxy, $-NH_2$, -O-alkyl-heterocycloalkyl, dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl optionally substituted with 1, 2 or 3 groups selected from alkyl, alkoxy and halogen;

R_{4b} is selected from H, halogen and methyl optionally substituted with 1-3 halogens;

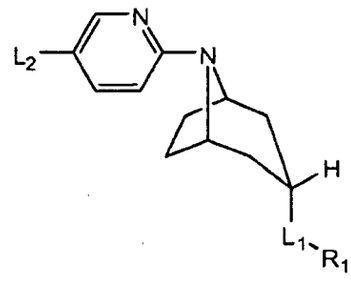
R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, alkyl, heterocycloalkyl, and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkyl, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl;

R_{17}, when present, is $-CH_2-$ or -CH(OH)-;

L_1 is selected from -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)C(O)NH-$, $-(CH_2)NHC(O)-$, $-(CH_2)NH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)NHSO_2-$, $-(CH_2)C(O)-$, $-(CH_2)O-$, and $-NH-(CH_2)-$; and

L_2 is -C(O)-NH-cyclopropyl or $-NH-C(O)-CH_3$.

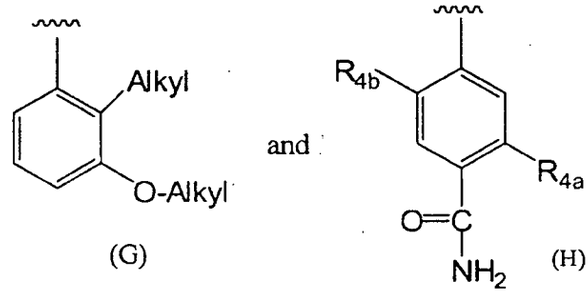
7. The compound according to claim 1 having Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from:



(G) (H)

wherein R_{4a} is selected from hydrogen, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hydroxy, alkenyl, alkynyl, hydroxyalkynyl, alkoxy, halogen, hydroxyalkyl, dihydroxyalkyl, -O-C(O)-NH_2, amino(imino)alkyl, -C(O)-NH_2, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkyl optionally substituted with 1-8 halogens, dialkylamino, -N(H)alkylheterocycloalkyl, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkoxy, $-NH_2$, -O-alkyl-heterocycloalkyl, dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl optionally substituted with 1, 2 or 3 groups selected from alkyl, alkoxy and halogen;

R_{4b} is selected from H, halogen and methyl optionally substituted with 1-3 halogens;

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, alkyl, heterocycloalkyl, and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted

with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkyl, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl;

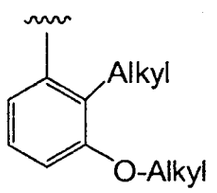
L_1 is selected from -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)C(O)NH-$, $-(CH_2)NHC(O)-$, $-(CH_2)NH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)NHSO_2-$, $-(CH_2)C(O)-$, $-(CH_2)O-$, and $-NH-(CH_2)-$; and

L_2 is -C(O)-NH-cyclopropyl or $-NH-C(O)-CH_3$.

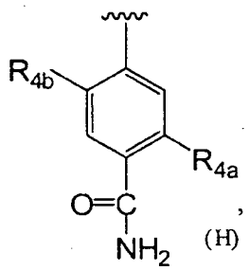
8. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein L_2 is -C(O)-NH-cyclopropyl, $-C(O)-NH-CH_3$, -C(O)-cyclopropyl, or $-C(O)-CH_3$.

9. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from one of the following of Group Z:

Group Z

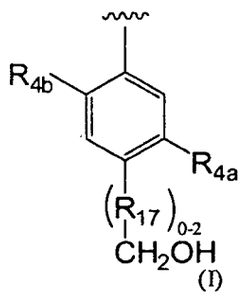


(G) ,



(H) ,

and



(I)

wherein R_{4a} is selected from hydrogen, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hydroxy, alkenyl, alkynyl, hydroxyalkynyl, alkoxy, halogen, hydroxyalkyl, dihydroxyalkyl, $-O-C(O)-NH_2$, amino(imino)alkyl, $-C(O)-NH_2$, -N(H)C(O)alkyl, alkylaminoalkyl, alkylaminoalkylamino, aminoalkylamino, arylalkylamino, heterocycloalkyl, dialkylaminoalkyl, alkyl optionally substituted with 1-8 halogens, dialkylamino, -N(H)alkylheterocycloalkyl, alkylsulfonylheterocycloalkylamino, cycloalkylalkylamino, cycloalkoxy, $-NH_2$, -O-alkyl-heterocycloalkyl,

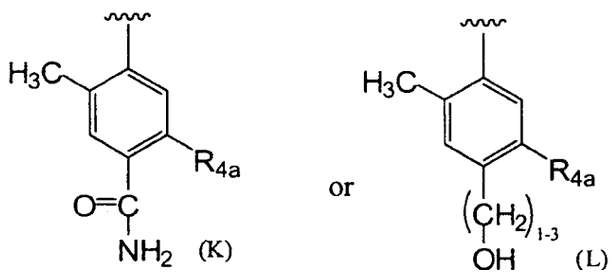
dialkylaminoalkoxy, alkylsulfonylalkylamino and -N(H)heterocycloalkyl optionally substituted with 1, 2 or 3 groups selected from alkyl, alkoxy and halogen;

R_{4b} is selected from H, halogen and methyl optionally substituted with 1-3 halogens;

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, alkyl, heterocycloalkyl, and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heterocycloalkylalkyl, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl; and

R_{17}, when present, is $-CH_2-$ or -CH(OH)-.

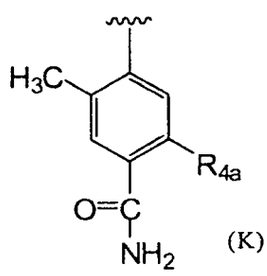
10. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is



wherein R_{4a} is selected from $-N(H)R_{16}$, $-OR_{16}$, and $-SR_{16}$; and

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, $-CH_3$ and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl.

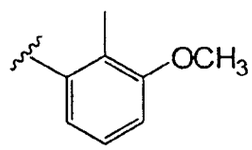
11. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is



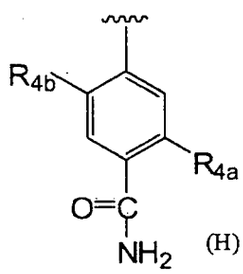
wherein R_{4a} is selected from $-N(H)R_{16}$, $-OR_{16}$, and $-SR_{16}$; and

R_{16} is selected from hydrogen, alkyl optionally substituted with 1-8 halogens, cycloalkyl optionally substituted with 1 or 2 groups selected from -OH, $-NH_2$, $-CH_3$ and $-CF_3$, cycloalkylalkyl, heterocycloalkyl optionally substituted with -OH or $-NH_2$, alkoxyalkyl, aryl optionally substituted with 1, 2 or 3 alkoxy, heteroaryl, gem-dicycloalkylalkyl and dialkylaminoalkyl.

12. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is

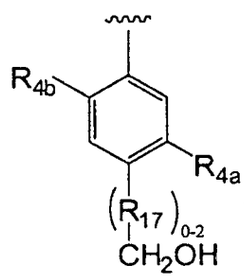


13. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is



(H)

or



(I)

wherein R_{4a} is alkylamino optionally substituted with 1-8 halogens;

R_{4b} is selected from H, halogen and methyl optionally substituted with 1-3 halogens;

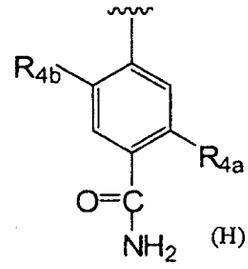
R_{17}, when present, is $-CH_2-$ or -CH(OH)-; and

L_1 is –N(H)C(O)-.

14. The compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein R_{4a} is 1-methylethylamino, ethylamino, 1-ethylpropylamino, 2-methylpropylamino, (2,2-dimethylpropyl)amino, (2-aminoethyl)amino, (2,2,3,3,3-pentafluoropropyl)amino, 1-methylpropylamino, (1S)-1-methylpropylamino, (2,2,2-trifluoroethyl)amino, 1-propylbutylamino, propylamino, 1,2-dimethylpropylamino, (3,3,3-trifluoropropyl)amino, (2,2,3,3,4,4,4-heptafluorobutyl)amino, butylamino, 1,2,2-trimethylpropylamino, 1-[(methyloxy)methyl]propylamino, 1-methylethyloxyethylamino, 1-methylpropylamino, pentylamino, (2,2,3,3,3-pentafluoropropyl)amino, butylamino, 2-[(1-methylethyl)oxy]ethylamino, (1S)-1-methylpropylamino, (1R)-1-methylpropylamino, (1S)-1,2-dimethylpropylamino, 1-

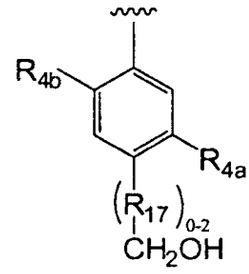
cyclopropylethylamino, (1R)-1,2-dimethylpropylamino, 1-ethyl-2-methylpropylamino, or 3-[(1-methylethyl)amino]propylamino.

15. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is



(H)

or



(I)

wherein R_{4a} is heterocycloalkylamino optionally substituted with alkyl;

R_{4b} is selected from H, halogen and methyl optionally substituted with 1-3 halogens;

R_{17}, when present, is $-CH_2-$ or -CH(OH)-; and

L_1 is –N(H)C(O)-.

16. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R_{4a} is tetrahydrofuran-3-ylamino, piperidin-4-ylamino, tetrahydro-2H-pyran-4-ylamino, (1-ethylpiperidin-4-yl)amino, (tetrahydrofuran-2-ylmethyl)amino, pyrrolidin-3-ylamino, (piperidin-3-ylmethyl)amino, (pyrrolidin-3-ylmethyl)amino, (3S)-tetrahydrofuran-3-ylamino, (3R)-tetrahydrofuran-3-ylamino, azetidin-1-yl, piperidin-1-ylamino, or (3S)-tetrahydrofuran-3-ylamino.

17. The compound according to Claim 1, wherein the compound of Formula I is selected from one of the following compounds:

NAME
N-cyclopropyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(methyloxy)ethyl]pyridine-3-carboxamide;
N-[2-(dimethylamino)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-morpholin-4-ylethyl)pyridine-3-carboxamide;

501

NAME
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyridin-3-ylmethyl)pyridine-3-carboxamide;
N-cyclopentyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide
N-[(2-chlorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(4-chlorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{2-[3,4-bis(methyloxy)phenyl]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-(furan-2-ylmethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-methylpropyl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(methyloxy)phenyl]methyl}pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(methyloxy)propyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-methylphenyl)methyl]pyridine-3-carboxamide;
N-(1,3-benzodioxol-5-ylmethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-prop-2-yn-1-ylpyridine-3-carboxamide;
N-{[3,4-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(4-methylpiperazin-1-yl)propyl]pyridine-3-carboxamide;
N-[2-(ethylthio)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S,2S)-2-[(phenylmethyl)oxy]cyclopentyl}pyridine-3-carboxamide;
N-[(6-chloropyridin-3-yl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(2-chloro-6-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;

NAME
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(methylthio)ethyl]pyridine-3-carboxamide;;
N-butyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(3-morpholin-4-ylpropyl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-pyridin-4-ylethyl)pyridine-3-carboxamide;
N-{2-[(1-methylethyl)oxy]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-pyridin-3-ylethyl)pyridine-3-carboxamide;
N-[4,4-bis(methyloxy)butyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(5-methylpyrazin-2-yl)methyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-endo-(propyloxy)propyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[3,4,5-tris(methyloxy)phenyl]methyl}pyridine-3-carboxamide;
N-{[3,5-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-({4-[(trifluoromethyl)oxy]phenyl}methyl)pyridine-3-carboxamide;
N-(cyclopropylmethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{[2,4-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(4-bromophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3S)-1-(phenylmethyl)pyrrolidin-3-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3R)-1-(phenylmethyl)pyrrolidin-3-yl]pyridine-3-carboxamide;

NAME
N-[3-(diethylamino)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{3-[(1-methylethyl)oxy]propyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-propylpyridine-3-carboxamide
N-[2-(diethylamino)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide
N-(3-methylbutyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3-methylphenyl)methyl]pyridine-3-carboxamide;
N-[(3-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2-methylphenyl)methyl]pyridine-3-carboxamide;
N-[(3-chlorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(tetrahydrofuran-2-ylmethyl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(1-methylpyrrolidin-2-yl)ethyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-piperidin-1-ylethyl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[2-(methyloxy)phenyl]methyl}pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[3-(methyloxy)phenyl]methyl}pyridine-3-carboxamide;
N-[(2-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(4-fluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-yl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;

NAME
N-(3,3-dimethylbutyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{[2,3-bis(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{[2-(ethyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[1-(phenylmethyl)piperidin-4-yl]pyridine-3-carboxamide;
ethyl 4-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino]piperidine-1-carboxylate;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-thienylmethyl)pyridine-3-carboxamide;
N-cyclobutyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[3-(ethyloxy)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[3-(dimethylamino)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(trifluoromethyl)phenyl]methyl}pyridine-3-carboxamide;
N-[(2,4-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(2,5-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(2,6-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(3,4-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[3-(1H-imidazol-1-yl)propyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(2-methylphenyl)pyridine-3-carboxamide;
N-(3,5-dimethylphenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-1,3-benzodioxol-5-yl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;

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6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(4-methylphenyl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(3-methylphenyl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[2-(methyloxy)phenyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[3-(methyloxy)phenyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[4-(methyloxy)phenyl]pyridine-3-carboxamide;
N-(3-chlorophenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-(4-fluorophenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[3-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-morpholin-4-ylphenyl)methyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3R)-pyrrolidin-3-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-piperidin-3-ylpyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-piperidin-4-ylpyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyrrolidin-3-ylmethyl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(1-methylpiperidin-4-yl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide;
N-(1-methylethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-cyclohexyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-methyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;

NAME
N-ethyl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(1S)-1,2-dimethylpropyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(1R)-1,2-dimethylpropyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(1S)-1-methyl-2-(methyloxy)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-azetidin-3-yl-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[4-(1-methylpiperidin-4-yl)phenyl]methyl}pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1R)-1-[4-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1R)-1-phenylethyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1S)-1-phenylethyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1S)-1-phenylpropyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-((1-phenylethyl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide;
N-[(1S)-1-(4-chlorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{(1S)-1-[2-fluoro-4-(methyloxy)phenyl]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{[2-fluoro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(2-chloro-3,6-difluorophenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(4-{[2-(diethylamino)ethyl]oxy}phenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;

NAME
N-[(1S)-2-amino-1-methyl-2-oxoethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(3-{[2-(diethylamino)ethyl]oxy}phenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{[4-fluoro-3-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{[3-fluoro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{[2-chloro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2,4,6-trifluorophenyl)methyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[3-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide;
N-{[2,6-difluoro-4-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(2-chloro-6-fluoro-3-methylphenyl)methyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[1-(4-chlorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(1-phenylpiperidin-4-yl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-pyrrolidin-1-ylphenyl)methyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2,3,6-trifluorophenyl)methyl]pyridine-3-carboxamide;
N-{[2-fluoro-6-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{[4-fluoro-2-(methyloxy)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{[2-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(2,4,5-trifluorophenyl)methyl]pyridine-3-carboxamide;
N-{[3-fluoro-4-(4-methylpiperazin-1-yl)phenyl]methyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;

NAME
N-(8-{5-[({[4-(4-methylpiperazin-1-yl)phenyl]methyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
N-[(1S)-1-(4-{[2-(diethylamino)ethyl]oxy}-2-fluorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[4-(4-methylpiperazin-1-yl)phenyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[4-(1-methylpiperidin-4-yl)phenyl]pyridine-3-carboxamide;
N-(4-{[2-(dimethylamino)ethyl]oxy}phenyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-hydroxy-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{8-[5-(hydrazinocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-3-(methyloxy)benzamide;
N-[(1S)-1-(4-{[2-(diethylamino)ethyl]oxy}phenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[1-(6-piperazin-1-ylpyridin-3-yl)ethyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(4-piperazin-1-ylphenyl)methyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-({4-[4-(2-methylpropyl)piperazin-1-yl]phenyl}methyl)pyridine-3-carboxamide;
N-[1-(4-bromo-2-fluorophenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{1-[3,4-bis(methyloxy)phenyl]ethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(1S)-1-methylpropyl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3R)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(3S)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide;
N-(2,3-dihydroxypropyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(1S,2S)-2-hydroxycyclopentyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;

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N-[(1S,2S)-2-hydroxycyclohexyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(1S)-2-hydroxy-1-methylethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[(2S)-2-hydroxypropyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-(2-hydroxyethyl)-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
2-[(1-ethylpropyl)amino]-N4-[8-(5-{[(3R)-pyrrolidin-3-ylamino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
2-[(1-ethylpropyl)amino]-N4-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(1-ethylpropyl)amino]-N4-{8-[5-({[(3S)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(1-ethylpropyl)amino]-N4-{8-[5-({[(3R)-1-ethylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
5-[(1-ethylpropyl)amino]-2-methyl-N-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(1-ethylpropyl)amino]-N4-[8-(5-{[(3S)-piperidin-3-ylamino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
5-[(1-ethylpropyl)amino]-2-methyl-N-{8-[5-({[(3R)-1-(1-methylethyl)piperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
6-(3-endo-{[(2,3-dimethylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide;
6-(3-endo-{[(3-hydroxy-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide;
6-(3-endo-{[(3-amino-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide;
N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
2-methyl-N1-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide;

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2-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,3-dicarboxamide;
3-methyl-4-({[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]amino}carbonyl)phenyl carbamate;
2-methyl-3-({[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]amino}carbonyl)phenyl carbamate;
6-[3-endo-({[4-(hydroxymethyl)-2-methylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide;
6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyridin-3-ylmethyl)pyridine-3-carboxamide;
N-[8-(5-{[(pyridin-3-ylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-[(5-methylpyrazin-2-yl)methyl]pyridine-3-carboxamide;
N-{8-[5-({[(5-methylpyrazin-2-yl)methyl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
6-[3-endo-({[4-(hydroxymethyl)-2-methylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(pyridin-3-ylmethyl)pyridine-3-carboxamide;
6-{3-endo-[({4-[amino(imino)methyl]phenyl}carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-N-(phenylmethyl)pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3,4-bis(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide;
6-[3-endo-({[3-(methyloxy)-2-propylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide;
6-[3-endo-({[3-(methyloxy)-2-prop-2-en-1-ylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide;
6-[3-endo-({[2-bromo-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide;
6-[3-endo-({[2-iodo-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide;
2,6-dimethyl-N1-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
N4-(8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide;
N4-(8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[2-(methylsulfonyl)ethyl]amino}benzene-1,4-dicarboxamide;

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N4-{8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(4-trans-hydroxycyclohexyl)amino]benzene-1,4-dicarboxamide;
2-[(4-trans-hydroxycyclohexyl)amino]-N4-{8-[5-({[1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-[8-{5-{[methyl(methyloxy)amino]carbonyl}pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
N4-{8-{5-[(cyclopentylamino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
5-[(1-ethylpropyl)amino]-N-{8-[5-({[(1-ethylpyrrolidin-2-yl)methyl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide;
6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-fluoro-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-chloro-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-(3-endo-{[(4-amino-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
6-[3-endo-({[4-(hydroxymethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
6-[3-endo-({[4-(hydroxymethyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-(4-hydroxybut-1-yn-1-yl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-({[2-(methyloxy)ethyl]amino}benzene-1,4-dicarboxamide;
N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(2-morpholin-4-ylethyl)oxybenzene-1,4-dicarboxylate;
N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(4-hydroxycyclohexyl)amino]benzene-1,4-dicarboxamide;
2-(acetylamino)-N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;

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N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[2-(methylsulfonyl)ethyl]amino}benzene-1,4-dicarboxamide;
N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(cyclobutylamino)benzene-1,4-dicarboxamide;
2,5-dimethyl-N-{8-[5-({[(3S)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
6-(3-endo-{[(3-hydroxy-2-methylphenyl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide;
4-methyl-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1H-1,2,3-benzotriazole-5-carboxamide;
2-(methyloxy)-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
6-[3-endo-({[2-methyl-3-(methylamino)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide;
6-[3-endo-({[3-(dimethylamino)-2-methylphenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide;
6-[3-endo-({[2-methyl-3-(methylthio)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide;
2-(cyclobutyloxy)-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
2-methyl-3-(methyloxy)-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
2-(cyclobutylamino)-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[3,4,5-tris(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide;
N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-(phenylamino)benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-(pyridin-4-ylamino)benzene-1,4-dicarboxylate;
N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[1-(methylsulfonyl)piperidin-4-yl]amino}benzene-1,4-dicarboxamide;
3-(ethylamino)-2,5-dimethyl-N1-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;

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2-[(4-hydroxycyclohexyl)amino]-N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
N4-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2-{[2-(methylsulfonyl)ethyl]amino}benzene-1,4-dicarboxamide;
6-{3-endo-[({3-[(4-hydroxycyclohexyl)amino]phenyl}carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide;
2,5-dimethyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
2,5-dichloro-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
2,5-dimethyl-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
N-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide;
2,5-dimethyl-N-{8-[5-({[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2,5-dimethyl-N-{8-[5-({[(3S)-1-methylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
N-{8-[5-({[(3R)-1-ethylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide;
2,5-dimethyl-N-{8-[5-({[(3R)-1-methylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2,5-dimethyl-N-{8-[5-({[(3R)-1-methylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2,5-dimethyl-N-[8-(5-{[(1-methylpiperidin-4-yl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
N-[8-(5-{[(1-ethylpiperidin-4-yl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2,5-dimethylbenzene-1,4-dicarboxamide;
2,5-dimethyl-N-{8-[5-({[1-(1-methylethyl)piperidin-4-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
N-{8-[5-({[(3S)-1-ethylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide;
2,5-dimethyl-N-{8-[5-({[(3R)-1-(1-methylethyl)piperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
N-{8-[5-({[(3S)-1-ethylpiperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide;

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NAME
2,5-dimethyl-N-{8-[5-({[(3S)-1-(1-methylethyl)piperidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2,5-dimethyl-N-{8-[5-({[(3S)-1-methylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
N-{8-[5-({[(3R)-1-ethylpyrrolidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2,5-dimethylbenzene-1,4-dicarboxamide;
N-[8-(5-{[(1-ethylazetidin-3-yl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2,5-dimethylbenzene-1,4-dicarboxamide;
2,5-dimethyl-N-{8-[5-({[1-(1-methylethyl)azetidin-3-yl]amino}carbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2,5-dimethyl-N-[8-(5-{[(1-methylazetidin-3-yl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
methyl (2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoate;
(2S)-[({6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridin-3-yl}carbonyl)amino][4-(methyloxy)phenyl]ethanoic acid;
N-{(1S)-2-amino-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{(1S)-2-(methylamino)-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-{(1S)-2-(ethylamino)-1-[4-(methyloxy)phenyl]-2-oxoethyl}-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N4-{8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(2-morpholin-4-ylethyl)amino]benzene-1,4-dicarboxamide;
N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide;
N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(trans-4-aminocyclohexyl)amino]benzene-1,4-dicarboxamide;
N-[1-(2-fluoro-4-piperidin-4-ylphenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
N-[1-(2,6-difluoro-4-piperidin-4-ylphenyl)ethyl]-6-[3-endo-({[2-methyl-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[2-(3-hydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide;
6-[3-endo-({[2-(3-hydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;

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6-[3-endo-({[2-{3-[(1-methylethyl)amino]propyl}-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide;
6-[3-endo-({[2-(4-hydroxybutyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-{3-endo-[({2-[4-(dimethylamino)butyl]-3-(methyloxy)phenyl}carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}pyridine-3-carboxamide;
6-[3-endo-({[2-(2,3-dihydroxypropyl)-3-(methyloxy)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]pyridine-3-carboxamide;
6-[3-endo-({[4-(1,2-dihydroxyethyl)phenyl]carbonyl}amino)-8-azabicyclo[3.2.1]oct-8-yl]-N-(phenylmethyl)pyridine-3-carboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(trans-4-hydroxycyclohexyl)amino]benzene-1,4-dicarboxamide;
N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-methyl-3-(methyloxy)benzamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(cyclohexylamino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(cyclopentylamino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(piperidin-4-ylamino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-methylethyl)amino]benzene-1,4-dicarboxamide;
N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-5-[(trans-4-hydroxycyclohexyl)amino]-2-methylbenzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(ethylamino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(cyclopropylamino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2-methylpropyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(tetrahydrofuran-3-ylamino)benzene-1,4-dicarboxamide;

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2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-methylbutanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-[8-(5-propanoylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(tetrahydro-2H-pyran-4-ylamino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-ethylpiperidin-4-yl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2-dimethylpropyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(tetrahydrofuran-2-ylmethyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(pyrrolidin-3-ylamino)benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(4,4,4-trifluorobutanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(phenylamino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2-aminoethyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2,3,3,3-pentafluoropropyl)amino]benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(2-methylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(piperidin-3-ylmethyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(pyrrolidin-3-ylmethyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-butanoylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(phenylmethyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(3S)-tetrahydrofuran-3-ylamino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-methylpropyl)amino]benzene-1,4-dicarboxamide;

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N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-5-[(1-ethylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2,2-trifluoroethyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(3R)-tetrahydrofuran-3-ylamino]benzene-1,4-dicarboxamide;
;N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-{[3-{[2-(dimethylamino)ethyl]oxy}-4-(methyloxy)phenyl]amino}benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopentylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclobutylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-aminobenzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1-propylbutyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(propylamino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-azetidin-1-ylbenzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-bromobenzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1,2-dimethylpropyl)amino]benzene-1,4-dicarboxamide;
N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-5-[(1-ethylpropyl)amino]-2-fluorobenzene-1,4-dicarboxamide;
N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-methyl-5-{[4-(trifluoromethyl)cyclohexyl]amino}benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(2,2,3,3,4,4,4-heptafluorobutyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(3,3,3-trifluoropropyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(butylamino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(3-{[2-(dimethylamino)ethyl]oxy}phenyl)amino]benzene-1,4-dicarboxamide;

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N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-[(1,2,2-trimethylpropyl)amino]benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-(piperidin-1-ylamino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({1-[(methyloxy)methyl]propyl}amino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({2-[(1-methylethyl)oxy]ethyl}amino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-{[(1S)-1-methylpropyl]amino}benzene-1,4-dicarboxamide;
N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-methyl-5-(pentylamino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({4-(methyloxy)-3-[(2-morpholin-4-ylethyl)oxy]phenyl}amino)benzene-1,4-dicarboxamide;
N4-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2-({3-[(1-methylethyl)amino]propyl}amino)benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(pyridin-4-ylamino)benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(2,2,3,3,3-pentafluoropropyl)amino]benzene-1,4-dicarboxamide;
2-chloro-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide;
2-(cyclopentylamino)-N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(3S)-tetrahydrofuran-3-ylamino]benzene-1,4-dicarboxamide;
2-(butylamino)-N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-({2-[(1-methylethyl)oxy]ethyl}amino)benzene-1,4-dicarboxamide;

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NAME
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cis-4-hydroxy-4-methylcyclohexyl)amino]benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1S)-1-methylpropyl]amino}benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(1-methylpropyl)amino]benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-(propylamino)benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]-2-fluorobenzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(trans-4-piperidin-1-ylcyclohexyl)amino]benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1S)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(1-cyclopropylethyl)amino]benzene-1,4-dicarboxamide;
N4-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-{[(1R)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethyl-2-methylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-cyclopropylethyl)amino]-2-methylbenzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-cyclopropylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[(1R)-1,2,2-trimethylpropyl]amino}benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1R)-1,2-dimethylpropyl]amino}-2-methylbenzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(3,3,3-trifluoro-1-methylpropyl)amino]benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[2-methyl-1-(trifluoromethyl)propyl]amino}benzene-1,4-dicarboxamide;

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NAME
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[2-methyl-1-(1-methylethyl)propyl]amino}benzene-1,4-dicarboxamide;
2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(1-methylethyl)amino]benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(dicyclopropylmethyl)amino]-2-methylbenzene-1,4-dicarboxamide;
5-(cyclopentylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[1-(trifluoromethyl)propyl]amino}benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(2-methylpropyl)amino]benzene-1,4-dicarboxamide;
5-[(cyclopentylmethyl)amino]-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide;
5-(cyclobutylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methylbenzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[(1S)-1-methylpropyl]amino}benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-ethylpropyl)amino]-2-(trifluoromethyl)benzene-1,4-dicarboxamide;
2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1R)-1-methylpropyl]amino}benzene-1,4-dicarboxamide;
2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(1-methylethyl)amino]benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(2,2-dimethylpropyl)amino]-2-methylbenzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(cyclopropylmethyl)amino]-2-methylbenzene-1,4-dicarboxamide;
2-bromo-5-(cyclopentylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(2-methylpropyl)amino]benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-[(3,3,3-trifluoropropyl)amino]benzene-1,4-dicarboxamide;

NAME
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-(propylamino)benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-methyl-5-{[1-(1-methylcyclopropyl)ethyl]amino}benzene-1,4-dicarboxamide;
2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(2,2-dimethylpropyl)amino]benzene-1,4-dicarboxamide;
2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1R)-1,2-dimethylpropyl]amino}benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[2-fluoro-1-(fluoromethyl)ethyl]amino}-2-methylbenzene-1,4-dicarboxamide;
2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-(propylamino)benzene-1,4-dicarboxamide;
N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-{[(1R)-1-methylpropyl]amino}-2-(trifluoromethyl)benzene-1,4-dicarboxamide;
2-bromo-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-5-[(3,3,3-trifluoropropyl)amino]benzene-1,4-dicarboxamide;
2-bromo-5-(cyclobutylamino)-N-{8-[5-(cyclopropylcarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(1-methylpiperidin-4-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-hydroxy-4-methylpentanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-phenylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-hydroxy-3-phenylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(4-methylpentanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
N4-{8-[5-(3-cyclohexylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-2-[(cyclopropylmethyl)amino]benzene-1,4-dicarboxamide;
5-[(1-ethylpropyl)amino]-2-methyl-N-(8-{5-[3-(1-methylpiperidin-4-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-piperidin-4-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(N,N-dimethyl-beta-alanyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;

NAME
2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(methyloxy)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-piperidin-1-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(ethyloxy)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-(8-{5-[N-(4-fluorophenyl)-beta-alanyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-morpholin-4-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(4-methylpiperazin-1-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(3-pyrrolidin-1-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-(8-{5-[3-(4-phenylpiperazin-1-yl)propanoyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)benzene-1,4-dicarboxamide;
2-[(1-ethylpropyl)amino]-N4-{8-[5-(3-piperidin-1-ylpropanoyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(piperidin-1-ylacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
N-[8-(5-acetylpyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-2,5-dimethylbenzene-1,4-dicarboxamide; and
2-[(cyclopropylmethyl)amino]-N4-{8-[5-(trifluoroacetyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}benzene-1,4-dicarboxamide;
or a pharmaceutically acceptable salt of any of the above compounds.

18. A pharmaceutical composition comprising the compound according to any of claims 1-17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

19. A method of inhibiting HSP90 in a cell, comprising contacting the cell, in which inhibition of HSP90 is desired, with the compound according to any of claims 1-17, or a pharmaceutically acceptable salt thereof.

20. A method of treating a disease or condition that involves HSP90 comprising administering to an animal, in need of said treatment, the compound according to any

of claims 1-17, or a pharmaceutically acceptable salt thereof.

21. The method according to claim 20, wherein the disease being treated is selected from breast cancer, CML, colorectal carcinoma, glioma, melanoma, multiple myeloma, non-small cell lung cancer, ovarian cancer, prostate cancer, renal cell carcinoma, small cell lung carcinoma, and unfolded protein response.

22. The method according to claim 20, wherein the disease being treated is selected from neurodegenerative disease, infectious disease, inflammatory disease, autoimmune disorder, stroke, ischemia, cardiac disorder, sepsis, fibrogenetic disorder and metabolic disease.

23. The method according to claim 20, wherein the disease being treated is a neurodegenerative disease characterized by accumulation of hyperphosphorylated or mutated forms of the microtubule-associated protein Tau.

24. A method of degrading aberrant Tau proteins in an animal, comprising administering a compound according to any of claims 1-17 to said animal.

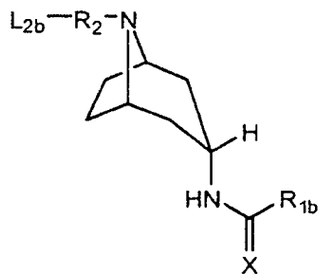
25. The method according to claim 20, wherein the disease being treated is infection from negative strand RNA viruses, influenza virus, hepatitis B, hepatitis C or herpes simplex virus type 1.

26. The method according to claim 20, further comprising administering radiation treatment or one or more therapeutic agents selected from Camptothecin, Topotecan, 9-Nitrocamptothecin, 9-Aminocamptothecin, Karenitecin, Irinotecan, Etoposide, Etoposide Phosphate, Teniposide, Amsacrine, Razoxane, Dexrazoxane, Mechlorethamine, Cyclophosphamide, Ifosfamide, Chlorambucil, Melphalan, Thiotepa, Trenimon, Triethylenemelamine, Dianhydrogalactitol, Dibromodulcitol, Busulfan, dimethylsulfate, Chloroethylnitrosourea, Carmustine, Lomustine, Methyl-Lomustine, Streptozotocin, Chlorozotocin, Prednimustine, Estramustine, Procarbazine, Dacarbazine, Hexamethylmelamine, Pentamethylmelamine, Temozolomide, Cisplatin, Carboplatin, Oxaliplatin, Bleomycin, Dactinomycin, Mithramycin, Rapamycin, Mitomycin C, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Methotrexate, Edatrexate, Trimethoprim, Nolatrexed, Raltitrexed, Hydroxyurea, 5-fluorouracil, Ftorafur, Capecitabine, Furtulon, Eniluracil, ara-C, 5-azacytidine, Gemcitabine, Mercaptopurine, Thioguanine, Pentostatin, antisense DNA, antisense RNA, an antisense DNA/RNA hybrid, a ribozyme, ultraviolet radiation,

Vincristine, Vinblastine, Paclitaxel, Docetaxel, L-Asparaginase, a kinase inhibitor, Imatinib, Mitotane, Aminoglutethimide, Diethylstilbestrol, Ethinyl estradiol, Tamoxifen, Anastrozole, Testosterone propionate, Fluoxymesterone, Flutamide, Leuprolide, Prednisone, Hydroxyprogesterone caproate, Medroxyprogesterone acetate, Megestrol acetate, Interferon-alfa, and Interleukin.

27. The method according to claim 20, further comprising administering radiation treatment or one or more therapeutic agents selected from proteosome inhibitors, EGFR inhibitors and DNA damaging agents.

28. A compound according to Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

R_{1b} is selected from heteroaryl optionally substituted with 1, 2 or 3 groups selected from halogen, phenyl and alkyl;

R_2 is a phenyl or a heteroaryl that can contain 1, 2 or 3 heteroatoms, wherein the aryl or heteroaryl can be substituted with 1, 2 or 3 groups selected from alkyl, -OH, alkoxy, and halogen;

R_{3b} is selected from hydrogen, $-CF_3$, $-NH_2$, -OH, alkyl optionally substituted with 1, 2 or 3 R_{5b}, alkoxy, dialkylaminoalkyl, cycloalkyl optionally substituted with arylalkoxy, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl, alkoxy, dialkylaminoalkoxy and heterocycloalkyl optionally substituted with alkyl or aryl, alkenyl, alkynyl, heterocycloalkyl optionally substituted with a group selected from alkyl, -C(O)O-alkyl and arylalkyl, arylalkyl optionally substituted with alkylheterocycloalkyl at any ring position of the aryl group, and heteroaryl;

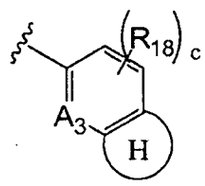
R_{5b} is selected from halogen, cycloalkyl, heteroaryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl and alkoxy, alkylthio, heterocycloalkyl optionally substituted with 1, 2, or 3 groups selected from alkyl, halogen, phenyl and oxo, aryl optionally substituted with 1, 2 or 3 groups selected from halogen, alkyl,

alkoxy, dialkylaminoalkoxy and heterocycloalkyl optionally substituted with alkyl, alkoxy, dialkylamino, -OH, -C(O)-NH_2, -C(O)-O-CH_3, -C(O)-N(H)(C_1-C_3)alkyl, heteroarylamino optionally substituted with halogen and -OCF_3;

L_{2b} is -C(O)-NH-R_{3b}, -CN or -C(O)-R_{3b}; and

X is O or S.

29. The compound according to claim 28, wheren R_{1b} is



(O)

wherein:

A_3 is =N- or =CH-;

each R_{18} is independently selected from -NH_2, halogen and alkyl;

the (H) ring is a 5 or 6 membered heterocyclic ring fused to the two carbon atoms to which the (H) ring is attached, wherein the (H) ring contains 1, 2 or 3 heteroatoms selected from N, O or S; and

c is 0, 1 or 2.

30. The compound according to claim 29, wherein Formula (O) is selected from 1H-benzimidazole optionally substituted with 1 or 2 methyl groups, 1H-indole optionally substituted with 1 or 2 methyl groups, benzofuran, 3,4-dihydro-2H-chromenyl optionally substituted with 1 or 2 methyl groups, 2,3-dihydrobenzofuranyl optionally substituted with 1 or 2 methyl groups, 2,3-dihydro-1,4-benzodioxin-6-yl optionally substituted with 1 or 2 methyl groups, 1H-1,2,3-benzotriazole optionally substituted with 1, 2 or 3 methyl groups, 9H-purin-9-yl optionally substituted with 1 or 2 groups selected from halogen and amino, 1,3-benzothiazole optionally substituted with 1 or 2 methyl groups, and 2,3-dihydro-1-benzofuran optionally substituted with 1 or 2 methyl groups.

31. The compound according to Claim 28, wherein the compound of Formula II is selected from one of the following compounds:

1,4-dimethyl-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1H-benzimidazole-5-carboxamide;
N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1,3-benzothiazole-5-carboxamide;
4-methyl-N-(8-{5-[({(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1H-1,2,3-benzotriazole-5-carboxamide;
6-(3-endo-{[(8-methyl-3,4-dihydro-2H-chromen-7-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(1-methylpiperidin-4-yl)phenyl]methyl}pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide;
N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-benzimidazole-5-carboxamide;
N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-indole-4-carboxamide;
6-(3-endo-{[(2-amino-6-chloro-9H-purin-9-yl)acetyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide;
6-(3-endo-{[(5-methyl-2,3-dihydro-1,4-benzodioxin-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide;
6-(3-endo-{[(4-methyl-1,3-benzodioxol-5-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide;
8-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]quinoline-7-carboxamide;
6-(3-endo-{[(8-methyl-3,4-dihydro-2H-chromen-7-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(phenylmethyl)pyridine-3-carboxamide;
4-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-benzimidazole-5-carboxamide;

4-methyl-N-(8-{5-[({[4-(4-methylpiperazin-1-yl)phenyl]methyl}amino)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-1H-benzimidazole-5-carboxamide;
6-(3-endo-{[(5-methyl-2,3-dihydro-1,4-benzodioxin-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide;
N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-indole-6-carboxamide;
1-methyl-N-[8-(5-{[(phenylmethyl)amino]carbonyl}pyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-endo-yl]-1H-indole-4-carboxamide;
N4-{8-[5-(aminocarbonyl)pyridin-2-yl]-8-azabicyclo[3.2.1]oct-3-endo-yl}-1H-indole-4,7-dicarboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[3-(methyloxy)phenyl]ethyl}pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{(1S)-1-[4-(4-methylpiperazin-1-yl)phenyl]ethyl}pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-{[4-(1-methylpiperidin-4-yl)phenyl]methyl}pyridine-3-carboxamide;
N-[(4-{[2-(diethylamino)ethyl]oxy}phenyl)methyl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
N-(cyclopropylmethyl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
N-[2-(diethylamino)ethyl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-methylpyrrolidin-3-yl]pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-(1-methylpiperidin-4-yl)pyridine-3-carboxamide;
N-[(1S)-1-(4-{[2-(diethylamino)ethyl]oxy}phenyl)ethyl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
7-methyl-N-(8-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-8-azabicyclo[3.2.1]oct-3-endo-yl)-2,3-dihydro-1-benzofuran-6-carboxamide;

N-(1-ethylpiperidin-3-yl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-methylpiperidin-3-yl]pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-(1-methylethyl)pyrrolidin-3-yl]pyridine-3-carboxamide;
N-[(3S)-1-ethylpyrrolidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[1-(1-methylethyl)piperidin-4-yl]pyridine-3-carboxamide;
N-(1-ethylpiperidin-4-yl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
N-[(3R)-1-ethylpiperidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
N-(1-ethylazetidin-3-yl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[1-(1-methylethyl)azetidin-3-yl]pyridine-3-carboxamide;
N-(1-methylazetidin-3-yl)-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
N-[(3R)-1-ethylpyrrolidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-(1-methylethyl)piperidin-3-yl]pyridine-3-carboxamide;
N-[(3S)-1-ethylpiperidin-3-yl]-6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)pyridine-3-carboxamide;
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3S)-1-(1-methylethyl)piperidin-3-yl]pyridine-3-carboxamide; and
6-(3-endo-{[(7-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-N-[(3R)-1-methylpiperidin-3-yl]pyridine-3-carboxamide,
or a pharmaceutically acceptable salt of any of the above compounds.

32. A pharmaceutical composition comprising the compound according any of claims 28-31, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

33. A method of treating a disease or condition that involves HSP90 comprising administering to an animal, in need of said treatment, the compound according to any of claims 28-31, or a pharmaceutically acceptable salt thereof.

34. The method according to claim 33, wherein the disease being treated is selected from breast cancer, CML, colorectal carcinoma, glioma, melanoma, multiple myeloma, non-small cell lung cancer, ovarian cancer, prostate cancer, renal cell carcinoma, small cell lung carcinoma, unfolded protein response, neurodegenerative disease, infectious disease, inflammatory disease, autoimmune disorder, stroke, ischemia, cardiac disorder, sepsis, fibrogenetic disorder, d metabolic disease, infection from negative strand RNA viruses, influenza virus, hepatitis B, hepatitis C, and herpes simplex virus type 1.

COMPUESTOS DE TROPANO

CAMPO DE LA INVENCIÓN

[0001] Esta descripción se refiere a, ciertos compuestos de tropano. En particular, esta descripción se refiere a ciertos compuestos de tropano útiles como inhibidores de HSP90.

ANTECEDENTES DE LA INVENCIÓN

[0002] La HSP90 (proteína de golpe de calor 90), es una de las proteínas celulares más abundantes. Existen al menos, cuatro miembros de la familia HSP90 en el genoma humano: la HSP90 inducible por estrés (HSP90α o HSP90AA1), la HSP90β citosólica constitutiva (HSP90AB1), la GRP94 localizad en el retículo endoplásmico (HSP90B), y la TRAP1 mitocondrial [2]. La HSP90 contiene aproximadamente 730 aminoácidos arreglados como 3 dominios principales: un dominio de enlace ATP N-terminal, un dominio central y un dominio de dimerización C-terminal. La HSP90 actúa principalmente como chaperona molecular, promoviendo el repliegue y estabilización de muchas proteínas celulares lábiles. En general, la HSP90 actúa en conjunto con la maquinaria de chaperona de HSP70, y también recluta múltiples proteínas co-chaperonas para regular su actividad. Más de 100 sustratos de HSP90 ("proteínas cliente"), han sido descritos en la técnica. La

HSP90 constituye ~1-2% de la proteína total en células normales y esta concentración puede doblarse bajo condiciones de estrés, reflejando su importancia en el mantenimiento de la homeostasis celular.

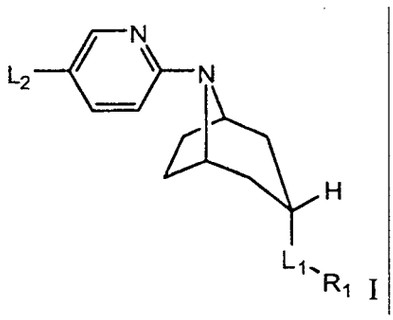
[0003] La expresión y actividad de HSP90 es frecuentemente sobre regulada en células tumorales y es particularmente asociada con escasa prognosis en cáncer de mama. Además, la HSP90 en células tumorales, parece existir en un estado hiperactivado con actividad de ATPasa elevada, la cual es altamente sensible a la inhibición de HSP90, comparada con la forma ampliamente latente encontrada en células normales. Este estado hiperactividado sugiere que los inhibidores de HSP90 puedan selectivamente dirigir células tumorales, con impacto relativamente bajo en tejidos normales. Muchas proteínas cliente de HSP90 están involucradas en varios aspectos de crecimiento y progreso del tumor. La HSP90 promueve el repliegue y/o estabilización de muchas proteínas oncogénicas que confieren crecimiento autónomo en las células (por ejemplo, EGFR y ErbB2, receptores de la hormona esteroide y B-Raf, y también regulan múltiples proteínas que promueven la supervivencia de células tumorales (por ejemplo, receptor IGF-1, PDK1 y Akt, RIP, IκB y survivina. La HSP90 puede también promover el progreso del ciclo celular aberrante estabilizando Cdk4, Cdk6 y ciclina D, Cdk2, y Plk1. Contrariamente, los inhibidores de HSP90 pueden regular

descendentemente la cinasa de punto de verificación del ciclo celular Chk1 y sensibilizar tumores a varias formas de quimioterapia. La inhibición de HSP90 puede también despuntar la angiogénesis de tumor, puesto que el factor inducible de hipoxia (HIF-1α) y las tirosinas cinasas del receptor del factor de crecimiento endoteliar vascular (VEGF) son clientes HSP90. La tirosina cinasa del receptor Met, la cual estimula la movilidad celular, migración e invasión, es también regulada descendentemente en respuesta a la inhibición de HSP90, ambas directamente y vía inhibición de HIF-1α. Aparte de su papel como chaperona celular, la HSP90α ha sido también implicada en la degradación de matriz extracelular e invasión de células tumorales, vía activación (y posiblemente estabilización) de la metaloproteinasa de matriz MMP2. La depleción o inhibición de HSP90 promueve la erosión de telómero y apoptósis, y también puede permitir la evolución de fenotipos resistentes al fármaco y metastásicos, heterogéneos, permitiendo la propagación de mutaciones metastables. La HSP90 ha sido implicada en la activación de la respuesta de proteína no plegada (UPR). La falla de la UPR (por ejemplo, vía inhibición de HSP90), conduce a una señal de estrés de ER y apoptosis. Por lo tanto, los inhibidores de HSP90 pueden promover la muerte de células tumorales indirectamente interrumpiendo la UPR, así como también dirigiendo directamente factores pro-supervivencia.

[0004] Por consiguiente, existe una necesidad para nuevos compuestos que puedan inhibir la HSP90.

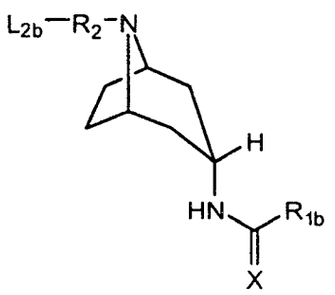
BREVE DESCRIPCIÓN DE LA INVENCIÓN

[0005] Un aspecto de la descripción se refiere a un compuesto de conformidad con la Fórmula I o II:



I

o



II

en donde R_1, R_{1b}, R_2, L_1, y L_2 y L_{2b} son como se definen en la especificación.

[0006] Otro aspecto de esta descripción, se refiere a un método para inhibir HSP90 en una célula, que comprende contactar la célula, en la cual se desea la inhibición de HSP90, con un compuesto de conformidad con la Fórmula I o II.

[0007] Otro aspecto de esta descripción, se refiere a un método para inhibir HSP90 en una célula, que comprende

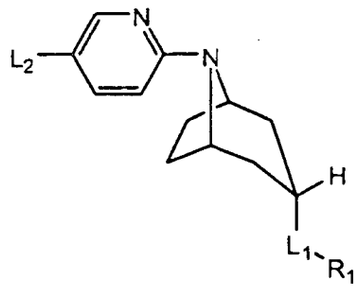
contactar una célula en la cual se desea la inhibición de HSP90 con una composición farmacéutica, que comprende el compuesto de conformidad con la Fórmula I o II, y un portador, excipiente o diluyente farmacéuticamente aceptable.

[0008] Otro aspecto de esta descripción se refiere a un método para tratar una de las enfermedades o condiciones descritas en la presente que involucra HSP90, que comprende administrar a un animal, en necesidad del tratamiento, el compuesto de conformidad con la Fórmula I o II, opcionalmente en combinación con uno o más agentes terapéuticos adicionales o terapias descritas en la presente.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

[0009] Existen muchos diferentes aspectos de la descripción descrita aquí posteriormente, y cada aspecto es no limitante con respecto al alcance de la descripción. Los términos "aspectos" y "modalidades", significan no ser limitantes con respecto de en donde los términos "aspecto" o "modalidad" aparecen en esta especificación. El término transicional "que comprende" como se usa en la presente, el cual es sinónimo con "que incluye", "que contiene" o "caracterizado por", es inclusive o abierto y no excluye adicional, elementos no mencionados o etapas de método.

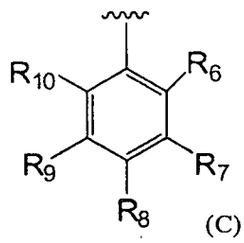
[0010] Un aspecto de la descripción se refiere a un compuesto de conformidad con la Fórmula I:



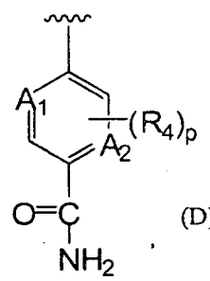
I

o una sal del mismo farmacéuticamente aceptable, en donde:

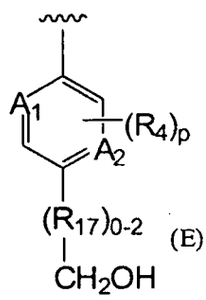
R_1 se selecciona a partir de



(C)

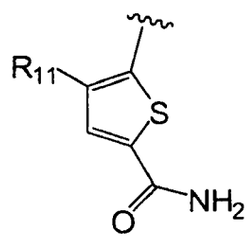


(D)



(E)

y



(Q) ;

R_3 se selecciona a partir de hidrógeno, $-CF_3$, $-NH_2$, -OH, alquilo opcionalmente sustituido con 1, 2 o 3 R_5, alcoxi, dialquilaminoalquilo, cicloalquilo opcionalmente sustituido con arilalcoxi, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo, alcoxi, dialquilaminoalcoxi y heterocicloalquilo opcionalmente sustituido con alquilo o arilo, alquenilo,

alquinilo, heterocicloalquilo opcionalmente sustituido con un grupo seleccionado a partir de alquilo, -C(O)O-alquilo y arilalquilo, arilalquilo opcionalmente sustituido con alquilheterocicloalquilo en cualquier posición del anillo del grupo arilo, y heteroarilo;

R_4, R_7, R_8, R_9 y R_{11} son cada uno seleccionados independientemente a partir de hidrógeno, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hidroxi, alquenilo, alquinilo, hidroxialquinilo, halógeno, hidroxialquilo, dihidroxialquilo, $-O-C(O)-NH_2$, amino(imino)alquilo, $-C(O)-NH_2$, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógeno, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, $-NH_2$, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de alquilo, alcoxi y halógeno;

R_5 se selecciona a partir de halógeno, cicloalquilo, cicloalquilalquilamino, heteroarilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo y alcoxi, alquiltio, heterocicloalquilo opcionalmente sustituido con 1, 2, o 3 grupos seleccionados a partir de alquilo, halógeno, fenilo y

oxo, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo, alcoxi, dialquilaminoalcoxi, y heterocicloalquilo opcionalmente sustituido con alquilo, alcoxi, dialquilamino, -OH, -C(O)-NH_2, -C(O)-O-CH_3, -C(O)-N(H)alquilo (C_1-C_3), heteroarilamino opcionalmente sustituido con halógeno, y -OCF_3;

R_6 y R_{10} son cada uno seleccionados a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, alquiltio, alquenilo, alquinilo, hidroxialquinilo, halógeno, hidroxialquilo, dihidroxialquilo, amino(imino)alquilo, -C(O)-NH_2, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilamino opcionalmente sustituido con 1-8 halógenos, dialquilamino, alcoxialquilamino, -N(H)alquilheterocicloalquilo, cicloalquilalquilamino, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalquilamino opcionalmente sustituido con un grupo seleccionado a partir de -OH, alquilo, -CF_3 y heterocicloalquilo, -N(H)cicloalquilo opcionalmente sustituido con -OH o -NH_2, -NH_2, -N(H)-heteroarilo, -N(H)-arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de alcoxi, heterocicloalquilalcoxi y dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo;

R_{16} se selecciona a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de -OH, $-NH_2$, alquilo, heterocicloalquilo, y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalquilo, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo;

R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-;

cada uno es A_1 o A_2 es N o C(H), en donde A_1 y A_2 pueden ser el mismo o diferente, siempre que A_1 pueda ser sustituido con R_4 solamente cuando A_1 es C(H), y siempre que A_2 pueda ser sustituido con R_4 solamente cuando A_2 es C(H);

L_1 se selecciona a partir de -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, $-(CH_2)_nC(O)NH-$, $-(CH_2)_nNHC(O)-$, $-(CH_2)_mNH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)_nNHSO_2-$, $-(CH_2)_mC(O)-$, $-(CH_2)_mO-$, y $-(CH_2)_mNH-(CH_2)_n-$;

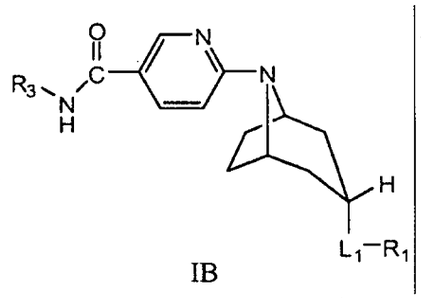
L_2 es $-C(O)-NH-R_3$, -CN, $-C(O)-N(CH_3)-OCH_3$, o $-C(O)-R_3$;

n es 0 o 1;

m es 0, 1 o 2; y

cada p es independientemente 0, 1, 2, 3 o 4.

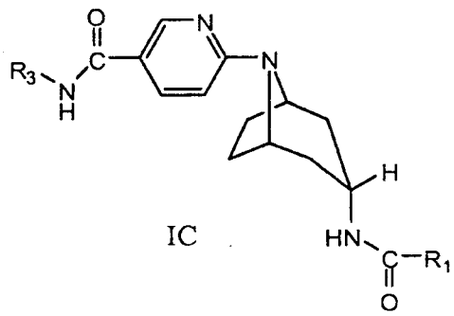
[0011] En otra modalidad, el compuesto de Fórmula I es un compuesto de Fórmula IB:



IB

o una sal del mismo farmacéuticamente aceptable, en donde L_1, R_1 y R_3 son como se definen en la Fórmula I.

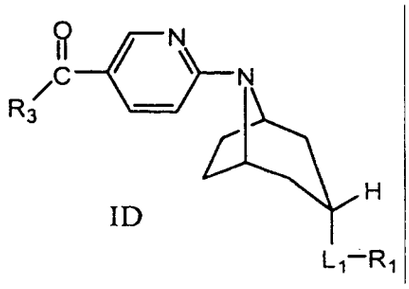
[0012] En otra modalidad, el compuesto de Fórmula I es un compuesto de Fórmula IC:



IC

o una sal del mismo farmacéuticamente aceptable, en donde R_1 y R_3 son como se definen en la Fórmula I.

[0013] Otra modalidad de Fórmula I es el compuesto de Fórmula ID:

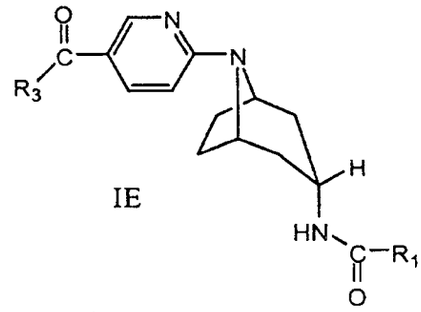


ID

o una sal del mismo farmacéuticamente aceptable,

en donde R_1, R_3 y L_1 son como se definen en la Fórmula I.

[0014] Otra modalidad de Fórmula I es el compuesto de Fórmula IE:

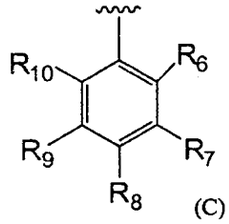


IE

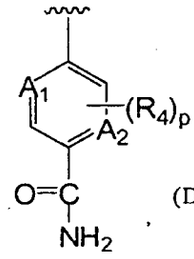
o una sal del mismo farmacéuticamente aceptable, en donde R_1 y R_3 son como se definen en la Fórmula I.

[0015] Otra modalidad se refiere a cualquiera de las Fórmulas I, IB, IC, ID o IE como se definen anteriormente, o una sal del mismo farmacéuticamente aceptable.

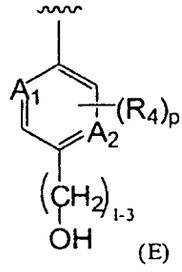
[0016] Otra modalidad se refiere a un compuesto de Fórmula I, en donde R_1 se selecciona a partir de



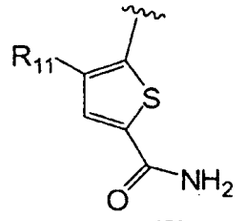
(C) ,



(D) ,



(E) y



(Q) ;

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R_3 se selecciona a partir de hidrógeno, $-CF_3$, $-NH_2$, -OH, alquilo opcionalmente sustituido con 1, 2 o 3 R_5, alcoxi, dialquilaminoalquilo, cicloalquilo opcionalmente sustituido con arilalcoxi, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo, alcoxi, dialquilaminoalcoxi y heterocicloalquilo opcionalmente sustituido con alquilo o arilo, alquenilo, alquinilo, heterocicloalquilo opcionalmente sustituido con un grupo seleccionado a partir de alquilo, -C(O)O-alquilo y arilalquilo, arilalquilo opcionalmente sustituido con alquilheterocicloalquilo en cualquier posición del anillo del grupo arilo, y heteroarilo;

R_4, R_7, R_8, R_9 y R_{11} son cada uno seleccionados independientemente a partir de hidrógeno, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hidroxi, alquenilo, alquinilo, hidroxialquinilo, alcoxi, halógeno, hidroxialquilo, dihidroxialquilo, $-O-C(O)-NH_2$, amino(imino)alquilo, $-C(O)-NH_2$, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógeno, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, $-NH_2$, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3

S49

grupos seleccionados a partir de alquilo, alcoxi y halógeno;

R_5 se selecciona a partir de halógeno, cicloalquilo, cicloalquilalquilamino, heteroarilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo y alcoxi, alquiltio, heterocicloalquilo opcionalmente sustituido con 1, 2, o 3 grupos seleccionados a partir de alquilo, halógeno, fenilo y oxo, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo, alcoxi, dialquilaminoalcoxi, y heterocicloalquilo (opcionalmente sustituido con alquilo), alcoxi, dialquilamino, -OH, -C(O)-NH_2, -C(O)-O-CH_3, -C(O)-N(H)(C_1-C_3)alquilo, heteroarilamino opcionalmente sustituido con halógeno, y -OCF_3;

R_6 y R_{10} son cada uno seleccionados a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, alquiltio, alquenilo, alquinilo, hidroxialquinilo, halógeno, hidroxialquilo, dihidroxialquilo, amino(imino)alquilo, -C(O)-NH_2, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilamino opcionalmente sustituido con 1-8 halógenos, dialquilamino, alcoxialquilamino, -N(H)alquilheterocicloalquilo, cicloalquilalquilamino, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalquilamino opcionalmente sustituido con un grupo

seleccionado a partir de -OH, alquilo, $-CF_3$ y heterocicloalquilo, -N(H)cicloalquilo opcionalmente sustituido con -OH o $-NH_2$), $-NH_2$, -N(H)-heteroarilo, -N(H)-arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de alcoxi, heterocicloalquilalcoxi y dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo;

R_{16} se selecciona a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de -OH, $-NH_2$, alquilo, heterocicloalquilo, y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalcoxi, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalcoxi;

cada uno es A_1 o A_2 es -N= o -CH=, en donde A_1 y A_2 pueden ser el mismo o diferente;

L_1 se selecciona a partir de -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)_nC(O)NH-$, $-(CH_2)_nNHC(O)-$, $-(CH_2)_mNH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)_nNHSO_2-$, $-(CH_2)_mC(O)-$, $-(CH_2)_mO-$, y $-(CH_2)_mNH-$;

L_2 es $-C(O)-NH-R_3$, -CN o $-C(O)-R_3$;

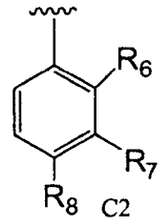
n es 0 o 1;

m es 0, 1 o 2; y

cada p es independientemente 0, 1, 2, 3 o 4.

[0017] Otra modalidad se refiere a un compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, en donde:

R_1 se selecciona a partir de



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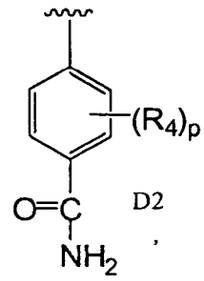

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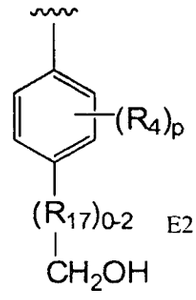


E2

R_3 se selecciona a partir de CF_3, ciclopropilo, ciclobutilo, ciclohexilo opcionalmente sustituido con hidroxilo, ciclopropilmetilo, N-propilo, 3-metilbutilo, (1S)-2-hidroxi-1-metiletilo, (2S)-2-hidroxipropilo, metoxietilo, etoxietilo, metilfenilo, fenilo, dimetilfenilo, metoxifenilo, dimetilaminoetilo, dimetilaminopropilo, dietilaminoetilo, dietilaminopropilo, ciclopentilo, halofenilo, fenilmetilo, feniletilo opcionalmente sustituido con hidroxilo en la posición etilo de feniletilo, fenilpropilo, fenilpiperidinilo, dietilaminoetiloxifenilmetilo, dietilaminoetiloxifeniletilo, pirrolidinilfenilmetilo, dietilaminoetiloxi-2-fluorofeniletilo, fenilalquilo (C_1-C_3)

SS2

opcionalmente sustituido en la posición fenilo de fenilalquilo (C_1-C_3) con 1-3 grupos seleccionados a partir de metoxi, halo y metilo, metilfenilalquilo (C_1-C_4) en donde la porción alquilo (C_1-C_4) de metilfenilalquilo (C_1-C_4) es opcionalmente sustituida con $-C(O)NH_2$, $-C(O)NHCH_3$ o $-C(O)NHCH_2CH_3$, tienilmetilo, furanilmetilo, piridiniletilo, piridinilmetilo, metilpirazinilmetilo, metilo, etilo, metilpropilo, 2-metilpropilo, 2,3-dihidroxipropilo, (1S)-1-metilpropilo, (1S)-1,2-dimetilpropilo, (1R)-1,2-dimetilpropilo, metiloxipropilo, etiloxipropilo, (1S)-1-metil-2-(metiloxi)etilo, 1,3-benzodioxolilo, 1,3-benzodioxlilmetilo, N-prop-2-in-1-ilo, N-[3-(4-metilpiperazin-1-il)propilo, N-[2-(etiltio)etilo], (1S,2S)-2-[(fenilmetil)oxi]ciclopentilo, 6-cloropiridinilmetilo, 2-cloro-6-fluorofenilmetilo, metiltioetilo, N-butilo, 1-metiletiloxietilo, 1-metiletiloxipropilo, 4,4-bismetiloxibutilo, metilpirazinilmetilo, propiloxipropilo, trifluorometiloxifenilmetilo, metiloxifeniletilo, (2,2-dimetil-1,3-dioxolan-4-il)metilo, fenilmetilpirrolidinilo, oxopirrolidinilpropilo, pirrolidiniletilo, metilpirrolidiniletilo, etilpirrolidinilmetilo, N-(1R,2R,4S)-biciclo[2.2.1]hept-2-ilo, 3,3-dimetilbutilo, etiloxifenilmetilo, fenilmetilpiperidinilo, etoxicarbonilpiperidinilo, trifluorometilfenilmetilo, imidazolilpropilo, (3R)-pirrolidin-3-ilo, morfoliniletilo,

SS3

morfolinilpropilo, piperidiniletilo, pirrolidinilo, piperidinilo, pirrolidinilmetilo, 1-metiletilpirrolidinilo, etilpirrolidinilo, metilpirrolidinilo, metiletilpiperidinilo, metilpiperidinilo, etilpiperidinilo, etilazetidinilo, azetidinilo, metilazetidinilo, 1-metiletilazetidinilo, metilpiperazinilfenilmetilo, piperazinilfenilmetilo, metilpiperazinilfenilo, metilpiperidinilfenilo, piperidinilfenilalquilo (C_1-C_3) opcionalmente sustituido con 1-4 halo, metilpiperazinilfenil(halo)metilo, metilpiperidinilfenilmetilo, metilpiperazinilfeniletilo, 2-metilpropilpiperazinilfenilmetilo, morfolinilfenilmetilo, piperazinilpiridiniletilo, $-CH(CH_3)C(O)-NH_2$, dimetilaminoetiloxifenilo, isopropilo, alquilo (C_1-C_5) opcionalmente sustituido con 1-7 halo, -OH, $-NH_2$, ciclohexilalquilo (C_1-C_5) opcionalmente sustituido con 1-2 grupos hidroxilo, fenilaminoetilo opcionalmente sustituido con halo, morfoliniletilo, fenilpiperaziniletilo, y metilpiperaziniletilo;

cada R_4, cuando se presenta, es independientemente seleccionado a partir de halo, 1-etilpropilamino, metilo, etilo, ciclohexilamino opcionalmente sustituido con hidroxilo, ciclobutilamino, 1-metilpropiloxi, metoxietoxi, $-CF_3$, piperidinilo o amino, morfolinilamino, dimetilaminobutilo, metiletilaminopropilo, metiletilaminopropilamino, ciclopentilamino,

piperidinilamino, metiletilamino, etilamino, 2-metilpropilamino, tetrahidropiranilamino, etilpiperidinilamino, 2,2-dimetilpropilamino, pirrolidinilamino, 1-metilpropilamino, 2-metilpropilamino, amino, 1,1-dimetiletilamino, tetrahidropiranilmetilamino, piperidinilamino opcionalmente sustituido con metilsulfonilo, fenilamino opcionalmente sustituido con 1-3 grupos seleccionados a partir de metoxi y dimetilaminoetiloxi, metilsulfoniletilamino, metoxietilamino, morfoliniletiloxi, -N(H)C(O)CH_3, ciclobutilamino, metoxi, ciclobutiloxi, ciclobutilamino, piridinilamino, etilamino, 1-metilciclopropiletilamino, metiletiloxietilamino, butilamino, piperidinilo, pentilamino, azetinilo, 1,2-dimetilpropilamino, 1-metiletilpropilamino, propilamino, 1-ciclopropilpropilamino, 1-propilbutilamino, 1-ciclopropiletilamino, diciclopropilmetilamino, 1,2,2-trimetilpropilamino, tetrahidrofuranilamino, alquilamino (C_1-C_5,) sustituido con 1-7 halo, morfoliniletiloxi y ciclopropilmetilamino;

R_6 se selecciona a partir de hidrógeno, alquilo (C_1-C_4) opcionalmente sustituido con hidroxi, alquilamino o dimetilamino (C_1-C_3), alquinilo (C_1-C_4) opcionalmente sustituido con hidroxilo, y halo;

R_7 se selecciona a partir de hidrógeno, -OH, -Oalquilo (C_1-C_3), -Salquilo (C_1-C_3), -N(H)alquilo (C_1-C_3),

SSS

cicloalquilamino (C_5-C_6) opcionalmente sustituido con hidroxilo, alquilamino o dimetilamino (C_1-C_3), -C(O)NH_2, y -O-C(O)NH_2;

R_8 se selecciona a partir de hidrógeno, -Oalquilo (C_1-C_3), -O-C(O)NH_2, y -C(=NH)-NH_2;

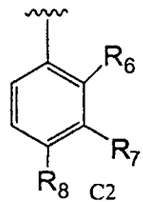
L_1 es -N(H)C(O)-;

L_2 es -C(O)-NH-R_3 o -C(O)-R_3; y

cada p es independientemente 0, 1, 2 o 3.

[0018] Otra modalidad se refiere a un compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, en donde:

R_1 se selecciona a partir de



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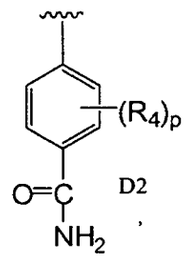

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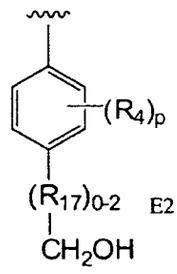


E2 ;

R_3 se selecciona a partir de hidrógeno, -CF_3, -NH_2, -OH, alquilo opcionalmente sustituido con 1, 2 o 3 R_5, alcoxi, dietilaminoetoxi, etilmetilaminoetoxi, dimetilaminoetoxi, ciclopentilo opcionalmente sustituido con arilalcoxi, ciclobutilo opcionalmente sustituido con

arilalcoxi, ciclopropilo opcionalmente sustituido con arilalcoxi, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo, alcoxi, dialquilaminoalcoxi, piperazinilo opcionalmente sustituido con alquilo o fenilo, morfolinilo opcionalmente sustituido con alquilo o fenilo, azetidinilo y piperidinilo opcionalmente sustituido con alquilo o fenilo, alquenilo, alquinilo, heterocicloalquilo seleccionado a partir de piperidinilo, pirrolidinilo, morfolinilo y piperizinilo, en donde el heterocicloalquilo es opcionalmente sustituido con un grupo seleccionado a partir de alquilo, -C(O)O-alquilo y arilalquilo, arilalquilo opcionalmente sustituido con alquilheterocicloalquilo en cualquier posición del anillo del grupo arilo, y heteroarilo;

R_6 se selecciona a partir de hidrógeno, alquilo (C_1-C_4) opcionalmente sustituido con hidroxi, alquilamino o dimetilamino (C_1-C_3), alquinilo (C_1-C_4) opcionalmente sustituido con hidroxilo, y halo;

R_7 se selecciona a partir de hidrógeno, -OH, -Oalquilo (C_1-C_3), -Salquilo (C_1-C_3), -N(H)alquilo (C_1-C_3), cicloalquilamino (C_5-C_6) opcionalmente sustituido con hidroxilo, alquilamino o dimetilamino (C_1-C_3), -C(O)NH_2, y -O-C(O)NH_2;

R_8 se selecciona a partir de hidrógeno, -Oalquilo (C_1-C_3), -O-C(O)NH_2, y -C(=NH)-NH_2;

SS 7

cada R_4, cuando se presenta, es independientemente seleccionado a partir de metilo, 1-metiletilamino, etilamino, 1-etilpropilamino, 2-metilpropilamino, (2,2-dimetilpropil)amino, (2-aminoetil)amino, (2,2,3,3,3-pentafluoropropil)amino, 1-metilpropilamino, (1S)-1-metilpropilamino, (2,2,2-trifluoroetil)amino, 1-propilbutilamino, propilamino, 1,2-dimetilpropilamino, (3,3,3-trifluoropropil)amino, (2,2,3,3,4,4,4-heptafluorobutil)amino, butilamino, 1,2,2-trimetilpropilamino, 1-[(metiloxi)metil]propilamino, 1-metiletiloxietilamino, 1-metilpropilamino, pentilamino, (2,2,3,3,3-pentafluoropropil)amino, butilamino, 2-[(1-metiletil)oxi]etilamino, (1S)-1-metilpropilamino, (1R)-1-metilpropilamino, (1S)-1,2-dimetilpropilamino, 1-ciclopropiletilamino, (1R)-1,2-dimetilpropilamino, 1-etil-2-metilpropilamino, y 3-[(1-metiletil)amino]propilamino;

L_1 es -N(H)C(O)-;

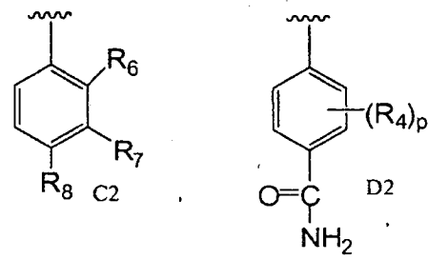
L_2 es -C(O)-NH-R_3 o -C(O)-R_3; y

cada p es independientemente 0, 1, 2 o 3.

[0019] Otra modalidad se refiere a un compuesto de Fórmula IB o ID, o una sal del mismo farmacéuticamente aceptable, en donde:

R_1 se selecciona a partir de

SS8



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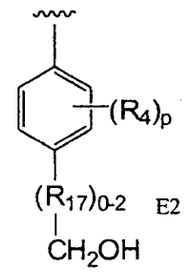

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R_3 se selecciona a partir de CF_3, ciclopropilo, ciclobutilo, ciclohexilo opcionalmente sustituido con hidroxilo, ciclopropilmetilo, N-propilo, 3-metilbutilo, (1S)-2-hidroxi-1-metiletilo, (2S)-2-hidroxipropilo, metoxietilo, etoxietilo, metilfenilo, fenilo, dimetilfenilo, metoxifenilo, dimetilaminoetilo, dimetilaminopropilo, dietilaminoetilo, dietilaminopropilo, ciclopentilo, halofenilo, fenilmetilo, feniletilo opcionalmente sustituido con hidroxilo en la posición etilo de feniletilo, fenilpropilo, fenilpiperidinilo, dietilaminoetiloxifenilmetilo, dietilaminoetiloxifeniletilo, pirrolidinilfenilmetilo, dietilaminoetiloxi-2-fluorofeniletilo, fenilalquilo (C_1-C_3) opcionalmente sustituido en la posición fenilo de fenilalquilo (C_1-C_3) con 1-3 grupos seleccionados a partir de metoxi, halo y metilo, metilfenilalquilo (C_1-C_4) en donde la porción alquilo (C_1-C_4) de metilfenilalquilo (C_1-C_4) es

opcionalmente sustituido con $-C(O)NH_2$, $-C(O)NHCH_3$ o $-C(O)NHCH_2CH_3$, tienilmetilo, furanilmetilo, piridiniletilo, piridinilmetilo, metilpirazinilmetilo, metilo, etilo, metilpropilo, 2-metilpropilo, 2,3-dihidroxipropilo, (1S)-1-metilpropilo, (1S)-1,2-dimetilpropilo, (1R)-1,2-dimetilpropilo, metiloxipropilo, etiloxipropilo, (1S)-1-metil-2-(metiloxi)etilo, 1,3-benzodioxolilo, 1,3-benzodioxlilmetilo, N-prop-2-in-1-ilo, N-[3-(4-metilpiperazin-1-il)propilo, N-[2-(etiltio)etilo], (1S,2S)-2-[(fenilmetil)oxi]ciclopentilo, 6-cloropiridinilmetilo, 2-cloro-6-fluorofenilmetilo, metiltioetilo, N-butilo, 1-metiletiloxietilo, 1-metiletiloxipropilo, 4,4-bismetiloxibutilo, metilpirazinilmetilo, propiloxipropilo, trifluorometiloxifenilmetilo, metiloxifeniletilo, (2,2-dimetil-1,3-dioxolan-4-il)metilo, fenilmetilpirrolidinilo, oxopirrolidinilpropilo, pirrolidiniletilo, metilpirrolidiniletilo, etilpirrolidinilmetilo, N-(1R,2R,4S)-biciclo[2.2.1]hept-2-ilo, 3,3-dimetilbutilo, etiloxifenilmetilo, fenilmetilpiperidinilo, etoxicarbonilpiperidinilo, trifluorometilfenilmetilo, imidazolilpropilo, (3R)-pirrolidin-3-ilo, morfoliniletilo, morfolinilpropilo, piperidiniletilo, pirrolidinilo, piperidinilo, pirrolidinilmetilo, 1-metiletilpirrolidinilo, etilpirrolidinilo, metilpirrolidinilo, metiletilpiperidinilo, metilpiperidinilo, etilpiperidinilo, etilazetidinilo,

azetidinilo, metilazetidinilo, 1-metiletilazetidinilo, metilpiperazinilfenilmetilo, piperazinilfenilmetilo, metilpiperazinilfenilo, metilpiperidinilfenilo, piperidinilfenilalquilo (C_1-C_3) opcionalmente sustituido con 1-4 halo, metilpiperazinilfenil(halo)metilo, metilpiperidinilfenilmetilo, metilpiperazinilfeniletilo, 2-metilpropilpiperazinilfenilmetilo, morfolinilfenilmetilo, piperazinilpiridiniletilo, $-CH(CH_3)C(O)-NH_2$, dimetilaminoetiloxifenilo, isopropilo, alquilo (C_1-C_5) opcionalmente sustituido con 1-7 halo,-OH, $-NH_2$, ciclohexilalquilo (C_1-C_5) opcionalmente sustituido con 1-2 grupos hidroxilo, fenilaminoetilo opcionalmente sustituido con halo, morfoliniletilo, fenilpiperaziniletilo, y metilpiperaziniletilo;

cada R_4, cuando se presenta, es independientemente seleccionado a partir de halo, 1-etilpropilamino, metilo, etilo, ciclohexilamino opcionalmente sustituido con hidroxilo, ciclobutilamino, 1-metilpropiloxi, metoxietoxi, $-CF_3$, piperidinilo o amino, morfolinilamino, dimetilaminobutilo, metiletilaminopropilo, metiletilaminopropilamino, ciclopentilamino, piperidinilamino, metiletilamino, etilamino, 2-metilpropilamino, tetrahidropiranilamino, etilpiperidinilamino, 2,2-dimetilpropilamino, pirrolidinilamino, 1-metilpropilamino, 2-metilpropilamino,

amino, 1,1 dimetiletilamino, tetrahidropiranilmetilamino, piperidinilamino opcionalmente sustituido con metilsulfonilo, fenilamino opcionalmente sustituido con 1-3 grupos seleccionados a partir de metoxi y dimetilaminoetiloxi, metilsulfoniletilamino, metoxietilamino, morfoliniletiloxi, -N(H)C(O)CH_3, ciclobutilamino, metoxi, ciclobutiloxi, ciclobutilamino, piridinilamino, etilamino, 1-metilciclopropiletilamino, metiletiloxietilamino, butilamino, piperidinilo, pentilamino, azetinilo, 1,2-dimetilpropilamino, 1-metiletilpropilamino, propilamino, 1-ciclopropilpropilamino, 1-propilbutilamino, 1-ciclopropiletilamino, diciclopropilmetilamino, 1,2,2-trimetilpropilamino, tetrahidrofuranilamino, alquilamino (C_1-C_5) sustituido con 1-7 halo, morfoliniletiloxi y ciclopropilmetilamino;

R_6 se selecciona a partir de hidrógeno, alquilo (C_1-C_4) opcionalmente sustituido con hidroxi, alquilamino o dimetilamino (C_1-C_3), alquinilo (C_1-C_4) opcionalmente sustituido con hidroxilo, y halo;

R_7 se selecciona a partir de hidrógeno, -OH, -Oalquilo (C_1-C_3), -Salquilo (C_1-C_3), -N(H)alquilo (C_1-C_3), cicloalquilamino (C_5-C_6) opcionalmente sustituido con hidroxilo, alquilamino o dimetilamino (C_1-C_3), -C(O)NH_2, y -O-C(O)NH_2;

R_8 se selecciona a partir de hidrógeno, -Oalquilo

(C_1-C_3), -O-C(O)NH_2, y -C(=NH)-NH_2;

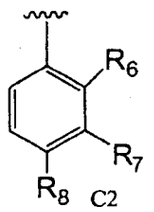
L_1 es -N(H)C(O)-;

L_2 es -C(O)-NH-R_3 o -C(O)-R_3; y

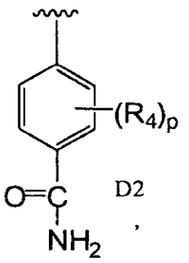
cada p es independientemente 0, 1, 2 o 3.

[0020] Otra modalidad se refiere a un compuesto de Fórmula IC o IE, o una sal del mismo farmacéuticamente aceptable, en donde:

R_1 se selecciona a partir de

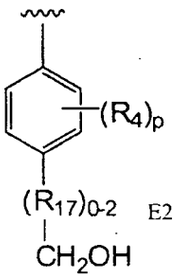


C2 ,



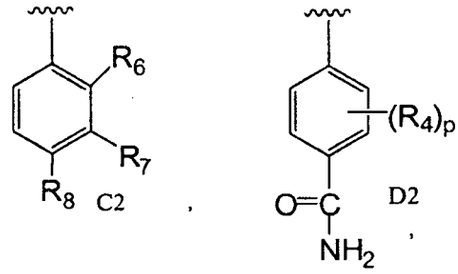
D2 ,

y

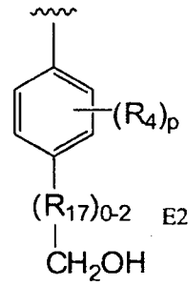


E2

R_1 se selecciona a partir de



y



;

R_3 se selecciona a partir de CF_3, ciclopropilo, ciclobutilo, ciclohexilo opcionalmente sustituido con hidroxilo, ciclopropilmetilo, N-propilo, 3-metilbutilo, (1S)-2-hidroxi-1-metiletilo, (2S)-2-hidroxipropilo, metoxietilo, etoxietilo, metilfenilo, fenilo, dimetilfenilo, metoxifenilo, dimetilaminoetilo, dimetilaminopropilo, dietilaminoetilo, dietilaminopropilo, ciclopentilo, halofenilo, fenilmetilo, feniletilo opcionalmente sustituido con hidroxilo en la posición etilo de feniletilo, fenilpropilo, fenilpiperidinilo, dietilaminoetiloxifenilmetilo, dietilaminoetiloxifeniletilo, pirrolidinilfenilmetilo, dietilaminoetiloxi-2-fluorofeniletilo, fenilalquilo (C_1-C_3) opcionalmente sustituido en la posición fenilo de fenilalquilo (C_1-C_3) con 1-3 grupos seleccionados a partir de

metoxi, halo y metilo, metilfenilalquilo (C_1-C_4) en donde la porción alquilo (C_1-C_4) de metilfenilalquilo (C_1-C_4) es opcionalmente sustituida con $-C(O)NH_2$, $-C(O)NHCH_3$ o $-C(O)NHCH_2CH_3$, tienilmetilo, furanilmetilo, piridiniletilo, piridinilmetilo, metilpirazinilmetilo, metilo, etilo, metilpropilo, 2-metilpropilo, 2,3-dihidroxipropilo, (1S)-1-metilpropilo, (1S)-1,2-dimetilpropilo, (1R)-1,2-dimetilpropilo, metiloxipropilo, etiloxipropilo, (1S)-1-metil-2-(metiloxi)etilo, 1,3-benzodioxolilo, 1,3-benzodioxlilmetilo, N-prop-2-in-1-ilo, N-[3-(4-metilpiperazin-1-il)propilo, N-[2-(etiltio)etilo], (1S,2S)-2-[(fenilmetil)oxi]ciclopentilo, 6-cloropiridinilmetilo, 2-cloro-6-fluorofenilmetilo, metiltioetilo, N-butilo, 1-metiletiloxietilo, 1-metiletiloxipropilo, 4,4-bismetiloxibutilo, metilpirazinilmetilo, propiloxipropilo, trifluorometiloxifenilmetilo, metiloxifeniletilo, (2,2-dimetil-1,3-dioxolan-4-il)metilo, fenilmetilpirrolidinilo, oxopirrolidinilpropilo, pirrolidiniletilo, metilpirrolidiniletilo, etilpirrolidinilmetilo, N-(1R,2R,4S)-biciclo[2.2.1]hept-2-ilo, 3,3-dimetilbutilo, etiloxifenilmetilo, fenilmetilpiperidinilo, etoxicarbonilpiperidinilo, trifluorometilfenilmetilo, imidazolilpropilo, (3R)-pirrolidin-3-ilo, morfoliniletilo, morfolinilpropilo, piperidiniletilo, pirrolidinilo, piperidinilo, pirrolidinilmetilo, 1-metiletilpirrolidinilo,

etilpirrolidinilo, metilpirrolidinilo, metiletilpiperidinilo, metilpiperidinilo, etilpiperidinilo, etilazetidinilo, azetidinilo, metilazetidinilo, 1-metiletilazetidinilo, metilpiperazinilfenilmetilo, piperazinilfenilmetilo, metilpiperazinilfenilo, metilpiperidinilfenilo, piperidinilfenilalquilo (C_1-C_3) opcionalmente sustituido con 1-4 halo, metilpiperazinilfenil(halo)metilo, metilpiperidinilfenilmetilo, metilpiperazinilfeniletilo, 2-metilpropilpiperazinilfenilmetilo, morfolinilfenilmetilo, piperazinilpiridiniletilo, $-CH(CH_3)C(O)-NH_2$, dimetilaminoetiloxifenilo, isopropilo, alquilo (C_1-C_5) opcionalmente sustituido con 1-7 halo,-OH, $-NH_2$, ciclohexilalquilo (C_1-C_5) opcionalmente sustituido con 1-2 grupos hidroxilo, fenilaminoetilo opcionalmente sustituido con halo, morfoliniletilo, fenilpiperaziniletilo, y metilpiperaziniletilo;

cada R_4, cuando se presenta, es independientemente seleccionado a partir de halo, 1-etilpropilamino, metilo, etilo, ciclohexilamino opcionalmente sustituido con hidroxilo, ciclobutilamino, 1-metilpropiloxi, metoxietoxi, $-CF_3$, piperidinilo o amino, morfolinilamino, dimetilaminobutilo, metiletilaminopropilo, metiletilaminopropilamino, ciclopentilamino, piperidinilamino, metiletilamino, etilamino, 2-metilpropilamino, tetrahidropiranilamino,

etilpiperidinilamino, 2,2-dimetilpropilamino, pirrolidinilamino, 1-metilpropilamino, 2-metilpropilamino, amino, 1,1 dimetiletilamino, tetrahidropiranilmetilamino, piperidinilamino opcionalmente sustituido con metilsulfonilo, fenilamino opcionalmente sustituido con 1-3 grupos seleccionados a partir de metoxi y dimetilaminoetiloxi, metilsulfoniletilamino, metoxietilamino, morfoliniletiloxi, -N(H)C(O)CH_3, ciclobutilamino, metoxi, ciclobutiloxi, ciclobutilamino, piridinilamino, etilamino, 1-metilciclopropiletilamino, metiletiloxietilamino, butilamino, piperidinilo, pentilamino, azetinilo, 1,2-dimetilpropilamino, 1-metiletilpropilamino, propilamino, 1-ciclopropilpropilamino, 1-propilbutilamino, 1-ciclopropiletilamino, diciclopropilmetilamino, 1,2,2-trimetilpropilamino, tetrahidrofuranilamino, alquilamino (C_1-C_5) sustituido con 1-7 halo, morfoliniletiloxi y ciclopropilmetilamino;

R_6 se selecciona a partir de hidrógeno, alquilo (C_1-C_4) opcionalmente sustituido con hidroxi, alquilamino o dimetilamino (C_1-C_3), alquinilo (C_1-C_4) opcionalmente sustituido con hidroxilo, y halo;

R_7 se selecciona a partir de hidrógeno, -OH, -Oalquilo (C_1-C_3), -Salquilo (C_1-C_3), -N(H)alquilo (C_1-C_3), cicloalquilamino (C_5-C_6) opcionalmente sustituido con hidroxilo, alquilamino o dimetilamino (C_1-C_3), -C(O)NH_2, y -O-

$C(O)NH_2$;

R_8 se selecciona a partir de hidrógeno, -Oalquilo (C_1-C_3), $-O-C(O)NH_2$, y $-C(=NH)-NH_2$;

L_1 es -N(H)C(O)-;

L_2 es $-C(O)-NH-R_3$ o $-C(O)-R_3$; y

cada p es independientemente 0, 1, 2 o 3.

[0021] En otras modalidades, R_1 del compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, es arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados independientemente a partir de (1) $-C(O)NH_2$, (2) metoxi, (3) alquilo, tal como metilo como un ejemplo no limitante, (4) alquilamino, tal como etilpropilamino, metilpropilamino o ciclopropilpropilpropilamino como ejemplos no limitantes, (5) cicloalquilamino opcionalmente sustituido con OH, tal como ciclohexilamino o ciclopentilamino como ejemplos no limitantes, y (6) heterocicloalquilamino, tal como furanilo o tetrahidro-2H-pirano como ejemplos no limitantes.

[0022] En otra modalidad del compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, L_1 es -NHC(O)-.

[0023] En otra modalidad del compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, L_1 se selecciona a partir de -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)C(O)NH-$, $-(CH_2)NHC(O)-$, $-(CH_2)NH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)NHSO_2-$, $-(CH_2)C(O)-$, $-(CH_2)O-$, y $-NH-(CH_2)-$.

[0024] En otra modalidad del compuesto de Fórmula I, o una

sal del mismo farmacéuticamente aceptable, L_2 es -C(O)-NH-ciclopropilo, -C(O)-NH-CH_3, -C(O)-ciclopropilo, o -C(O)-CH_3.

[0025] En otra modalidad del compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, L_2 es -C(O)-NH-ciclopropilo o -C(O)-NH-CH_3.

[0026] En otra modalidad del compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, L_2 es -C(O)-NH-CH_3.

[0027] En otra modalidad del compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, L_2 es -C(O)-NH-ciclopropilo.

[0028] En otra modalidad del compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, L_2 es -C(O)-ciclopropilo o -C(O)-CH_3.

[0029] En otra modalidad del compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, L_2 es -C(O)-ciclopropilo.

[0030] En otra modalidad del compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, L_2 es -C(O)-CH_3.

[0031] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, y IE, o una sal del mismo farmacéuticamente aceptable, R_1 se selecciona a partir de:

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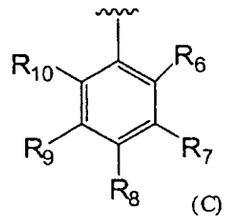
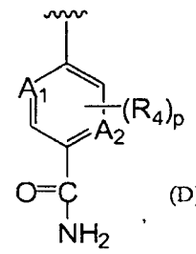
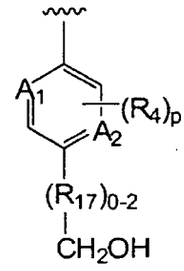


(C)



(D)

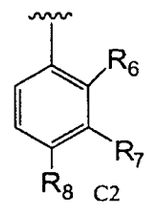
y



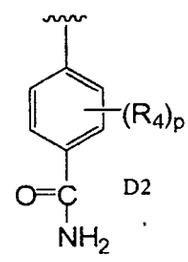
(E)

en donde A_1, A_2, R_4, R_6, R_7, R_8, R_9, R_{10}, R_{17}, y p son como se definen anteriormente.

[0032] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, y IE, o una sal del mismo farmacéuticamente aceptable, R_1 se selecciona a partir de:

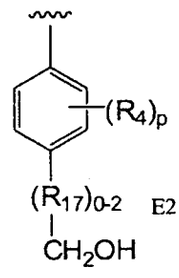


C2



D2

y



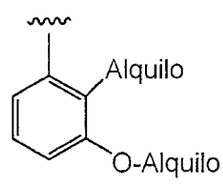
E2

;

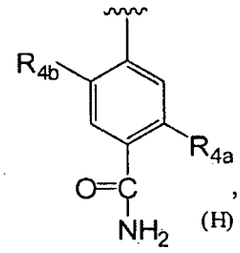
en donde R_4, R_6, R_7, R_8, R_{17}, y p son como se definen anteriormente.

[0033] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, o IE, R_1 se selecciona a partir de uno de los siguientes del Grupo Z:

Grupo Z

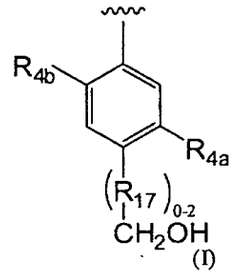


(G) ,



(H) ,

y



(I)

en donde R_{4a} se selecciona a partir de hidrógeno, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hidroxi, alquenilo, alquinilo, hidroxialquinilo, alcoxi, halógeno, hidroxialquilo, dihidroxialquilo, $-O-C(O)-NH_2$, amino(imino)alquilo, $-C(O)-NH_2$, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógenos, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, $-NH_2$, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -

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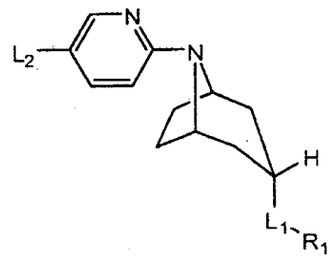
N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de alquilo, alcoxi y halógeno;

R_{4b} se selecciona a partir de H, halógeno y metilo opcionalmente sustituido con 1-3 halógenos;

R_{16} se selecciona a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de -OH, $-NH_2$, alquilo, heterocicloalquilo, y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalquilo, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo; and

R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-.

[0034] Otro aspecto de la descripción se refiere a un compuesto de conformidad con la Fórmula I:

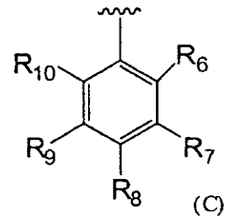


I

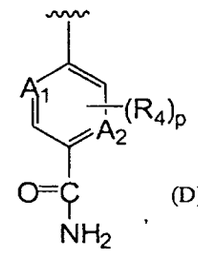
o una sal del mismo farmacéuticamente aceptable, en donde:

R_1 se selecciona a partir de:

5 +2

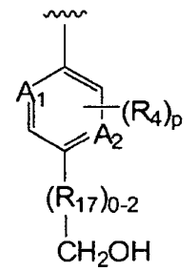


(C)



(D)

y



(E)

R_3 se selecciona a partir de hidrógeno, $-CF_3$, $-NH_2$, -OH, alquilo opcionalmente sustituido con 1, 2 o 3 R_5, alcoxi, dialquilaminoalquilo, cicloalquilo opcionalmente sustituido con arilalcoxi, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo, alcoxi, dialquilaminoalcoxi y heterocicloalquilo opcionalmente sustituido con alquilo o arilo, alquenilo, alquinilo, heterocicloalquilo opcionalmente sustituido con un grupo seleccionado a partir de alquilo, -C(O)O-alquilo y arilalquilo, arilalquilo opcionalmente sustituido con alquilheterocicloalquilo en cualquier posición del anillo del grupo arilo, y heteroarilo;

R_4, R_7, R_8, R_9 y R_{11} son cada uno seleccionados independientemente a partir de hidrógeno, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hidroxi, alquenilo, alquinilo, hidroxialquinilo, alcoxi, halógeno, hidroxialquilo, dihidroxialquilo, -O-C(O)-

NH_2, amino(imino)alquilo, -C(O)-NH_2, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógeno, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, -NH_2, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de alquilo, alcoxi y halógeno;

R_5 se selecciona a partir de halógeno, cicloalquilo, cicloalquilalquilamino, heteroarilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo y alcoxi, alquiltio, heterocicloalquilo opcionalmente sustituido con 1, 2, o 3 grupos seleccionados a partir de alquilo, halógeno, fenilo y oxo, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo, alcoxi, dialquilaminoalcoxi, y heterocicloalquilo opcionalmente sustituido con alquilo, alcoxi, dialquilamino, -OH, -C(O)-NH_2, -C(O)-O-CH_3, -C(O)-N(H)alquilo (C_1-C_3), heteroarilamino opcionalmente sustituido con halógeno, y -OCF_3;

R_6 y R_{10} son cada uno seleccionados a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, alquiltio, alquenilo, alquinilo, hidroxialquinilo,

halógeno, hidroxialquilo, dihidroxialquilo, amino(imino)alquilo, -C(O)-NH_2, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilamino opcionalmente sustituido con 1-8 halógenos, dialquilamino, alcoxialquilamino, -N(H)alquilheterocicloalquilo, cicloalquilalquilamino, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalquilamino opcionalmente sustituido con un grupo seleccionado a partir de -OH, alquilo, -CF_3 y heterocicloalquilo, -N(H)cicloalquilo opcionalmente sustituido con -OH o -NH_2, -NH_2, -N(H)-heteroarilo, -N(H)-arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de alcoxi, heterocicloalquilalcoxi y dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo;

R_{16} se selecciona a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de -OH, -NH_2, alquilo, heterocicloalquilo, y -CF_3, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o -NH_2, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalquilo, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo;

R_{17}, cuando se presenta, es -CH_2- o -CH(OH)-;

cada uno es A_1 o A_2 es N o C(H), en donde A_1 y A_2 pueden ser el mismo o diferente, siempre que A_1 pueda ser sustituido con R_4 solamente cuando A_1 es C(H), y siempre que A_2 pueda ser sustituido con R_4 solamente cuando A_2 es C(H);

L_1 se selecciona a partir de -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)C(O)NH-$, $-(CH_2)NHC(O)-$, $-(CH_2)NH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)NHSO_2-$, $-(CH_2)C(O)-$, $-(CH_2)O-$, y $-NH-(CH_2)-$;

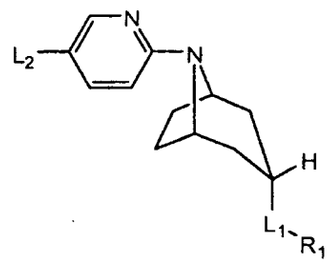
L_2 es -C(O)-NH-ciclopropilo o $-NH-C(O)-CH_3$;

n es 0 o 1;

m es 0, 1 o 2; y

cada p es independientemente 0, 1, 2, 3 o 4.

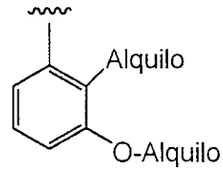
[0035] Otro aspecto de la descripción se refiere a un compuesto de conformidad con la Fórmula I:



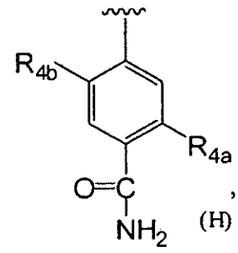
I

o una sal del mismo farmacéuticamente aceptable, en donde:

R_1 se selecciona a partir de:

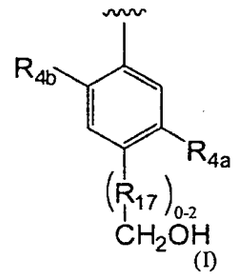


(G) ,



(H) ,

y



(I)

en donde R_{4a} se selecciona a partir de hidrógeno, -OR_{16}, -SR_{16}, -N(H)R_{16}, hidroxi, alquenilo, alquinilo, hidroxialquinilo, alcoxi, halógeno, hidroxialquilo, dihidroxialquilo, -O-C(O)-NH_2, amino(imino)alquilo, -C(O)-NH_2, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógenos, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, -NH_2, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de alquilo, alcoxi y halógeno;

R_{4b} se selecciona a partir de H, halógeno y metilo opcionalmente sustituido con 1-3 halógenos;

R_{16} se selecciona a partir de hidrógeno, alquilo

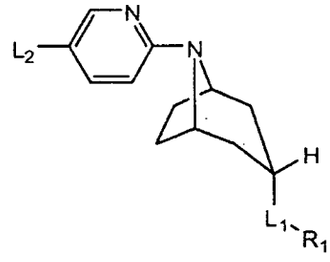
opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de -OH, $-NH_2$, alquilo, heterocicloalquilo, y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalquilo, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo;

R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-;

L_1 se selecciona a partir de -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)C(O)NH-$, $-(CH_2)NHC(O)-$, $-(CH_2)NH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)NHSO_2-$, $-(CH_2)C(O)-$, $-(CH_2)O-$, y $-NH-(CH_2)-$; y

L_2 es -C(O)-NH-ciclopropilo o $-NH-C(O)-CH_3$.

[0036] Otro aspecto de la descripción se refiere a un compuesto de conformidad con la Fórmula I:

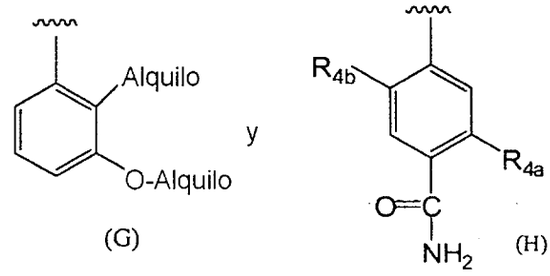


I

o una sal del mismo farmacéuticamente aceptable, en donde:

R_1 se selecciona a partir de:

S78



(G) (H)

en donde R_{4a} se selecciona a partir de hidrógeno, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hidroxi, alquenilo, alquinilo, hidroxialquinilo, alcoxi, halógeno, hidroxialquilo, dihidroxialquilo, $-O-C(O)-NH_2$, amino(imino)alquilo, $-C(O)-NH_2$, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógenos, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, $-NH_2$, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de alquilo, alcoxi y halógeno;

R_{4b} se selecciona a partir de H, halógeno y metilo opcionalmente sustituido con 1-3 halógenos;

R_{16} se selecciona a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de -OH, $-NH_2$, alquilo, heterocicloalquilo, y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente

579

sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalquilo, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo;

L_1 se selecciona a partir de -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)C(O)NH-$, $-(CH_2)NHC(O)-$, $-(CH_2)NH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)NHSO_2-$, $-(CH_2)C(O)-$, $-(CH_2)O-$, y $-NH-(CH_2)-$; y

L_2 es -C(O)-NH-ciclopropilo o $-NH-C(O)-CH_3$.

[0037] Para propósitos de esta especificación, el lenguaje para la definición de R_{16}, como se define en la Fórmula I, es decir, en el sentido que R_{16} puede ser hidrógeno, o R_{16} puede ser alquilo opcionalmente sustituido con 1-8 grupos halógeno, o R_{16} puede ser cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de -OH, $-NH_2$, alquilo, heterocicloalquilo, y $-CF_3$, o R_{16} puede ser cicloalquilalquilo, o R_{16} puede ser heterocicloalquilo opcionalmente sustituido con -OH o -NH, o R_{16} puede ser alcoxialquilo, o R_{16} puede ser arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, o R_{16} puede ser heterocicloalquilalquilo, o R_{16} puede ser heteroarilo, o R_{16} puede ser gem-dicicloalquilalquilo, o R_{16} puede ser dialquilaminoalquilo. Esta interpretación del lenguaje para R_{16} significa ser ejemplar para la interpretación del lenguaje en las definiciones para las otras variables listadas en esta especificación.

[0038] Cuando cualquiera de las modalidades en esta especificación se refiere a un compuesto de Fórmula I, IB, IC, ID o IE, es decir, en el sentido que esta modalidad incluye cada una de las Formula I, IB, IC, ID o IE, individualmente o en cualquier combinación entre sí. Por ejemplo, cuando cualquiera de las modalidades en esta especificación se refiere a un compuesto de Fórmula I, IB, IC, ID o IE, esta puede ser interpretada por incluir solamente compuestos que tienen la Fórmula I, o solamente compuestos que tienen la Fórmula IB, o solamente compuestos que tienen la Fórmula IC, o solamente compuestos que tienen la Fórmula ID, o solamente compuestos que tienen la Fórmula IE, o una combinación de algunos dos de la Fórmula I, IB, IC, ID o IE, (tal como, por ejemplo, un compuesto de Fórmula IB o IC, o un compuesto de Fórmula ID o IE, en donde todas las variables L_1, R_1 y R_3 son como se definen en la Fórmula I) o una combinación de algunos tres de la Fórmula I, IB, IC, ID o IE, o una combinación de algunos cuatro de la Fórmula I, IB, IC, ID o IE, o todos de las Fórmula I, IB, IC, ID y IE.

[0039] A menos que se especifique de otro modo, los compuestos descritos en la presente, significan incluir sales farmacéuticamente aceptables de estos compuestos, en donde esto es explícitamente declarado o no, como modalidades alternativas a las formas de base libre de los compuestos en esta descripción.

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[0040] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, R_{4a} se selecciona a partir de $-N(H)R_{16}$, $-OR_{16}$, y SR_{16};

R_{4b} se selecciona a partir de H, alquilo opcionalmente sustituido con uno o más halógenos, y halógeno; y

R_{16} se selecciona a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de -OH, $-NH_2$, $-CH_3$ y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con alquilo, -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalquilo, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo.

[0041] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, R_{4a} es ciclohexilamino opcionalmente sustituido con -OH.

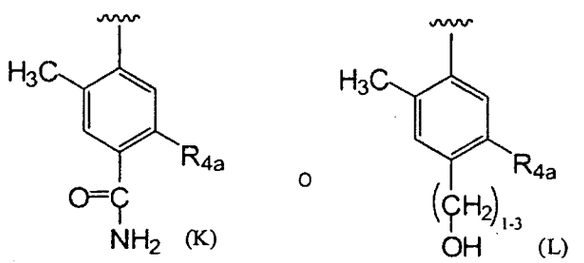
[0042] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, R_{4b} es alquilo opcionalmente sustituido con 1-8 fluoro.

[0043] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente

S82

aceptable, R_{16} es ciclopropilo, ciclopentilo o ciclohexilo, en donde cada ciclopropilo, ciclopentilo o ciclohexilo puede ser opcionalmente sustituido con 1 o 2 -OH.

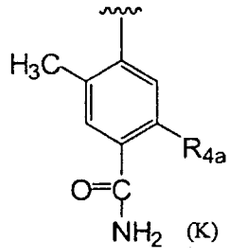
[0044] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, R_1 es



en donde R_{4a} se selecciona a partir de $-N(H)R_{16}$, $-OR_{16}$, y $-SR_{16}$; y

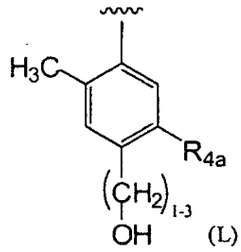
R_{16} se selecciona a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de -OH, $-NH_2$, $-CH_3$ y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo.

[0045] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, R_1 es



(K)

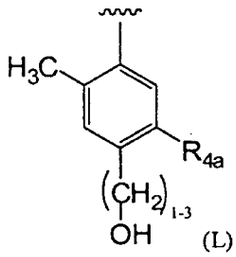
o



(L)

en donde R_{16} se selecciona a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de -OH, $-NH_2$, $-CH_3$ y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo.

[0046] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, R_1 es



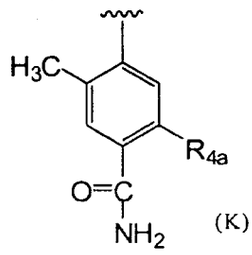
(L)

en donde R_{4a} se selecciona a partir de $-N(H)R_{16}$, $-OR_{16}$, y $-SR_{16}$; y

R_{16} se selecciona a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a

partir de -OH, $-NH_2$, $-CH_3$ y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo.

[0047] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, R_1 es

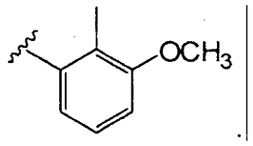


(K)

en donde R_{4a} se selecciona a partir de $-N(H)R_{16}$, $-OR_{16}$, y $-SR_{16}$; y

R_{16} se selecciona a partir de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de -OH, $-NH_2$, $-CH_3$ y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo.

[0048] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, R_1 es



[0049] En otra modalidad del compuesto de Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, los sustituyentes heterocicloalquilo de arilo en R_3 es piperazinilo, morfolinilo, azetidinilo o piperidinilo. En otra modalidad, los sustituyentes heterocicloalquilo de arilo en R_3 para la Fórmula I, IB, IC, ID y IE son piperazinilo, morfolinilo o piperidinilo, en donde el piperazinilo, morfolinilo o piperidinilo es N-sustituido con alquilo o fenilo. En otras modalidades, los sustituyentes heterocicloalquilo de arilo en R_3 para la Fórmula I, IB, IC, ID o IE son piperazinilo, morfolinilo, azetidinilo o piperidinilo, y R_1 es de la Fórmula (G), (H), (I), (K), (L), (N) o (P).

[0050] Cuando cualquiera de las modalidades de esta especificación se refiere a un compuesto de Fórmula (G), (H), (I), (K), (L), (N) o (P), es decir, en el sentido que esta modalidad incluye cada una de las Fórmulas (G), (H), (I), (K), (L), (N) o (P) individualmente o en cualquier combinación de entre sí. Por ejemplo, cuando cualquiera de las modalidades en esta especificación se refiere a un compuesto de Fórmula (G), (H), (I), (K), (L), (N) o (P), esto puede ser interpretado por incluir solamente compuestos que

tienen la Fórmula (G), o solamente compuestos que tienen la Fórmula (H), o solamente compuestos que tienen la Fórmula (I), o solamente compuestos que tienen la Fórmula (K), o solamente compuestos que tienen la Fórmula (L), o solamente compuestos que tienen la Fórmula (N), o solamente compuestos que tienen la Fórmula (P), o una combinación de algunos dos de la Fórmula (G), (H), (I), (K), (L), (N) o (P), o una combinación de algunos tres de la Fórmula (G), (H), (I), (K), (L), (N) o (P), o una combinación de algunos cuatro de la Fórmula (G), (H), (I), (K), (L), (N) o (P), o una combinación de algunos cinco de la Fórmula (G), (H), (I), (K), (L), (N) o (P), o una combinación de algunos seis de la Fórmula (G), (H), (I), (K), (L), (N) o (P), o todos de la Fórmula (G), (H), (I), (K), (L), (N) y (P).

[0051] Ejemplos no limitantes del heterocicloalquilo para la Fórmula I, IB, IC, ID o IE, cuando R_3 es heterocicloalquilo, incluyen, piperidinilo, pirrolidinilo, morfolinilo y piperizinilo. En otra modalidad, este grupo heterocicloalquilo es piperidinilo o pirrolidinilo. En otra modalidad, este grupo heterocicloalquilo es piperidinilo. En otra modalidad, este grupo heterocicloalquilo es pirrolidinilo. En otras modalidades, el heterocicloalquilo para la Fórmula I, IB, IC, ID o IE, cuando R_3 es heterocicloalquilo, incluye piperidinilo, pirrolidinilo, morfolinilo y piperizinilo, y R_1 es de la Fórmula (G), (H),

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(I), (K), (L), (N) o (P).

[0052] Ejemplos no limitantes del dialquilaminoalcoxi en R_3 para la Fórmula I, IB, IC, ID y IE incluyen dietilaminoetoxi, etilmetilaminoetoxi y dimetilaminoetoxi.

[0053] En otras modalidades, el dialquilaminoalcoxi en R_3 para la Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, es dietilaminoetoxi, etilmetilaminoetoxi o dimetilaminoetoxi, y R_1 es de la Fórmula (G), (H), (I), (K), (L), (N) o (P).

[0054] Ejemplos no limitantes del heterocicloalquilo para la Fórmula I, IB, IC, ID y IE, o una sal del mismo farmacéuticamente aceptable, cuando R_5 es heterocicloalquilo, incluyen piperidinilo o piperizinilo, en otra modalidad, el piperidinilo o piperazinilo es N-sustituido con metilo. En otras modalidades, el heterocicloalquilo para la Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, cuando R_5 es heterocicloalquilo, es piperidinilo o piperizinilo, y R_1 es de la Fórmula (G), (H), (I), (K), (L), (N) o (P).

[0055] Ejemplos no limitantes de los sustituyentes heterocicloalquilo de arilo en R_5 para la Fórmula I, IB, IC, ID y IE, o una sal del mismo farmacéuticamente aceptable, incluyen piperazinilo, morfolinilo y piperidinilo. En otras modalidades, el sustituyente heterocicloalquilo de arilo en R_5 para la Fórmula I, IB, IC, ID y IE, o una sal del mismo

farmacéuticamente aceptable, es piperazinilo, morfolinilo o piperidinilo, y R_1 es de la Fórmula (G), (H), (I), (K), (L), (N) o (P).

[0056] En otras modalidades, R_3 para el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, es cicloalquilo, tal como ciclopentilo, ciclobutilo o ciclopropilo como ejemplos no limitantes. En otras modalidades, R_3 para el compuesto de Fórmula I, IB, IC, ID o IE es ciclopentilo, ciclobutilo o ciclopropilo, y R_1 es de la Fórmula (G), (H), (I), (K), (L), (N) o (P).

[0057] En otras modalidades, R_3 para el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, es heterocicloalquilo, tal como pirrolidinilo, piperidinilo o azetidinilo como ejemplos no limitantes. En otras modalidades, R_3 para el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, es ciclopentilo, ciclobutilo o ciclopropilo, y R_1 es de la Fórmula (G), (H), (I), (K), (L), (N) o (P).

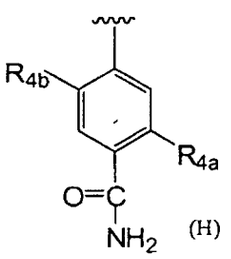
[0058] En otras modalidades, R_3 para el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, es heteroarilo. En otras modalidades, R_3 para el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, es

heteroarilo, y R_1 es de la Fórmula (G), (H), (I), (K), (L), (N) o (P).

[0059] En otras modalidades, R_3 para el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, es H. En otras modalidades, R_3 para el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, es H, y R_1 es de la Fórmula (G), (H), (I), (K), (L), (N) o (P).

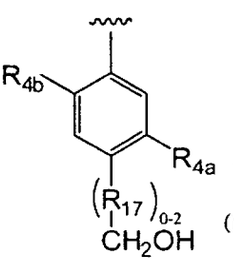
[0060] En otras modalidades, R_3 para el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, es arilalquilo, tal como fenilmetilo como un ejemplo no limitante. En otras modalidades, R_3 para el compuesto de Fórmula I, IB, IC, ID o IE es arilalquilo, y R_1 es de la Fórmula (G), (H), (I), (K), (L), (N) o (P).

[0061] En otras modalidades del compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, R_1 es



(H)

o



(I)

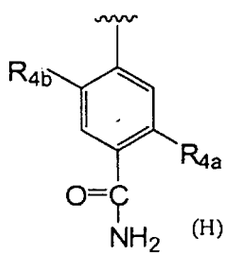
en donde R_{4a} es cicloalquilamino opcionalmente sustituido con -OH, alquilo, $-CF_3$, o heterocicloalquilo;

R_{4b} se selecciona a partir de H, halo y metilo

opcionalmente sustituido con 1-3 halógenos; y R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-. En esta modalidad, L_1 puede ser -N(H)C(O)-.

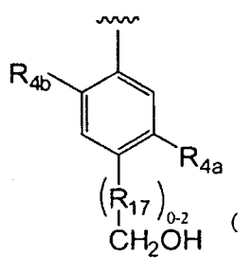
[0062] Ejemplos no limitantes de R_{4a} para cualquiera de las modalidades anteriores incluyen trans-4-hidroxiciclohexilamino, ciclohexilamino, ciclopentilamino, ciclopropilamino, cis-4-hidroxi-4-metilciclohexilamino, 4-(trifluorometil)ciclohexilamino y trans-4-piperidin-1-ilciclohexilamino.

[0063] En otras modalidades del compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, R_1 es



(H)

o



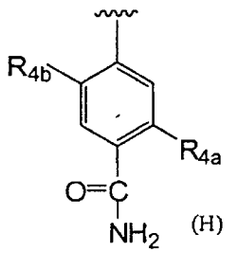
(I)

en donde R_{4a} es trans-4-hidroxiciclohexilamino, ciclohexilamino, ciclopentilamino, ciclopropilamino, cis-4-hidroxi-4-metilciclohexilamino, 4-(trifluorometil)ciclohexilamino o trans-4-piperidin-1-ilciclohexilamino;

R_{4b} se selecciona a partir de H, halo y metilo opcionalmente sustituido con 1-3 halógenos; y

R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-.

[0064] En otras modalidades del compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, R_1 o una sal del mismo farmacéuticamente aceptable, es



(H)

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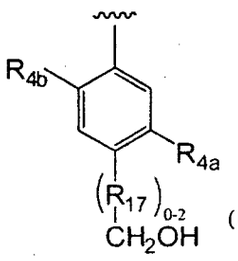


(I)

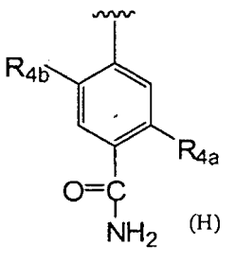
en donde R_{4a} es cicloalquilalquilamino;

R_{4b} se selecciona a partir de H, halo y metilo opcionalmente sustituido con 1-3 halógenos. En esta modalidad, L_1 puede ser -N(H)C(O)-; y

R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-.

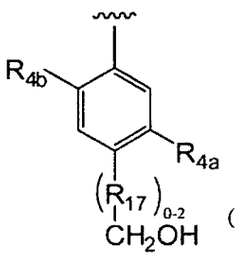
[0065] Un ejemplo no limitante de R_{4a} para cualquiera de las modalidades anteriores incluye ciclopropilmetilamino.

[0066] En otras modalidades del compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, R_1 es



(H)

o



(I)

en donde R_{4a} es alquilamino opcionalmente sustituido

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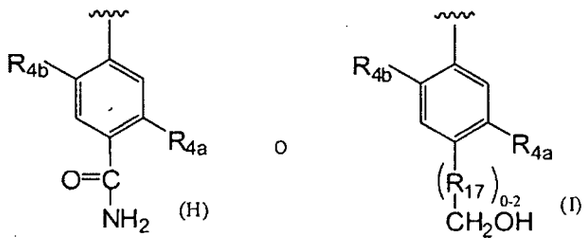
con 1-8 halo;

R_{4b} se selecciona a partir de H, halo y metilo opcionalmente sustituido con 1-3 halógenos; y R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-. En esta modalidad, L_1 puede ser -N(H)C(O)-.

[0067] Ejemplos no limitantes de R_{4a} para cualquiera de las modalidades anteriores incluyen 1-metiletilamino, etilamino, 1-etilpropilamino, 2-metilpropilamino, (2,2-dimetilpropil)amino, (2-aminoetil)amino, (2,2,3,3,3-pentafluoropropil)amino, 1-metilpropilamino, (1S)-1-metilpropilamino, (2,2,2-trifluoroetil)amino, 1-propilbutilamino, propilamino, 1,2-dimetilpropilamino, (3,3,3-trifluoropropil)amino, (2,2,3,3,4,4,4-heptafluorobutil)amino, butilamino, 1,2,2-trimetilpropilamino, 1-[(metiloxi)metil]propilamino, 1-metiletiloxietilamino, 1-metilpropilamino, pentilamino, (2,2,3,3,3-pentafluoropropil)amino, butilamino, 2-[(1-metiletil)oxi]etilamino, (1S)-1-metilpropilamino, (1R)-1-metilpropilamino, (1S)-1,2-dimetilpropilamino, 1-ciclopropiletilamino, (1R)-1,2-dimetilpropilamino, 1-etil-2-metilpropilamino, y 3-[(1-metiletil)amino]propilamino.

[0068] En otras modalidades del compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, R_1 es

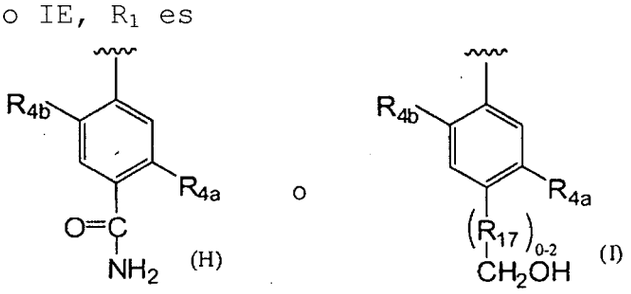


en donde R_{4a} es heterocicloalquilamino opcionalmente sustituido con alquilo;

R_{4b} se selecciona a partir de H, halógeno y metilo opcionalmente sustituido con 1-3 halógenos; y R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-. En esta modalidad, L_1 puede ser -N(H)C(O)-.

[0069] Ejemplos no limitantes de R_{4a} para cualquiera de las modalidades anteriores incluyen tetrahidrofuran-3-ilamino, piperidin-4-ilamino, tetrahidro-2H-piran-4-ilamino, (1-etilpiperidin-4-il)amino, (tetrahidrofuran-2-ilmetil)amino, pirrolidin-3-ilamino, (piperidin-3-ilmetil)amino, (pirrolidin-3-ilmetil)amino, (3S)-tetrahidrofuran-3-ilamino, (3R)-tetrahidrofuran-3-ilamino, azetidin-1-ilo, piperidin-1-ilamino, y (3S)-tetrahidrofuran-3-ilamino.

[0070] En otras modalidades del compuesto de Fórmula I, IB, IC, ID o IE, R_1 es



en donde R_{4a} es -N(H)-arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalcoxi o dialquilaminoalcoxi;

R_{4b} se selecciona a partir de H, halógeno y metilo opcionalmente sustituido con 1-3 halógenos; y

R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-.

En esta modalidad, L_1 puede ser -N(H)C(O)-.

[0071] Ejemplos no limitantes de R_{4a} para cualquiera de las modalidades anteriores incluyen fenilamino, (fenilmetil)amino, (3-{[2-(dimetilamino)etil]oxi}fenil)amino, 3-{[2-(dimetilamino)-4-(metiloxi)etil]oxi}fenil)amino y {4-(metiloxi)-3-[(2-morfolin-4-iletil)oxi]fenil}amino.

[0072] En otra modalidad, R_1 en la Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, se selecciona a partir de uno del Grupo Z; R_{4a} es (2,2,3,3,3-pentafluoropropil)amino, butilamino, 2-[(1-metiletil)oxi]etilamino, (1S)-1-metilpropil]amino, (1-metilpropil)amino, (1R)-1-metilpropil]amino, 2-(propilamino), (1S)-1,2-dimetilpropil]amino, (1-ciclopropiletil)amino, (1R)-1,2-dimetilpropil]amino o 2,2-dimetilpropilamino; y R_{4b} es H.

[0073] En otra modalidad, R_1 en la Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, se selecciona a partir de uno del Grupo Z; R_{4a} es 1-etilpropilamino; y R_{4b} es cloro, fluoro, bromo, o metilo.

[0074] En otras modalidades, R_1 en la Fórmula I, IB, IC,

ID, o IE, o una sal del mismo farmacéuticamente aceptable, es seleccionado a partir de uno del Grupo Z; R_{4a} es 1-etil-2-metilpropil)amino, (1R)-1-metilpropilamino, 1-ciclopropiletilamino, 1-ciclopropilpropilamino, (1R)-1,2,2-trimetilpropilamino, (1R)-1,2-dimetilpropilamino, 3,3,3-trifluoro-1-metilpropilamino, 2-metil-1-trifluorometilpropilamino, 2-metil-1-(1-metiletil)propilamino, 1-metiletilamino, diciclopropilmetilamino, ciclopentilamino, trifluorometilpropilamino, 2-metilpropilamino, ciclopentilmetilamino, ciclobutilamino, (1S)-1-metilpropilamino, 3,3,3-trifluoropropilamino, propilamino o 2-fluoro-1-(fluorometil)etilamino; y R_{4b} es metilo.

[0075] En otras modalidades, R_1 en la Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, se selecciona a partir de uno del Grupo Z; R_{4a} es 1-etilpropilamino o (1R)-1-metilpropilamino; y R_{4b} es CF_3.

[0076] En otras modalidades, R_1 en la Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, se selecciona a partir de uno del Grupo Z; R_{4a} es (1R)-1-metilpropilamino, 1-metiletilamino, ciclopentilamino, 2-metilpropilamino, 2,2-dimetilpropilamino, (1R)-1,2-dimetilpropilamino, propilamino, (3,3,3-trifluoropropil)amino o ciclobutilamino; y R_{4b} es Br.

[0077] En otras modalidades, R_1 en la Fórmula I, IB, IC,

ID, o IE, o una sal del mismo farmacéuticamente aceptable, se selecciona a partir de uno del Grupo Z; R_{4a} es (ciclopropilmetil)amino, (1-etilpropil)amino, (cis-4-hidroxi-4-metilciclohexil)amino o (trans-4-piperidin-1-ilciclohexil)amino; y R_{4b} es H.

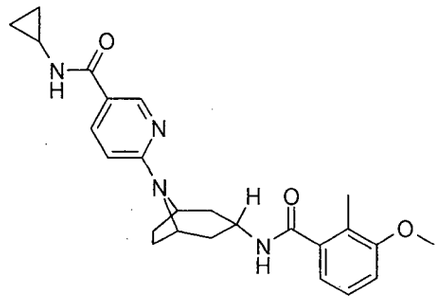
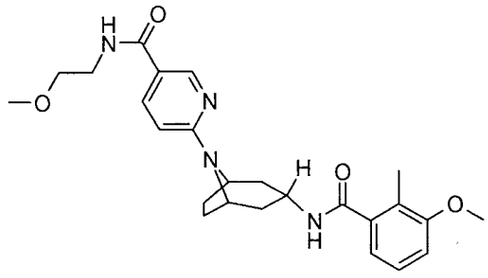
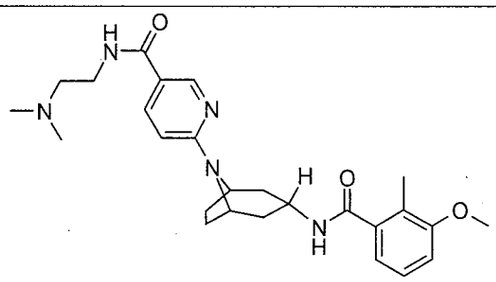
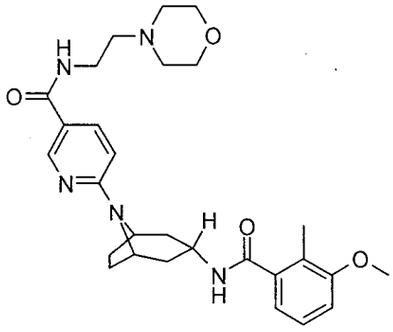
[0078] En otras modalidades, R_1 en la Fórmula I, IB, IC, ID, o IE se selecciona a partir de uno del Grupo Z; R_{4a} es ciclopropilmetilamino o 1-(1-metilciclopropil)etilamino; y R_{4b} es metilo.

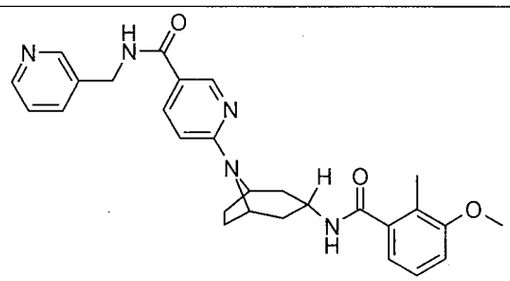
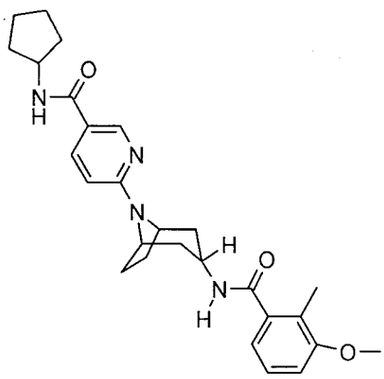
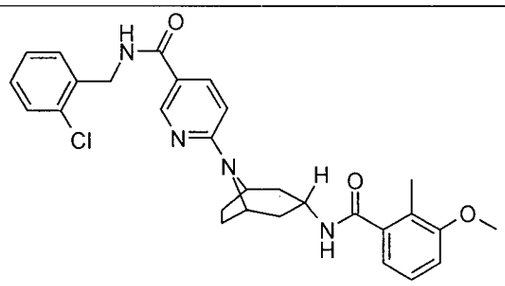
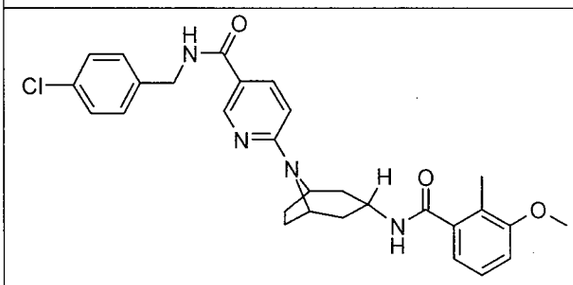
[0079] En otras modalidades, R_1 en la Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, se selecciona a partir de uno del Grupo Z; R_{4a} es piridin-4-ilamino; y R_{4b} es H.

[0080] En otra modalidad, R_1 en la Fórmula I, IB, IC, ID, o IE, o una sal del mismo farmacéuticamente aceptable, se selecciona a partir de uno del Grupo Z; R_{4a} es (3S)-tetrahidrofuran-3-ilamino; y R_{4b} es metilo.

[0081] En otra modalidad, el compuesto de Fórmula I se selecciona a partir de uno de los siguientes compuestos de la Tabla I, o una sal farmacéuticamente aceptable de cualquiera de los compuestos en la Tabla I:

TABLA I

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-ciclopropil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(metiloxi)etil]piridin-3-carboxamida **ACTIVIDAD = D**
	N-[2-(dimetilamino)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-morfolin-4-iletil)piridin-3-carboxamida **ACTIVIDAD = C**

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(piridin-3-ilmetil)piridin-3-carboxamida **ACTIVIDAD = A**
	N-ciclopentil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-[(2-clorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-[(4-clorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**

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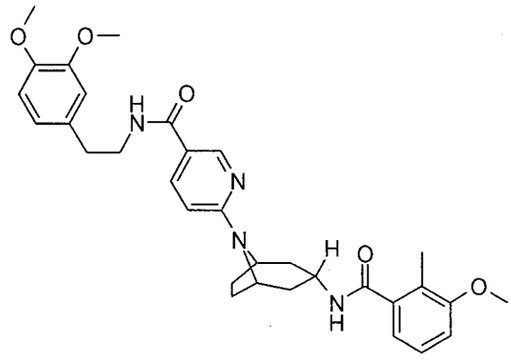
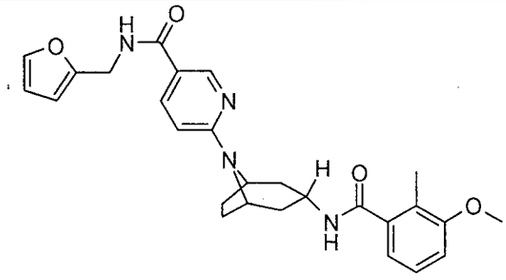
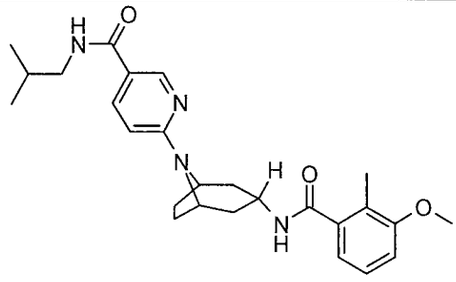
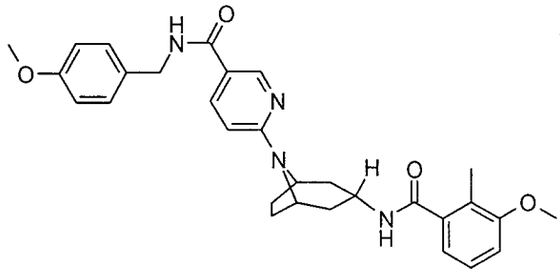
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{2-[3,4-bis(metiloxi)fenil]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	N-(furan-2-ilmetil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-metilpropil)piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(metiloxi)fenil]metil}piridin-3-carboxamida **ACTIVIDAD = A**

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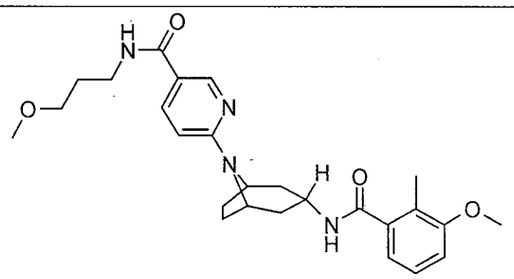
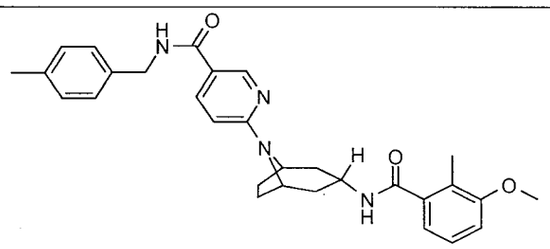
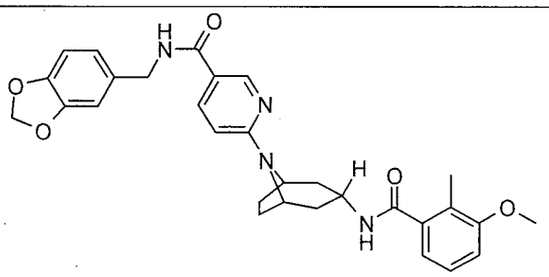
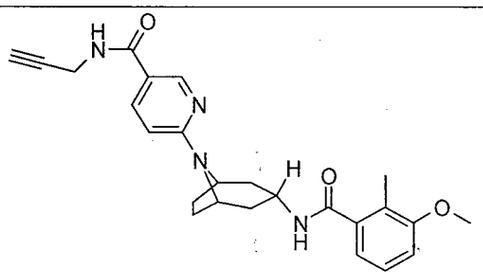
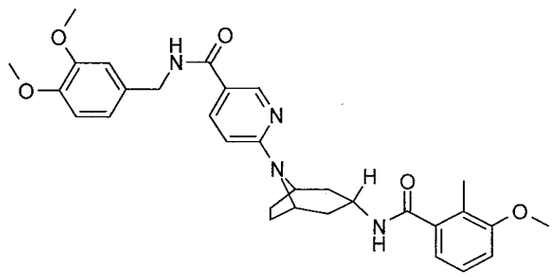
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(metiloxi)propil]piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-metilfenil)metil]piridin-3-carboxamida **ACTIVIDAD = A**
	N-(1,3-benzodioxol-5-ilmetil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-prop-2-in-1-ilpiridin-3-carboxamida **ACTIVIDAD = C**
	N-{[3,4-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD =**

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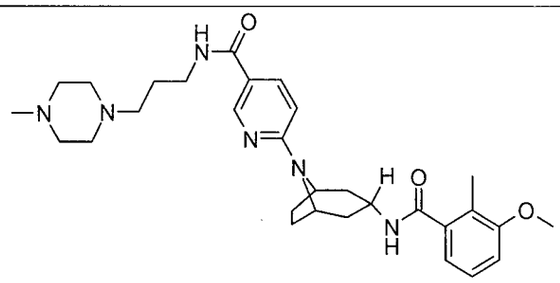
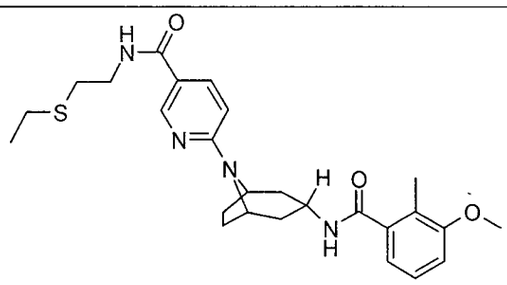
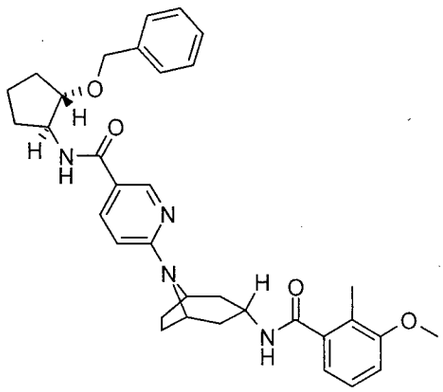
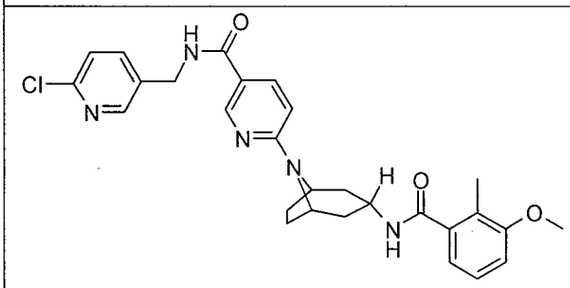
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(4-metilpiperazin-1-il)propil]piridin-3-carboxamida **ACTIVIDAD = B**
	N-[2-(etiltio)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S,2S)-2-[(fenilmetil)oxi]ciclopentil}piridin-3-carboxamida **ACTIVIDAD = D**
	N-[(6-cloropiridin-3-il)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**

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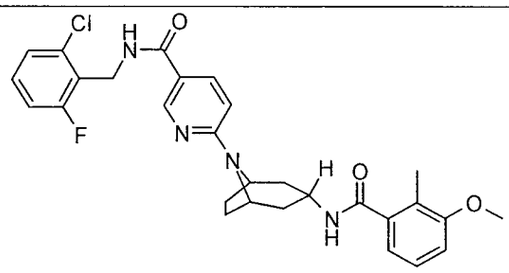
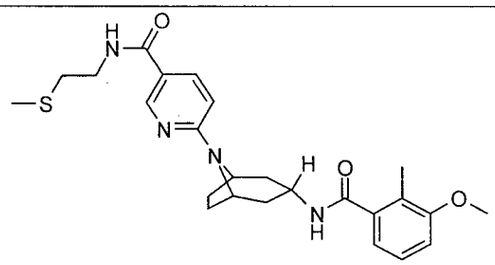
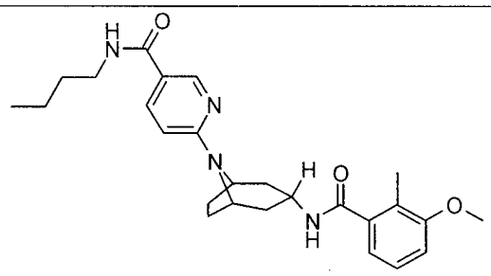
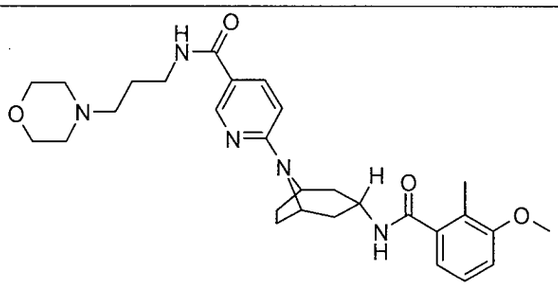
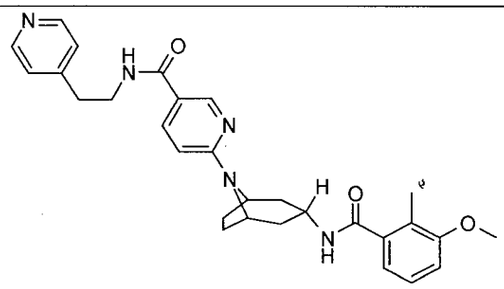
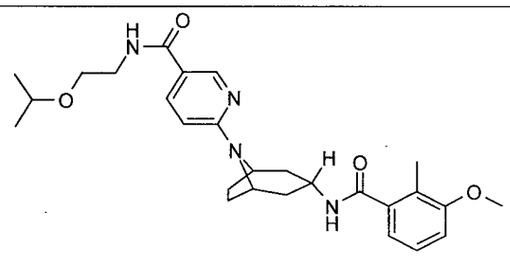
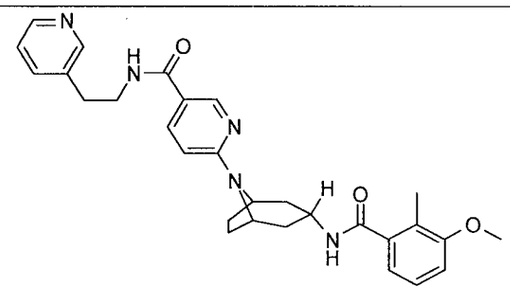
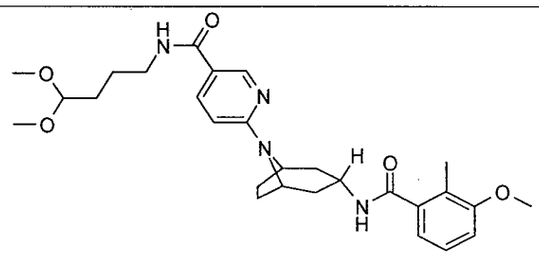
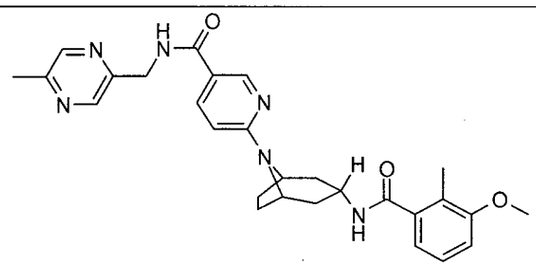
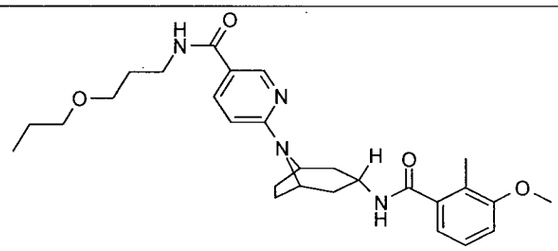
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[(2-cloro-6-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(metiltio)etil]piridin-3-carboxamida **ACTIVIDAD = C**
	N-butil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(3-morfolin-4-ilpropil)piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-piridin-4-iletil)piridin-3-carboxamida **ACTIVIDAD = C**

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{2-[(1-metiletil)oxi]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-piridin-3-iletil)piridin-3-carboxamida **ACTIVIDAD = C**
	N-[4,4-bis(metiloxi)butil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(5-metilpirazin-2-il)metil]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-endo-(propiloxi)propil]piridin-3-carboxamida **ACTIVIDAD = B**

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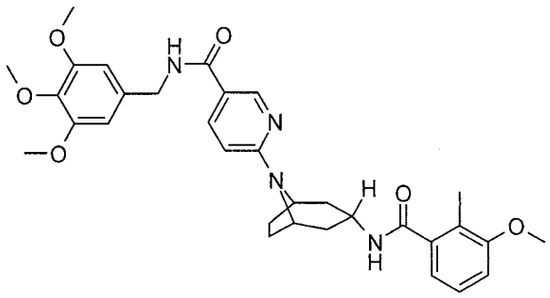
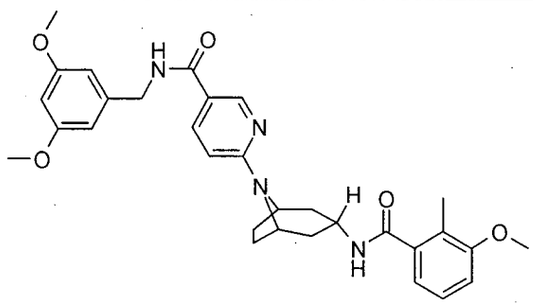
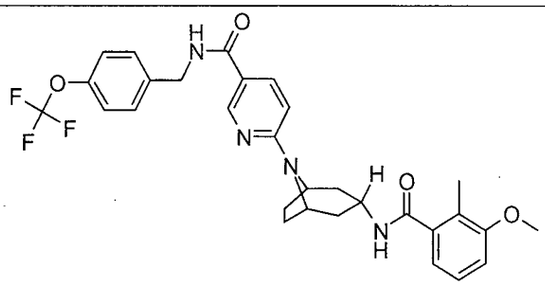
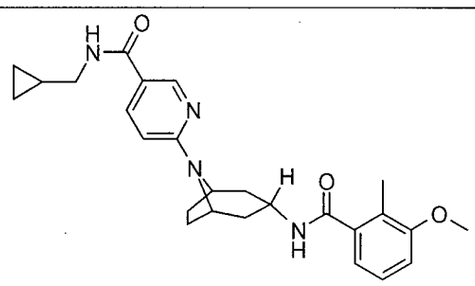
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[3,4,5-tris(metiloxi)fenil]metil}piridin-3-carboxamida **ACTIVIDAD = C**
	N-{[3,5-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-({4-[(trifluorometil)oxi]fenil}metil)piridin-3-carboxamida **ACTIVIDAD = D**
	N-(ciclopropilmetil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**

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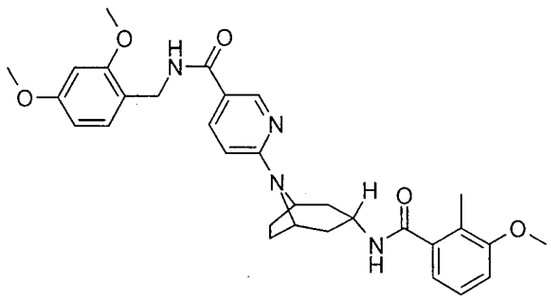
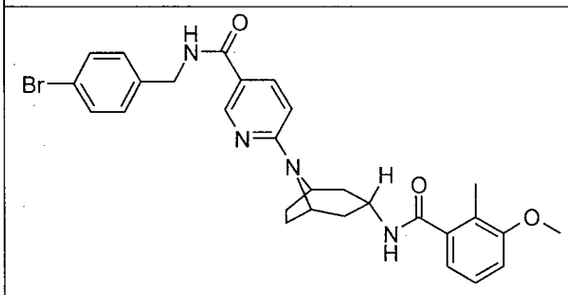
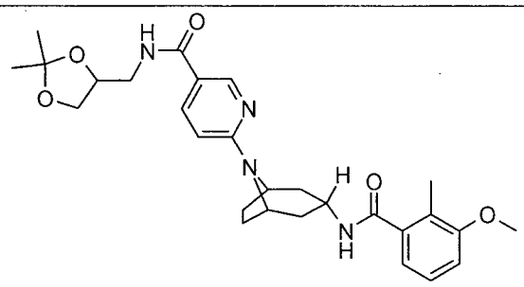
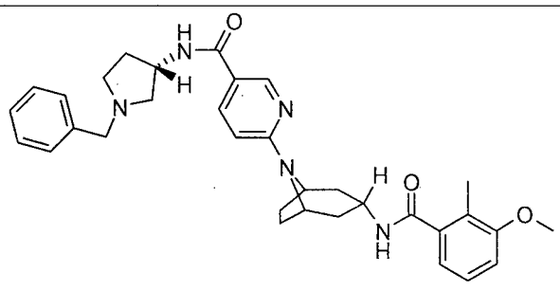
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{[2,4-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-[(4-bromofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-[(2,2-dimetil-1,3-dioxolan-4-il)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3S)-1-(fenilmetil)pirrolidin-3-il]piridin-3-carboxamida **ACTIVIDAD = B**

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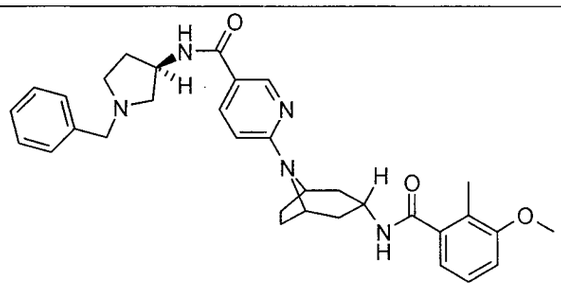
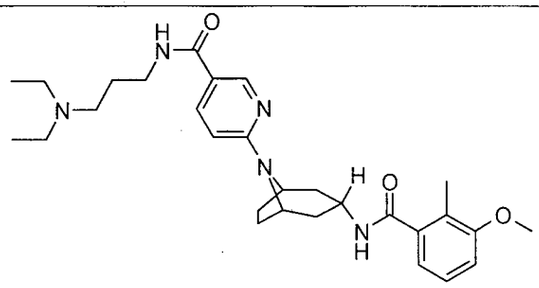
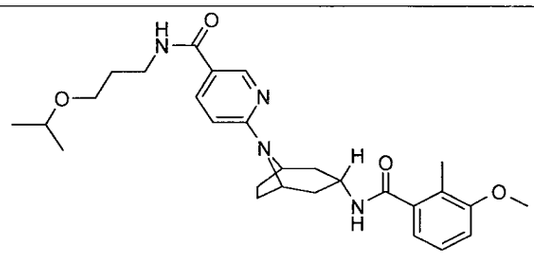
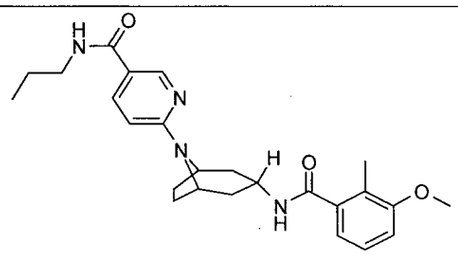
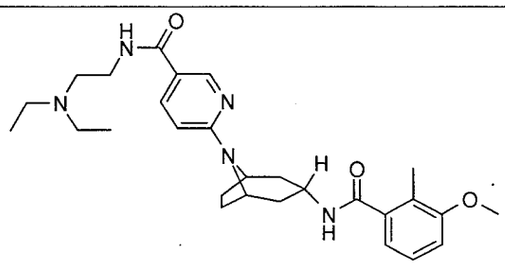
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3R)-1-(fenilmetil)pirrolidin-3-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-[3-(dietilamino)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-{3-[(1-metiletil)oxi]propil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-propilpiridin-3-carboxamida **ACTIVIDAD = C**
	N-[2-(dietilamino)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**

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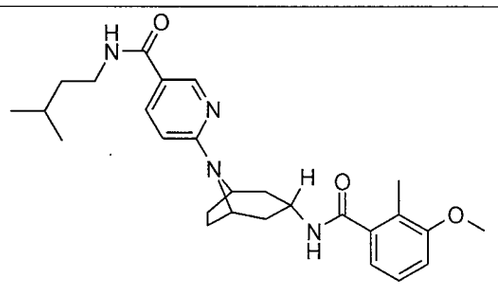
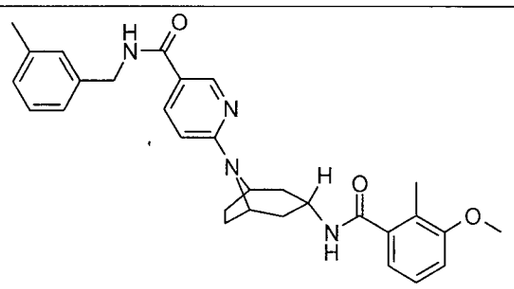
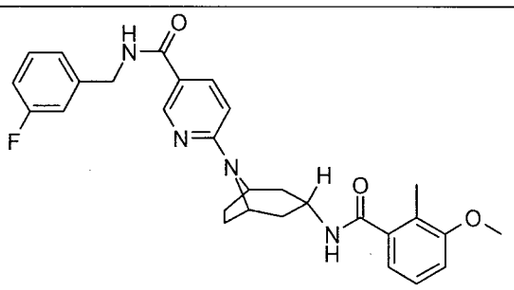
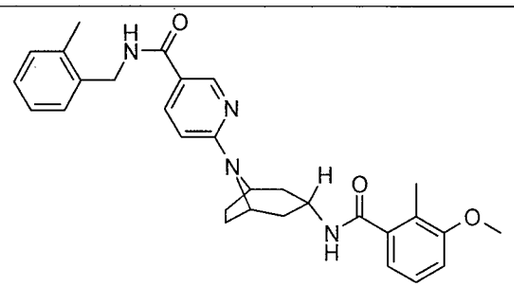
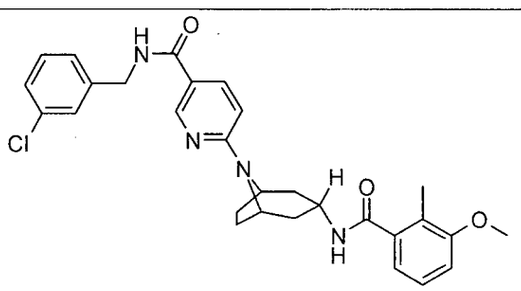
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-(3-metilbutil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3-metilfenil)metil]piridin-3-carboxamida **ACTIVIDAD = D**
	N-[(3-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2-metilfenil)metil]piridin-3-carboxamida **ACTIVIDAD = A**
	N-[(3-clorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**

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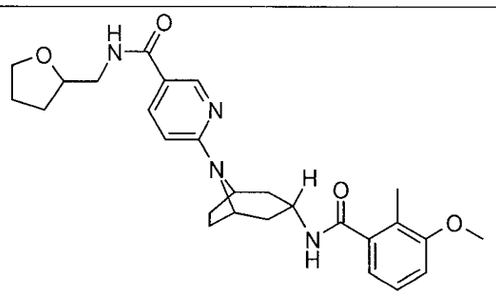
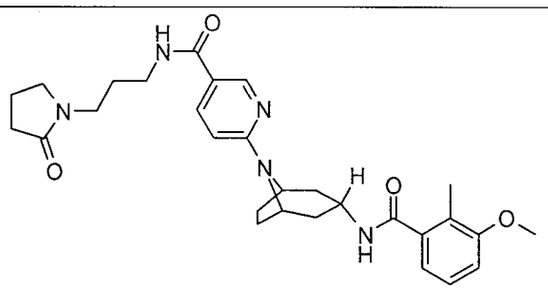
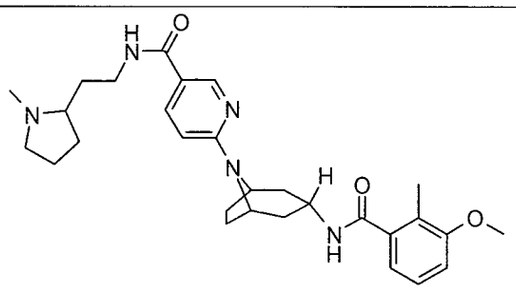
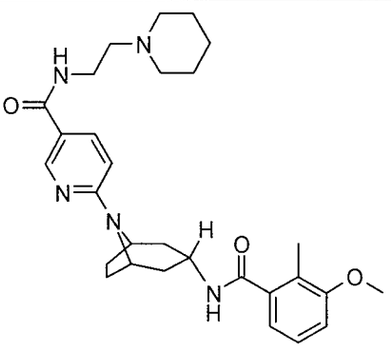
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(tetrahidrofuran-2-ilmetil)piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(2-oxopirrolidin-1-il)propil]piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(1-metilpirrolidin-2-il)etil]piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-piperidin-1-iletil)piridin-3-carboxamida **ACTIVIDAD = C**

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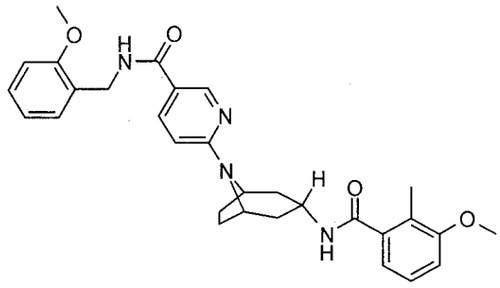
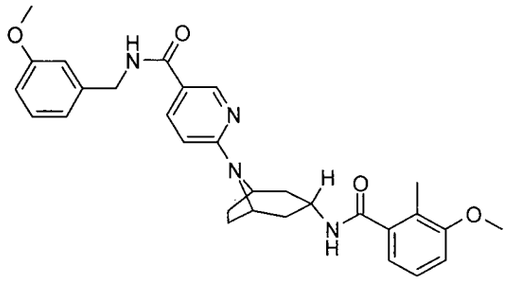
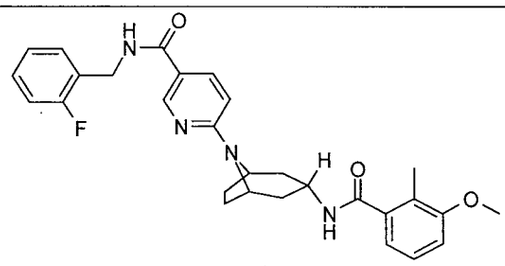
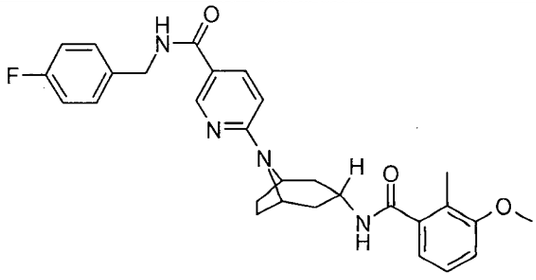
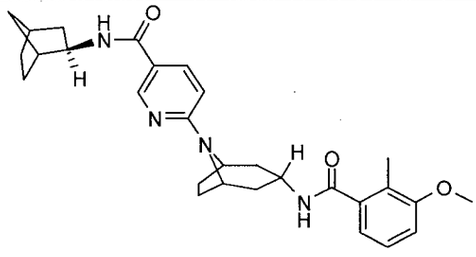
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[2-(metiloxi)fenil]metil}piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[3-(metiloxi)fenil]metil}piridin-3-carboxamida **ACTIVIDAD = D**
	N-[(2-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-[(4-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-[(1R,2R,4S)-biciclo[2.2.1]hept-2-il]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**

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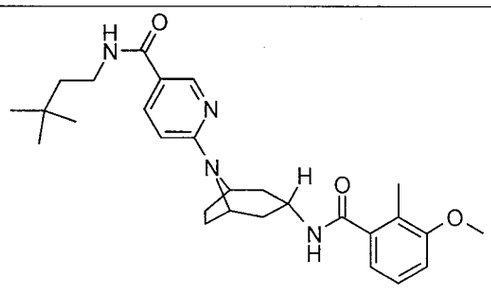
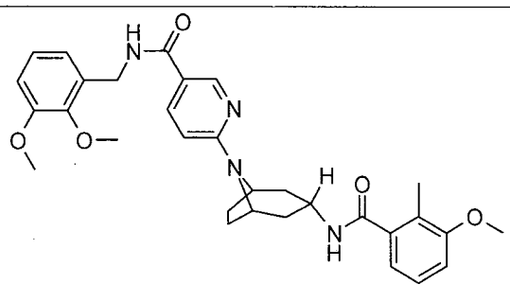
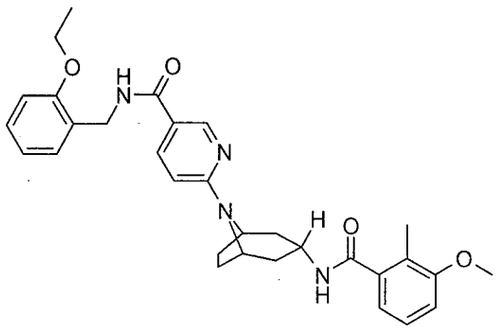
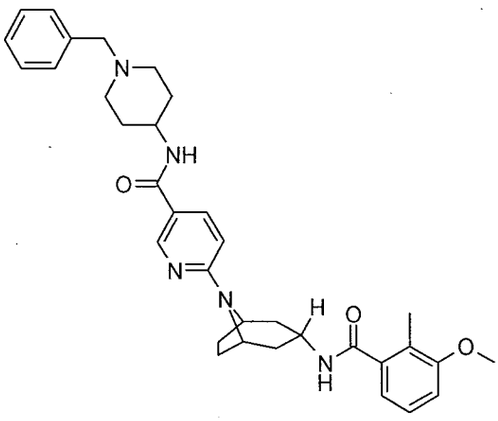
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-(3,3-dimetilbutil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	N-{[2,3-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	N-{[2-(etiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[1-(fenilmetil)piperidin-4-il]piridin-3-carboxamida **ACTIVIDAD = A**

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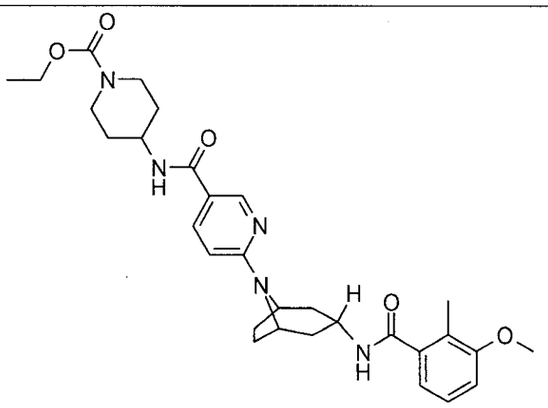
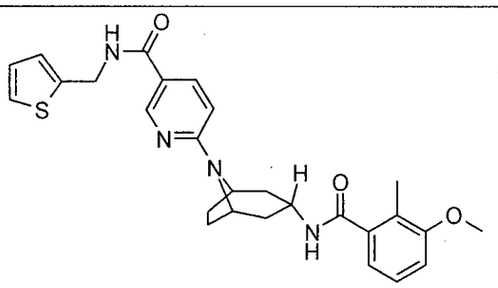
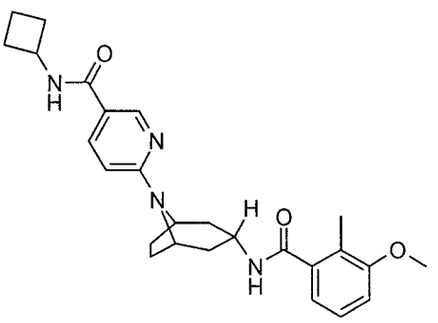
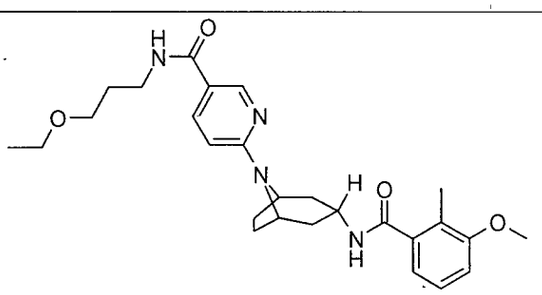
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	4-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino]piperidine-1-carboxilato de etilo **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-tienilmetil)piridin-3-carboxamida **ACTIVIDAD = A**
	N-ciclobutil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-[3-(etiloxi)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**

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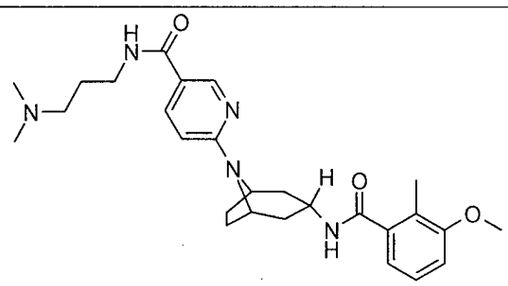
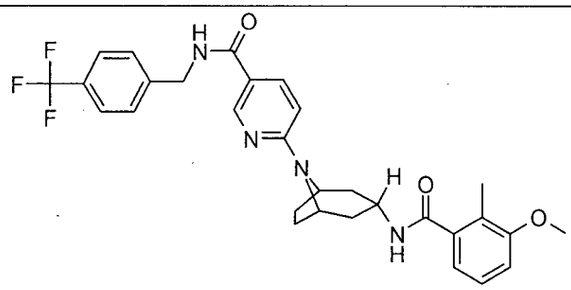
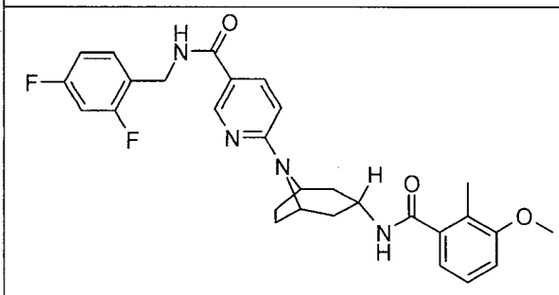
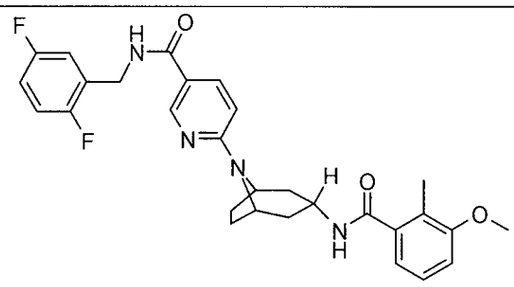
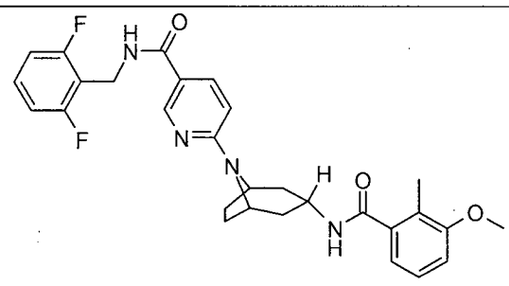
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[3-(dimetilamino)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(trifluorometil)fenil]metil}piridin-3-carboxamida **ACTIVIDAD = C**
	N-[(2,4-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-[(2,5-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-[(2,6-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**

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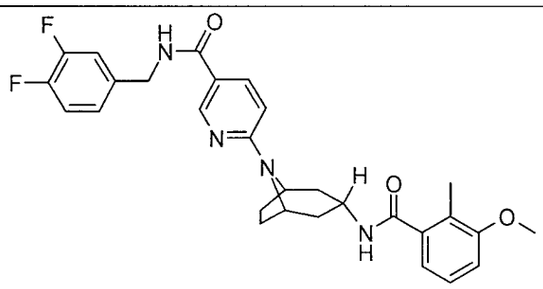
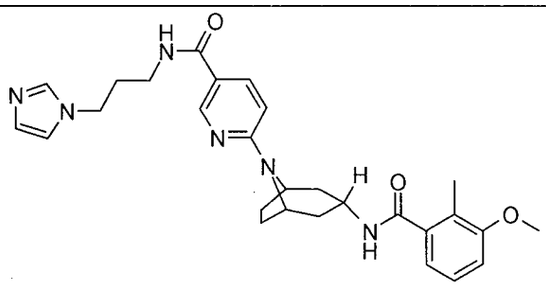
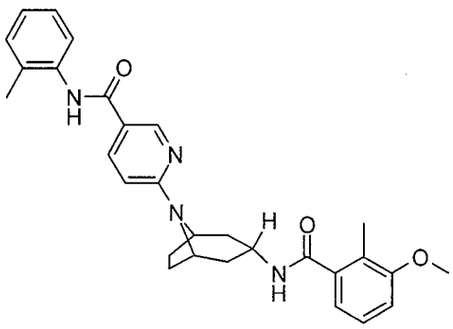
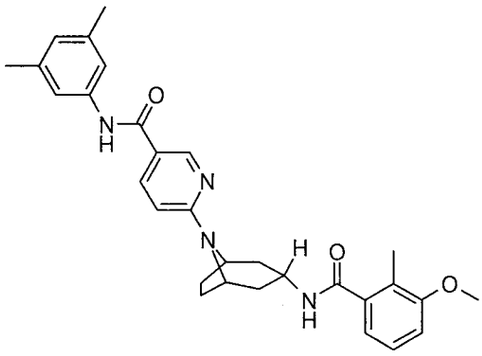
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[(3,4-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-[3-(1H-imidazol-1-il)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-metilfenil)piridin-3-carboxamida **ACTIVIDAD = D**
	N-(3,5-dimetilfenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**

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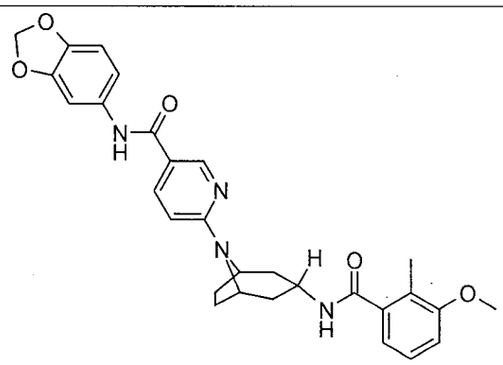
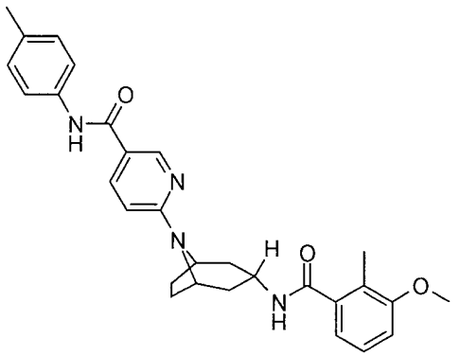
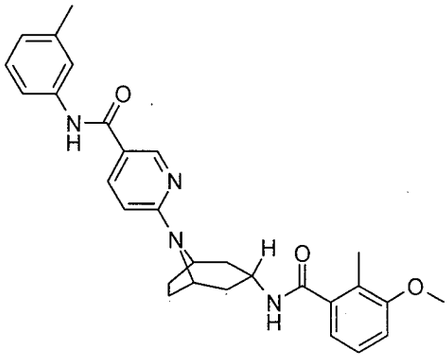
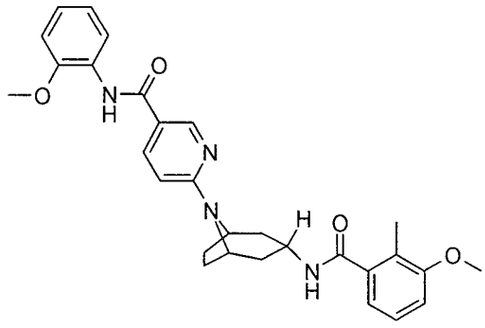
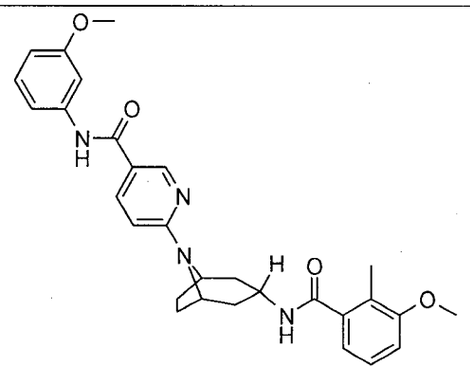
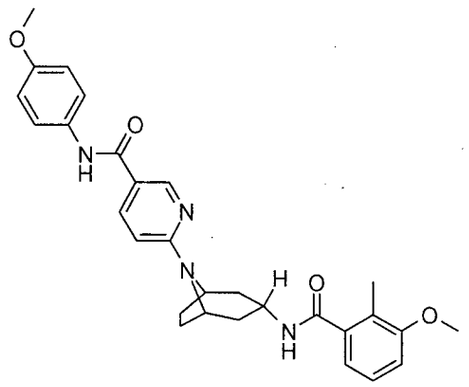
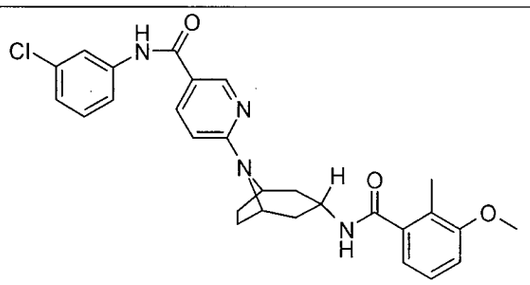
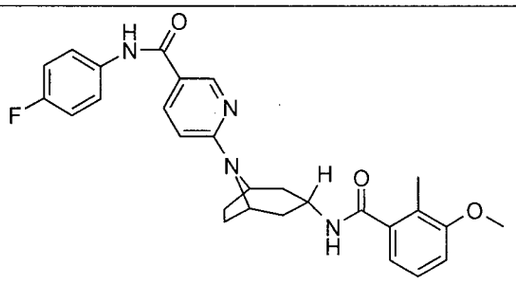
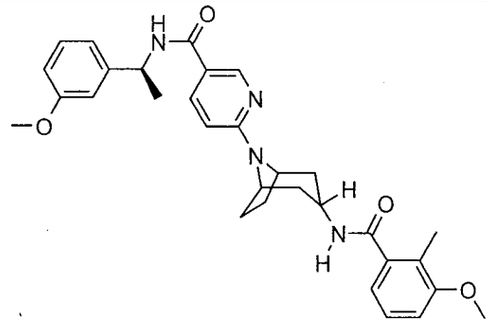
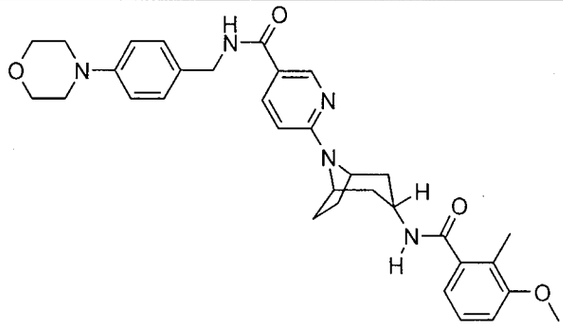
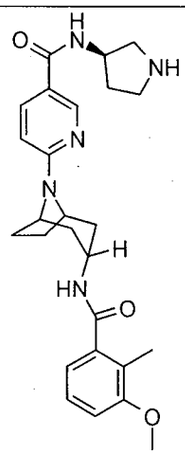
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-1,3-benzodioxol-5-il-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(4-metilfenil)piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(3-metilfenil)piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(metiloxi)fenil]piridin-3-carboxamida **ACTIVIDAD = D**

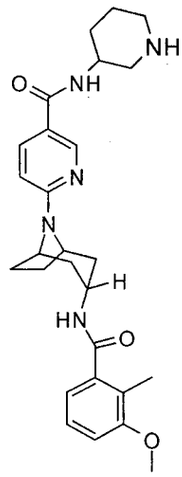
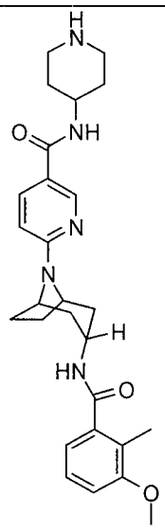
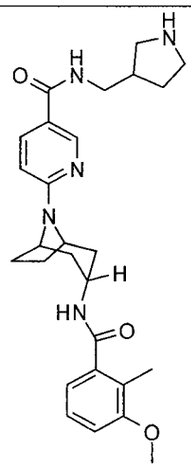
61S

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(metiloxi)fenil]piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[4-(metiloxi)fenil]piridin-3-carboxamida **ACTIVIDAD = B**
	N-(3-clorofenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	N-(4-fluorofenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**

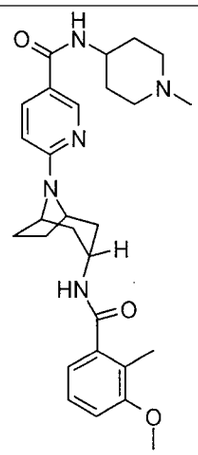
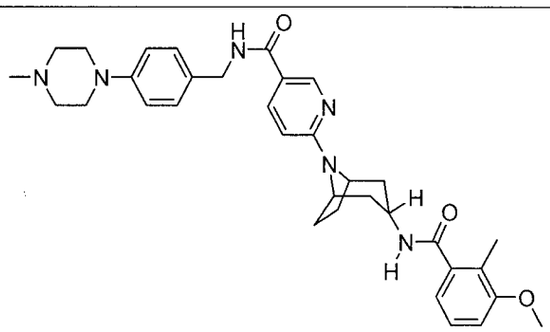
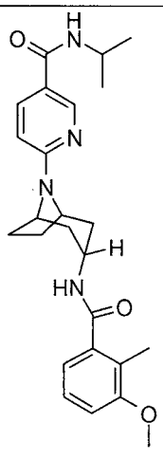
616

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[3-(metiloxi)fenil]etil}piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-morfolin-4-ilfenil)metil]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3R)-pirrolidin-3-il]piridin-3-carboxamida **ACTIVIDAD = B**

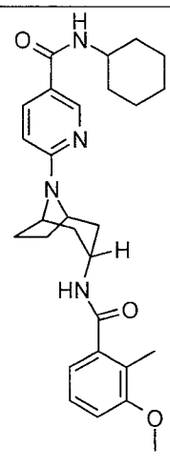
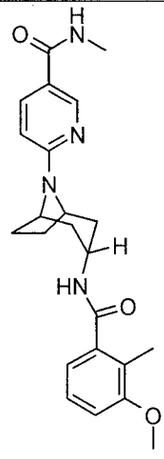
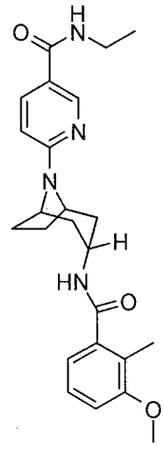
617

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-piperidin-3-ilpiridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-piperidin-4-ilpiridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(pirrolidin-3-ilmetil)piridin-3-carboxamida **ACTIVIDAD = A**

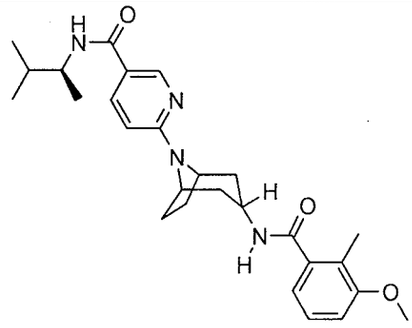
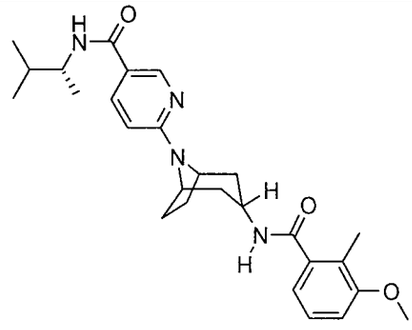
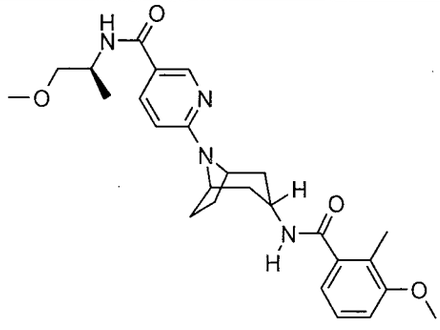
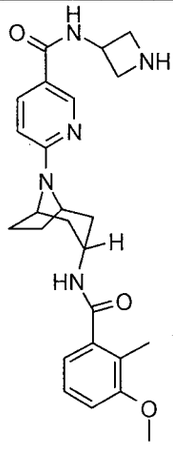
618

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(1-metilpiperidin-4-il)piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida **ACTIVIDAD = A**
	N-(1-metiletil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**

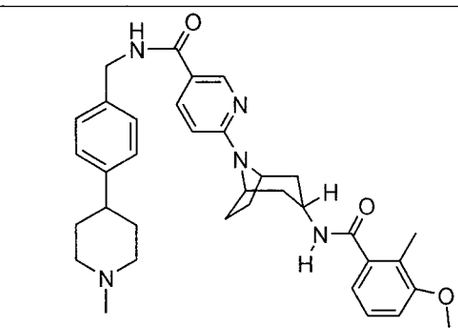
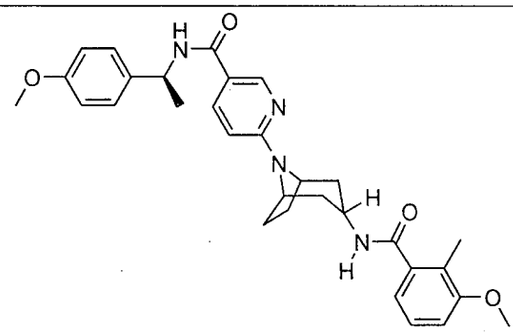
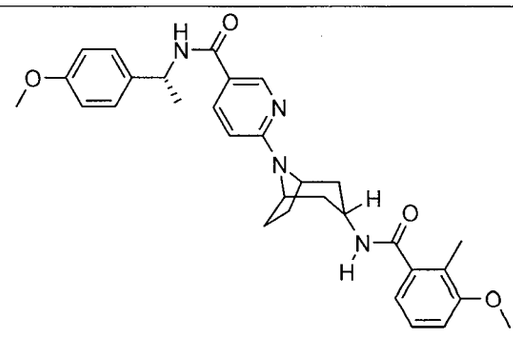
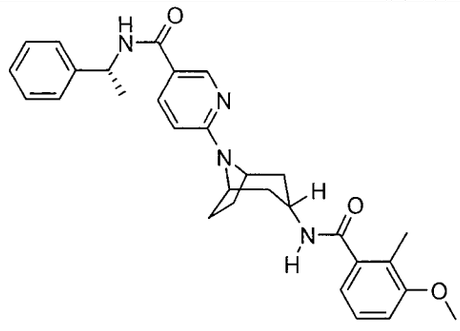
619

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-ciclohexil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-metil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	N-etil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**

620.

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[(1S)-1,2-dimetilpropil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	N-[(1R)-1,2-dimetilpropil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	N-[(1S)-1-metil-2-(metiloxi)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	N-azetidin-3-il-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**

621

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(1-metilpiperidin-4-il)fenil]metil}piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(metiloxi)fenil]etil}piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1R)-1-[4-(metiloxi)fenil]etil}piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1R)-1-feniletil]piridin-3-carboxamida **ACTIVIDAD = D**

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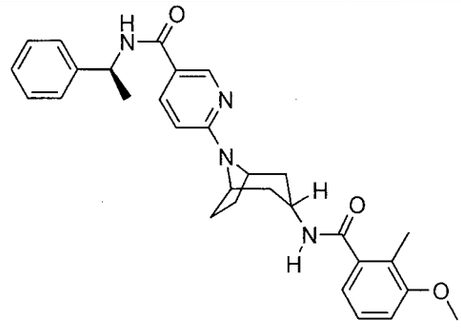
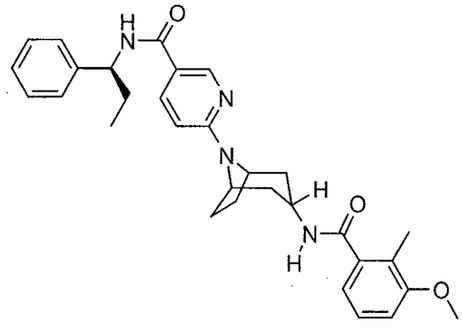
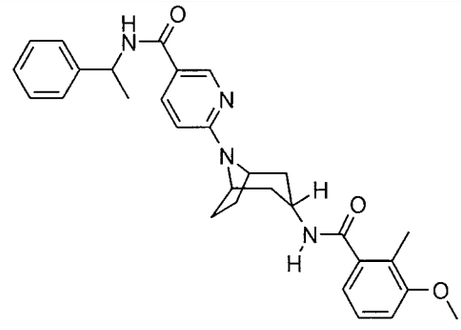
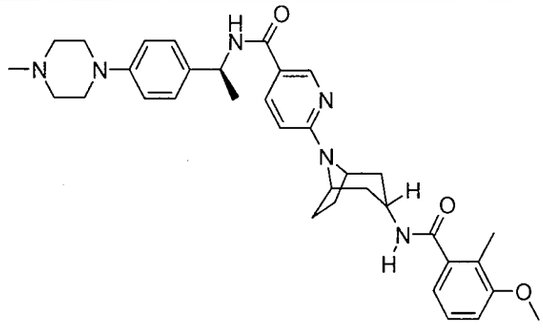
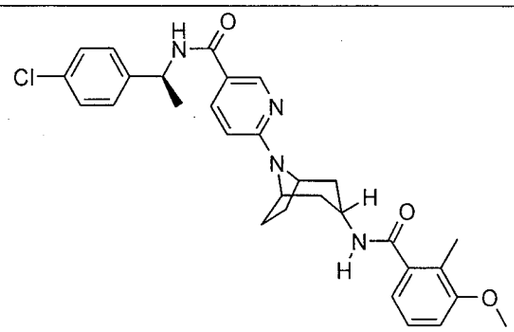
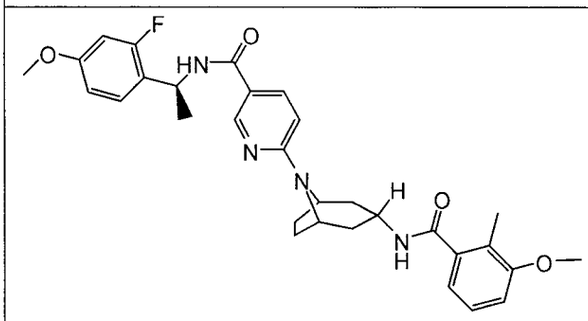
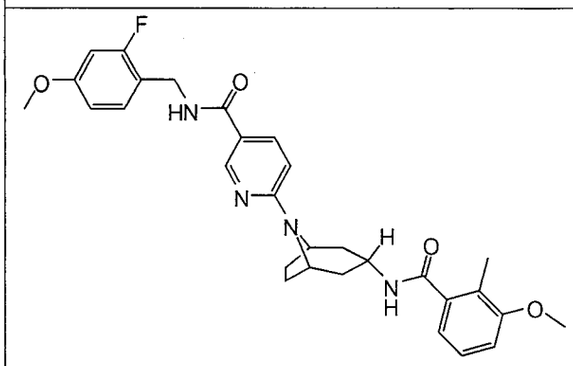
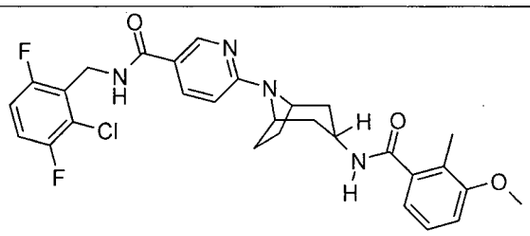
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1S)-1-feniletil]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1S)-1-fenilpropil]piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-((1-feniletil)piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida **ACTIVIDAD = A**

623

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[(1S)-1-(4-clorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-{(1S)-1-[2-fluoro-4-(metiloxi)fenil]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-{[2-fluoro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-[(2-cloro-3,6-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**

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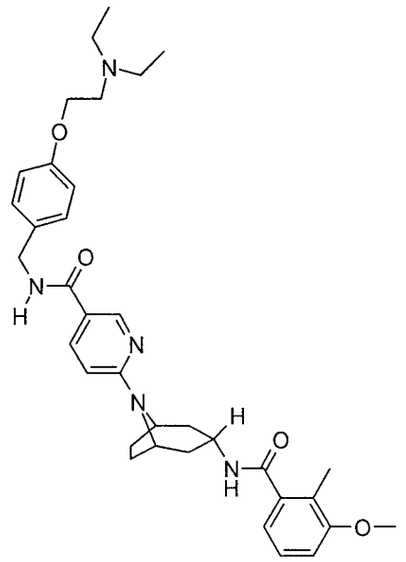
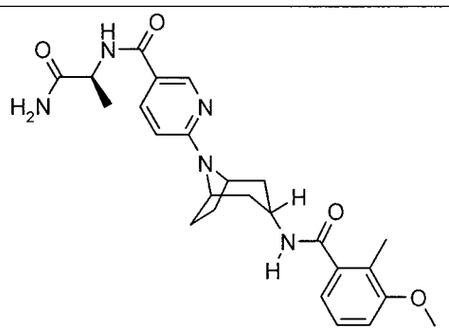
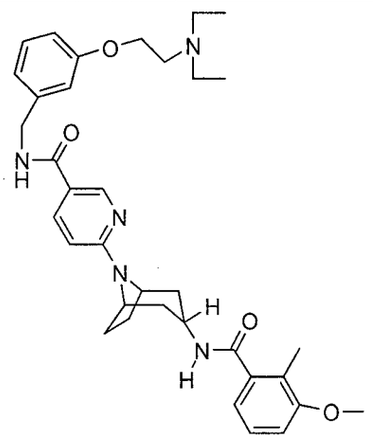
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[(4-{[2-(dietilamino)etil]oxi}fenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-[(1S)-2-amino-1-metil-2-oxoetil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-[(3-{[2-(dietilamino)etil]oxi}fenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**

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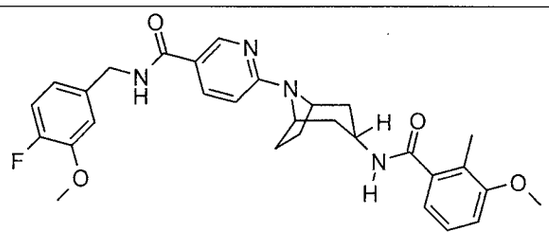
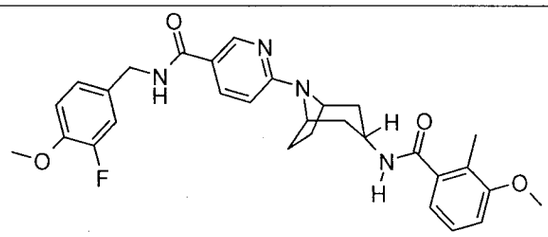
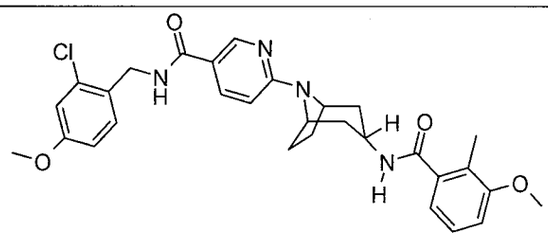
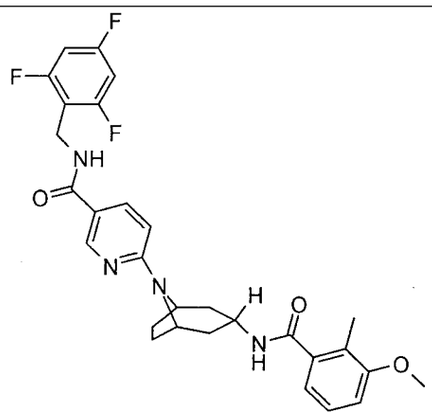
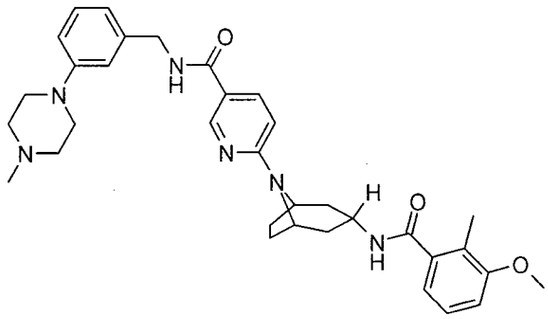
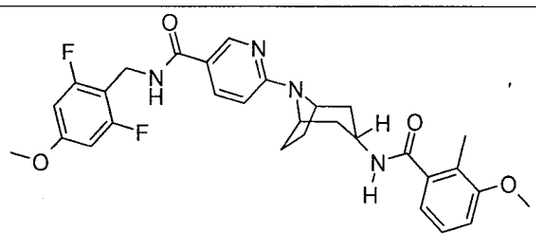
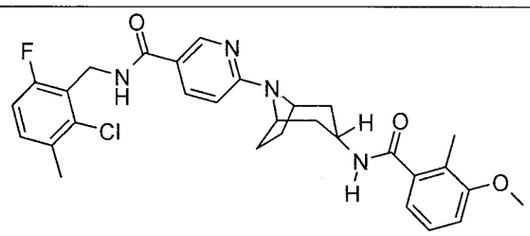
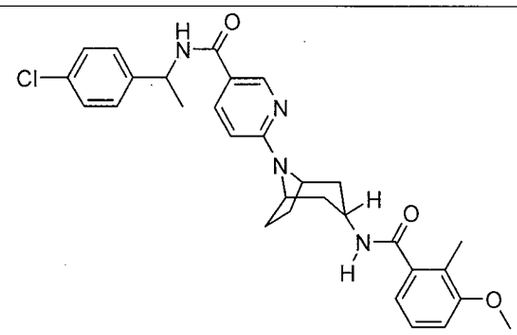
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{[4-fluoro-3-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-{[3-fluoro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-{[2-cloro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2,4,6-trifluorofenil)metil]piridin-3-carboxamida **ACTIVIDAD = A**

616.

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[3-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida **ACTIVIDAD = A**
	N-{[2,6-difluoro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-[(2-cloro-6-fluoro-3-metilfenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-[1-(4-clorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**

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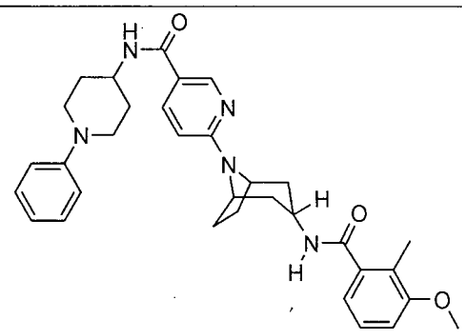
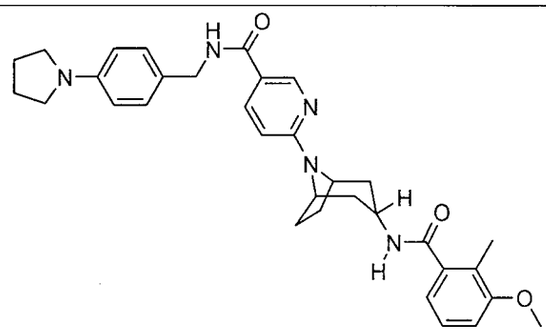
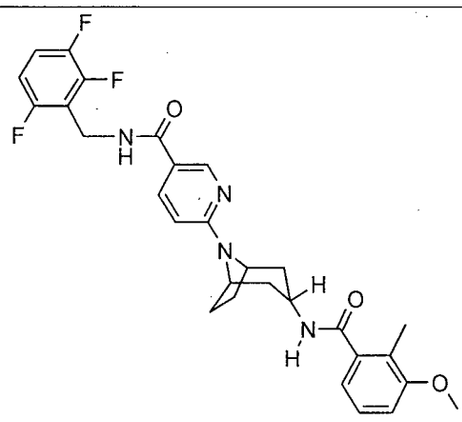
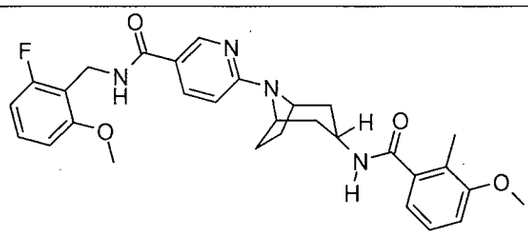
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(1-fenilpiperidin-4-il)piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-pirrolidin-1-ilfenil)metil]piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2,3,6-trifluorofenil)metil]piridin-3-carboxamida **ACTIVIDAD = B**
	N-{[2-fluoro-6-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**

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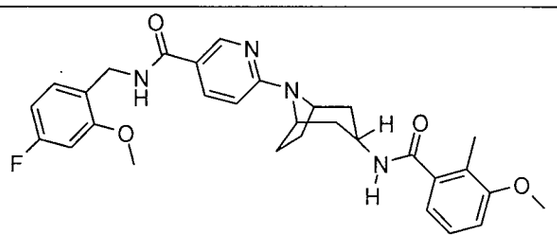
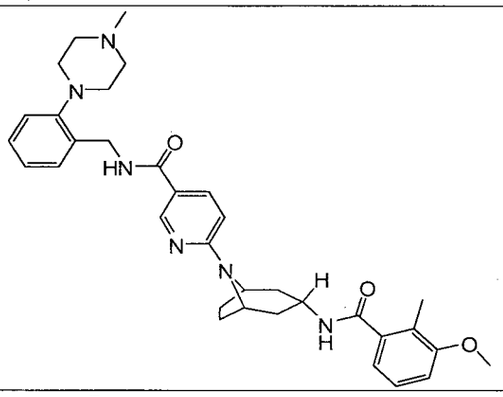
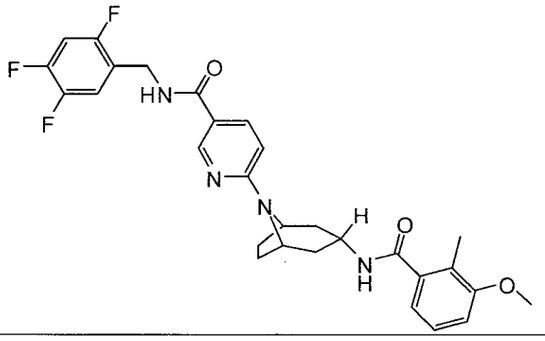
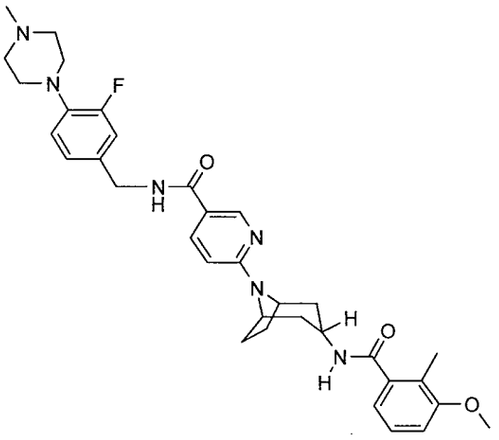
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{[4-fluoro-2-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[2-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2,4,5-trifluorofenil)metil]piridin-3-carboxamida **ACTIVIDAD = B**
	N-{[3-fluoro-4-(4-metilpiperazin-1-il)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**

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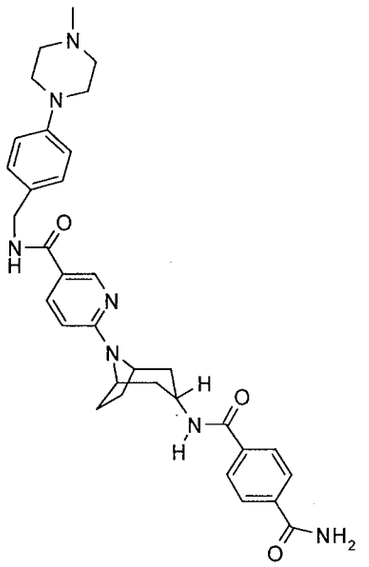
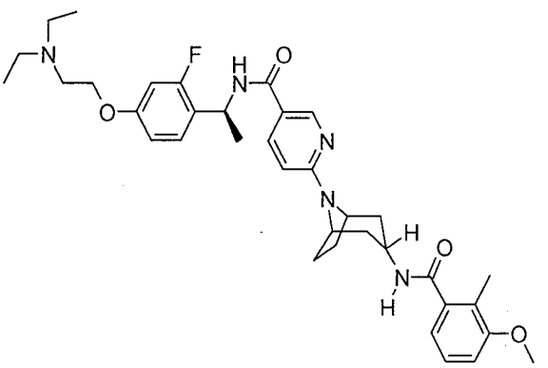
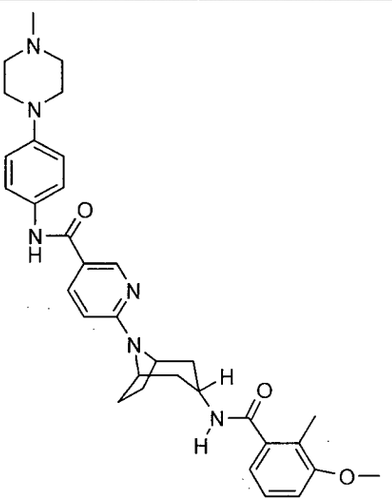
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-(8-{5-[({[4-(4-metilpiperazin-1-il)fenil]metil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-[(1S)-1-(4-{[2-(dietilamino)etil]oxi}-2-fluorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[4-(4-metilpiperazin-1-il)fenil]piridin-3-carboxamida **ACTIVIDAD = A**

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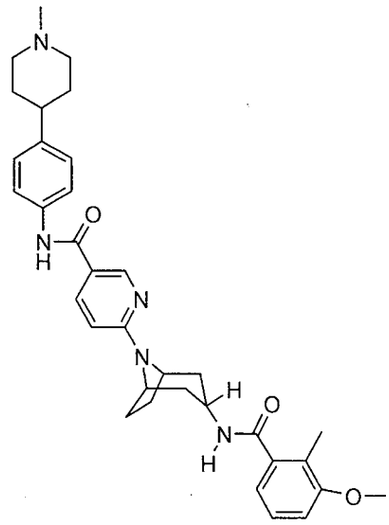
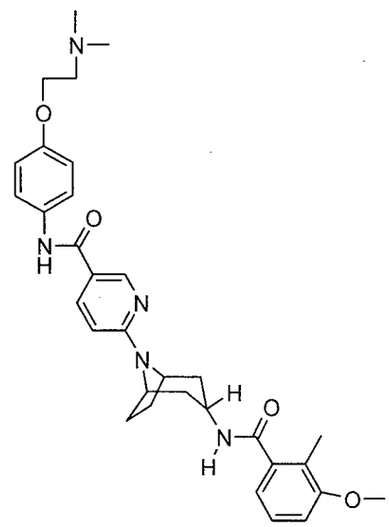
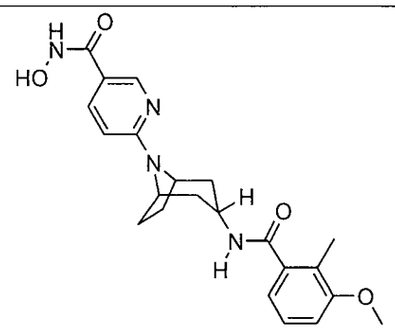
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[4-(1-metilpiperidin-4-il)fenil]piridin-3-carboxamida **ACTIVIDAD = C**
	N-(4-{[2-(dimetilamino)etil]oxi}fenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-hidroxi-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**

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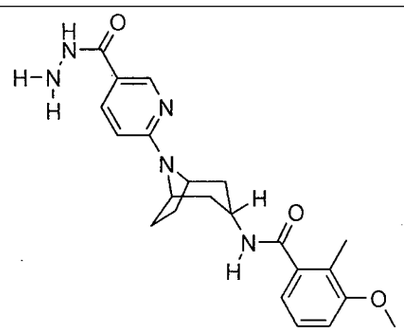
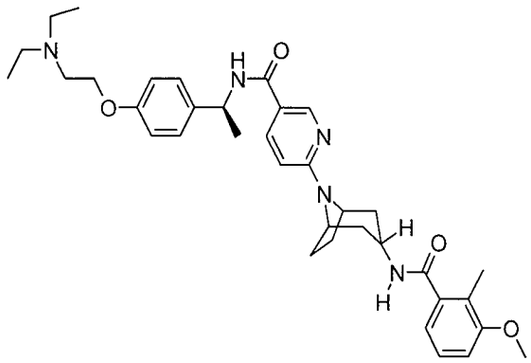
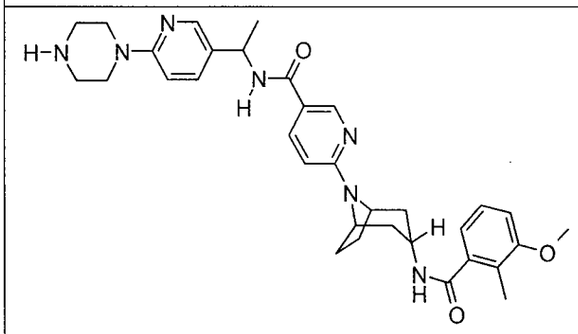
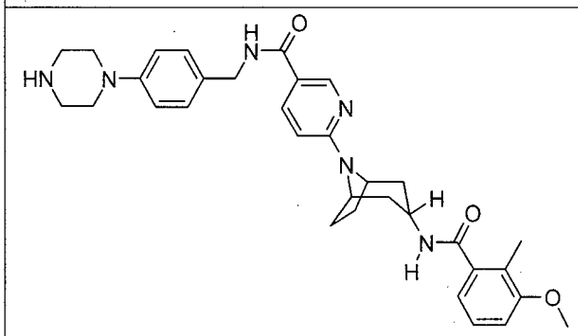
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{8-[5-(hidrazinocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-3-(metiloxi)benzamida **ACTIVIDAD = D**
	N-[(1S)-1-(4-{[2-(dietilamino)etil]oxi}fenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[1-(6-piperazin-1-ilpiridin-3-il)etil]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-piperazin-1-ilfenil)metil]piridin-3-carboxamida **ACTIVIDAD = A**

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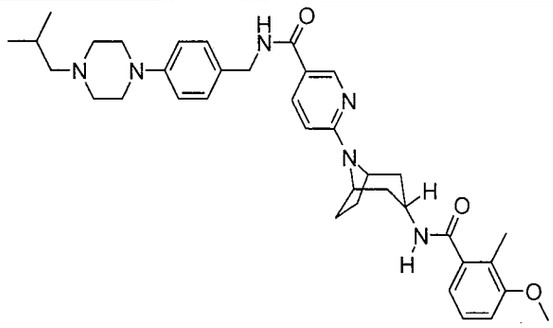
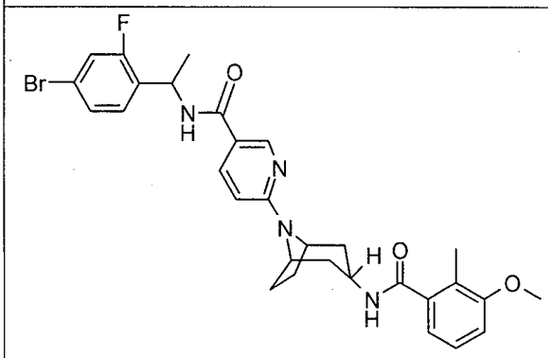
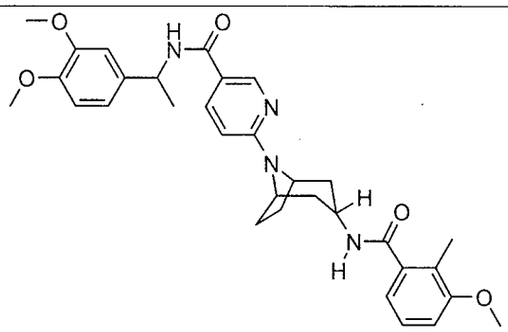
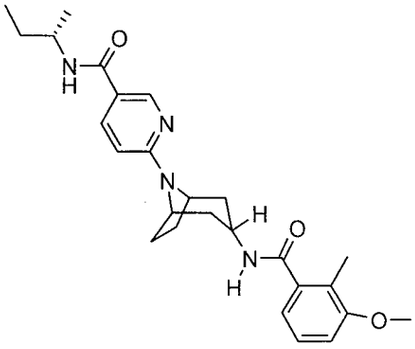
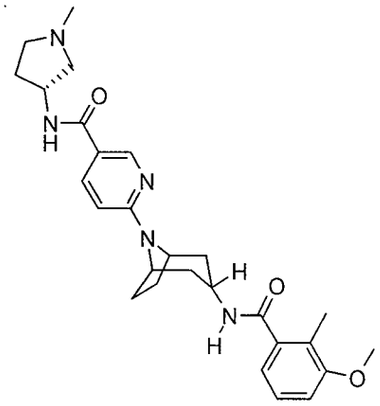
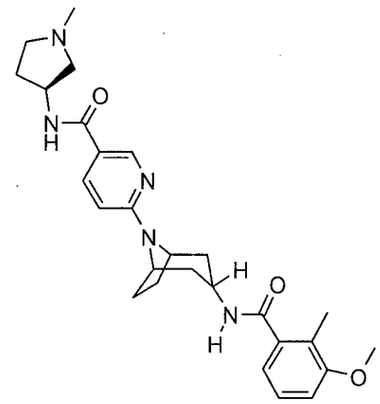
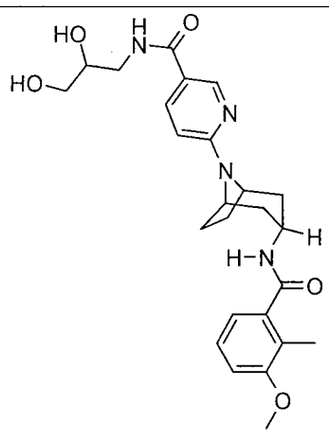
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-({4-[4-(2-metilpropil)piperazin-1-il]fenil}metil)piridin-3-carboxamida **ACTIVIDAD = A**
	N-[1-(4-bromo-2-fluorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	N-{1-[3,4-bis(metiloxi)fenil]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1S)-1-metilpropil]piridin-3-carboxamida **ACTIVIDAD = D**

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3R)-1-metilpirrolidin-3-il]piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3S)-1-metilpirrolidin-3-il]piridin-3-carboxamida **ACTIVIDAD = C**
	N-(2,3-dihidroxipropil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**

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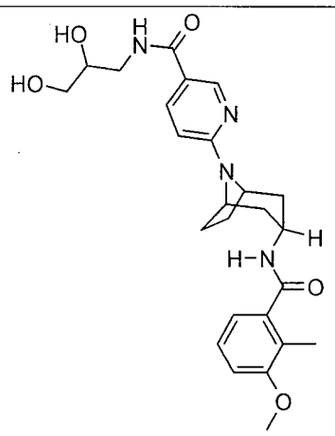
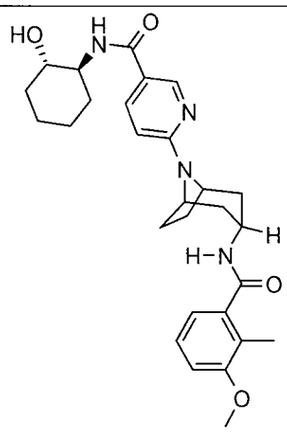
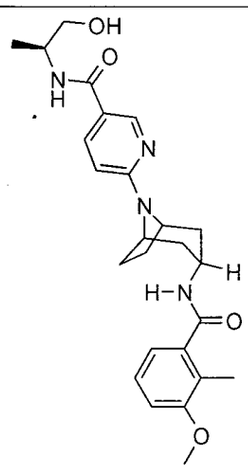
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[(1S,2S)-2-hidroxiciclopentil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-[(1S,2S)-2-hidroxiciclohexil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	N-[(1S)-2-hidroxi-1-metiletil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**

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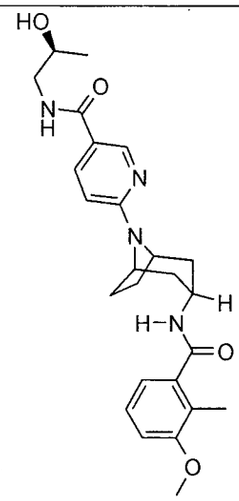
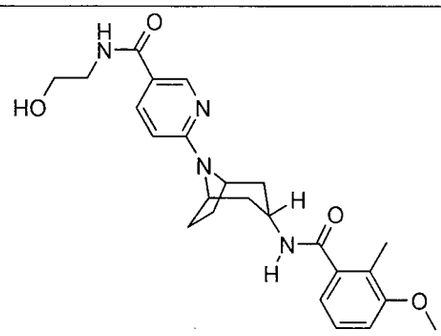
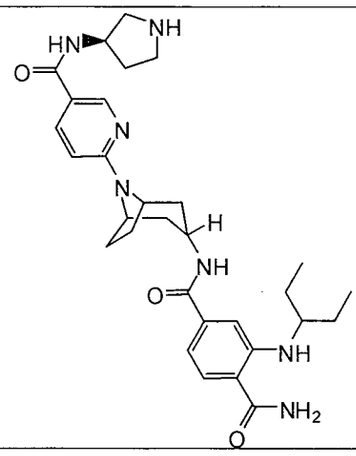
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[(2S)-2-hidroxipropil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	N-(2-hidroxietil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	2-[(1-etilpropil)amino]-N4-[8-(5-{[(3R)-pirrolidin-3-ilamino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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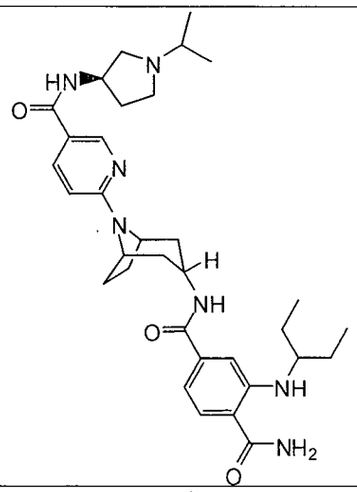
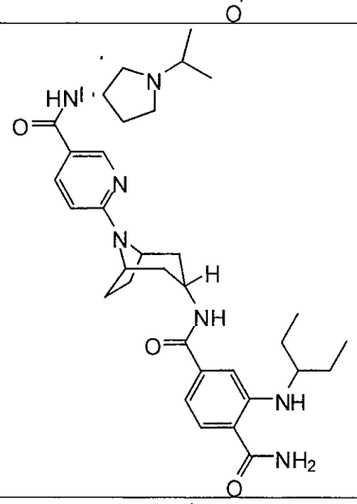
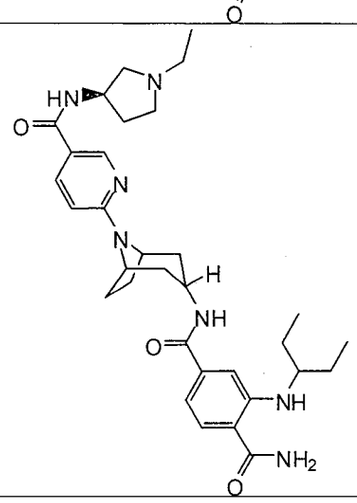
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-[(1-etilpropil)amino]-N4-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(1-etilpropil)amino]-N4-{8-[5-({[(3S)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(1-etilpropil)amino]-N4-{8-[5-({[(3R)-1-etilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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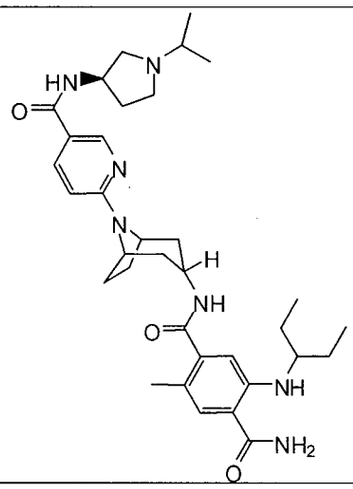
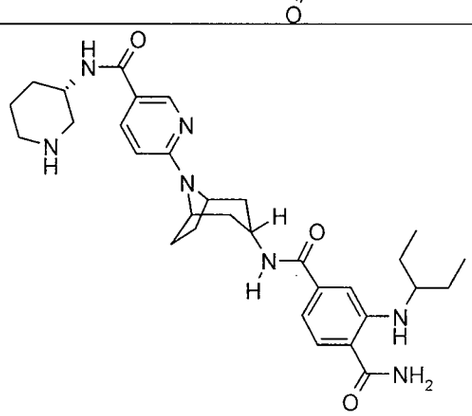
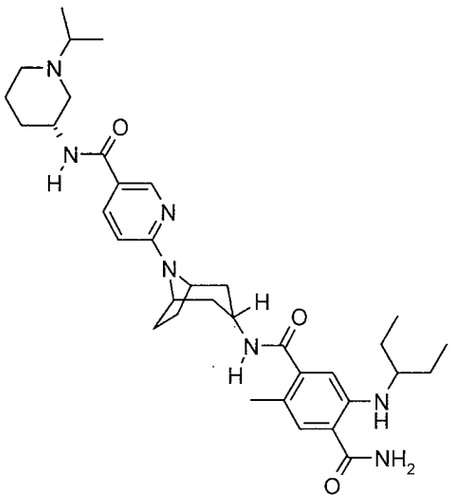
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	5-[(1-etilpropil)amino]-2-metil-N-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(1-etilpropil)amino]-N4-[8-(5-{[(3S)-piperidin-3-ilamino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	5-[(1-etilpropil)amino]-2-metil-N-{8-[5-({[(3R)-1-(1-metiletil)piperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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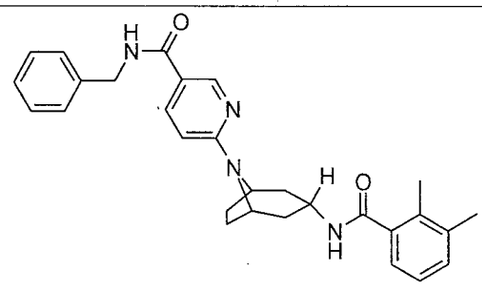
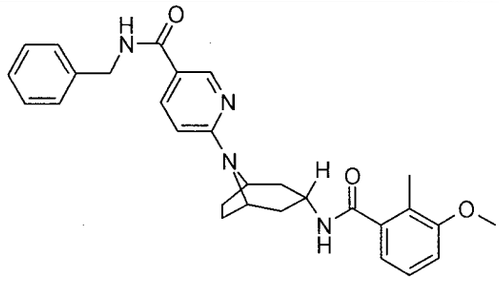
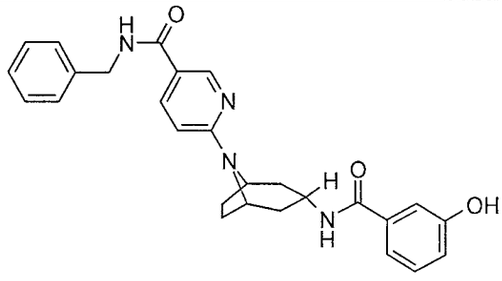
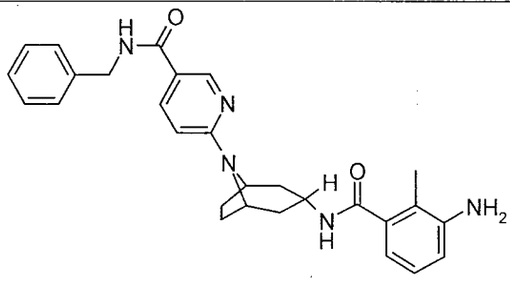
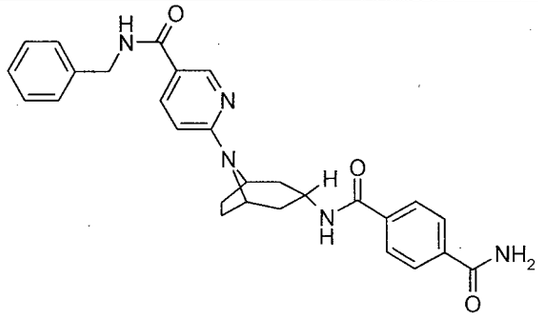
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-(3-endo-{[(2,3-dimetilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = A**
	6-(3-endo-{[(3-hidroxi-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = C**
	6-(3-endo-{[(3-amino-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = D**
	N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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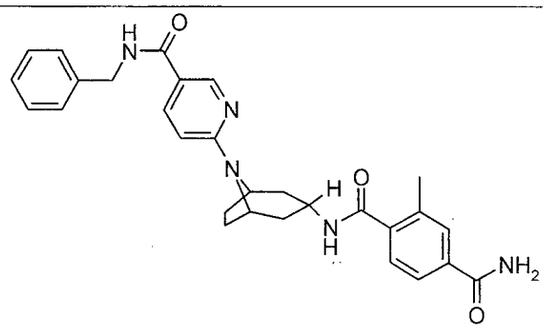
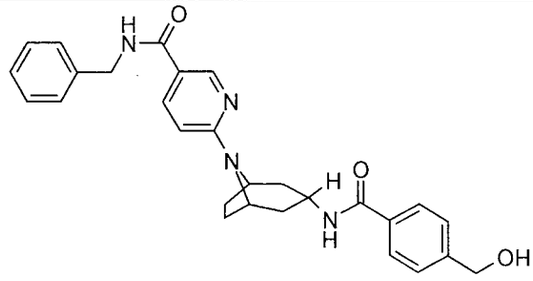
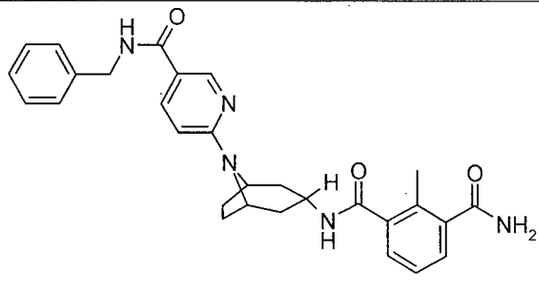
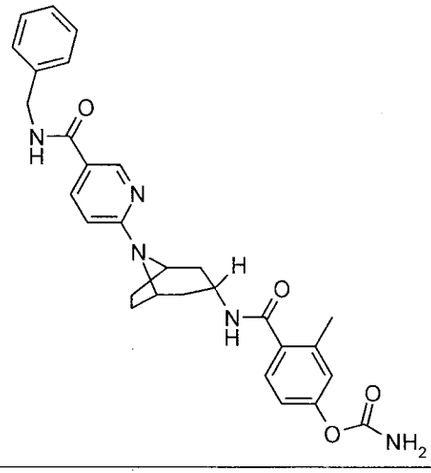
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-metil-N1-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida **ACTIVIDAD = B**
	6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = A**
	2-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,3-dicarboxamida **ACTIVIDAD = D**
	3-metil-4-({[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]amino}carbonil)fenilcarbamato **ACTIVIDAD = D**

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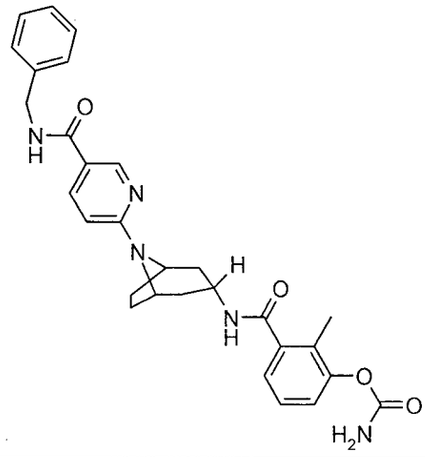
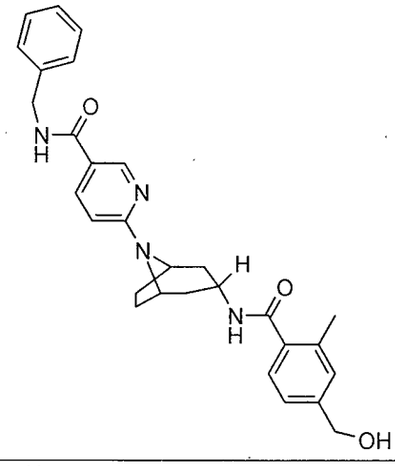
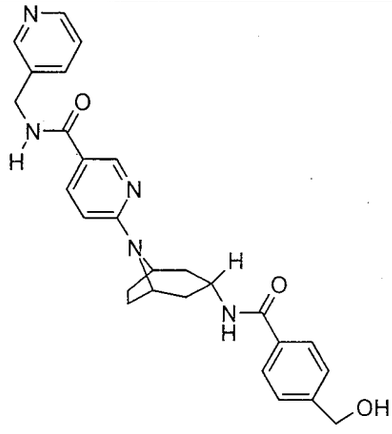
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-metil-3-({[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]amino}carbonil)fenil carbamato **ACTIVIDAD = D**
	6-[3-endo-({[4-(hidroximetil)-2-metilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(piridin-3-ilmetil)piridin-3-carboxamida **ACTIVIDAD = A**

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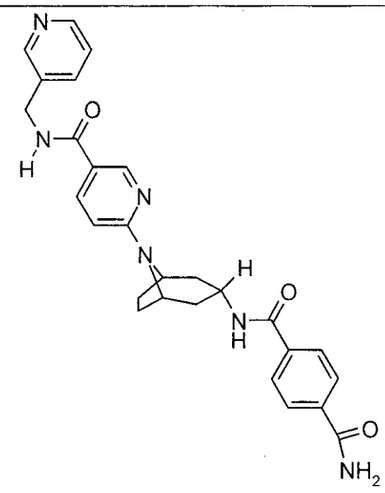
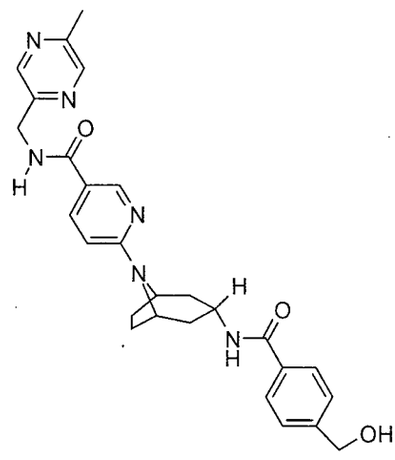
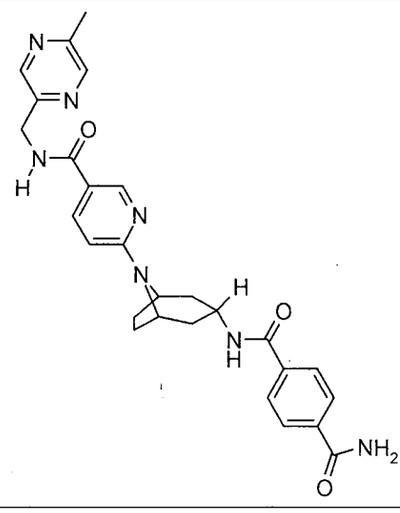
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[8-(5-{[(piridin-3-ilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(5-metilpirazin-2-il)metil]piridin-3-carboxamida **ACTIVIDAD = A**
	N-{8-[5-({[(5-metilpirazin-2-il)metil]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = C**

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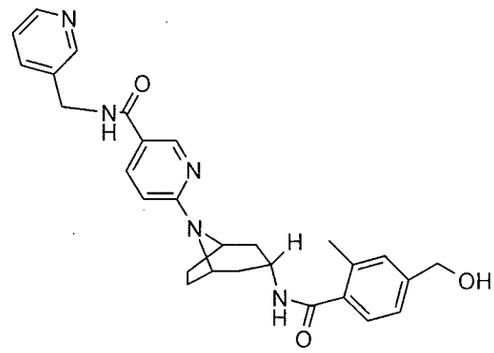
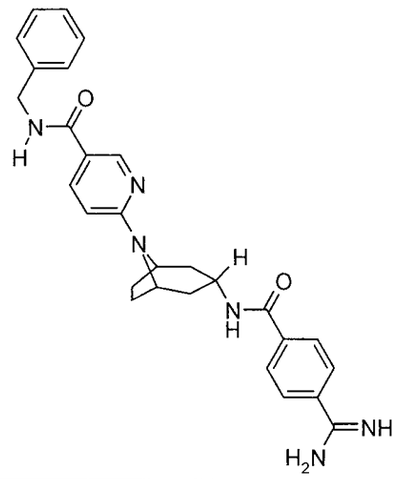
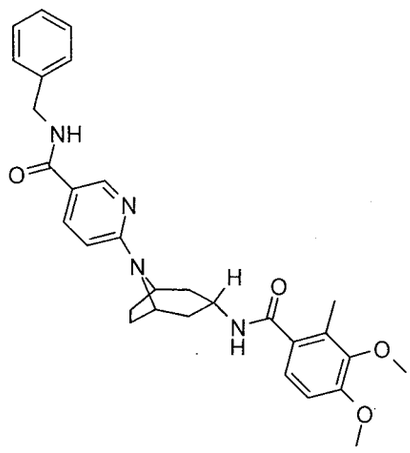
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[4-(hidroximetil)-2-metilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(piridin-3-ilmetil)piridin-3-carboxamida **ACTIVIDAD = A**
	6-{3-endo-[({4-[amino(imino)metil]fenil}carbonil)amino]-8-azabiciclo[3.2.1]oct-8-il}-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[2-metil-3,4-bis(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = D**

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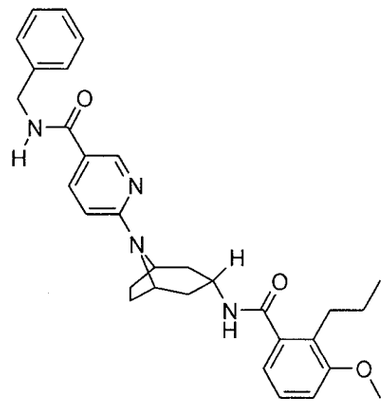
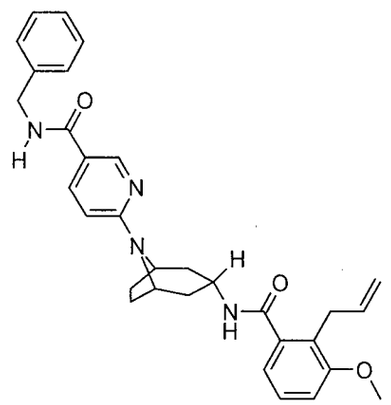
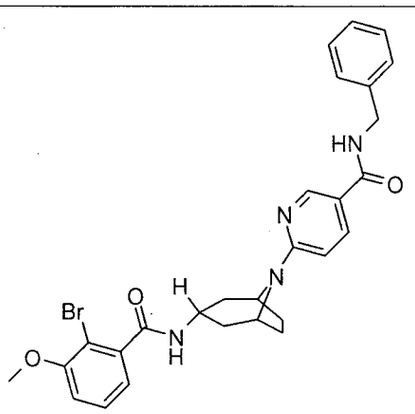
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[3-(metiloxi)-2-propilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[3-(metiloxi)-2-prop-2-en-1-ilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-bromo-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = C**

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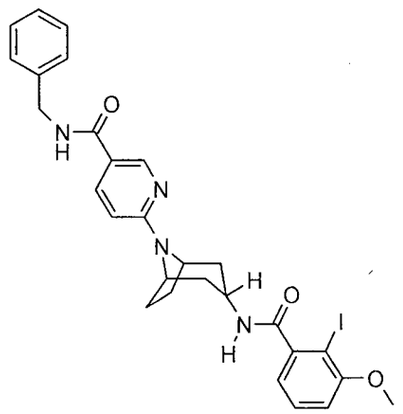
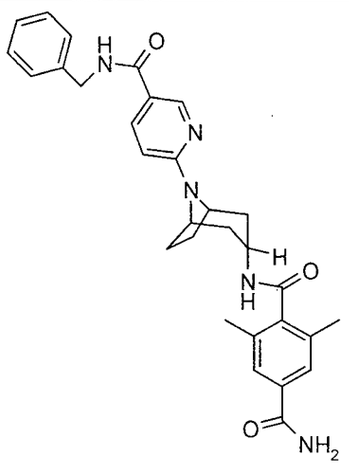
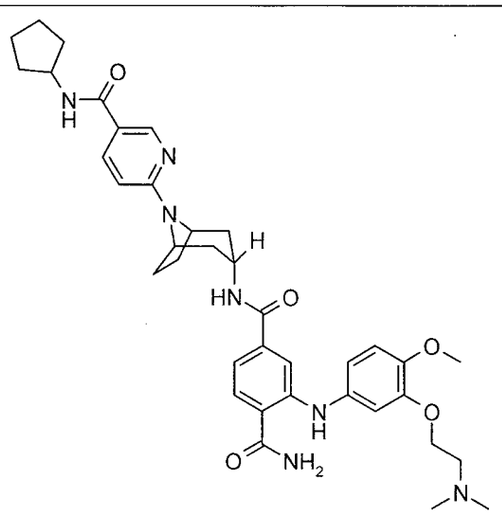
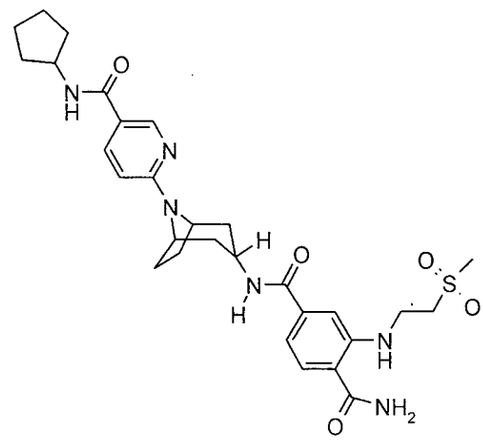
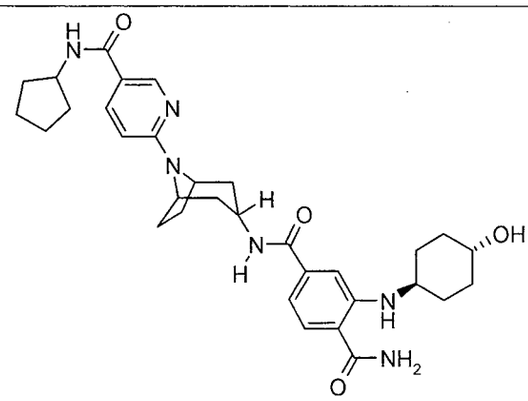
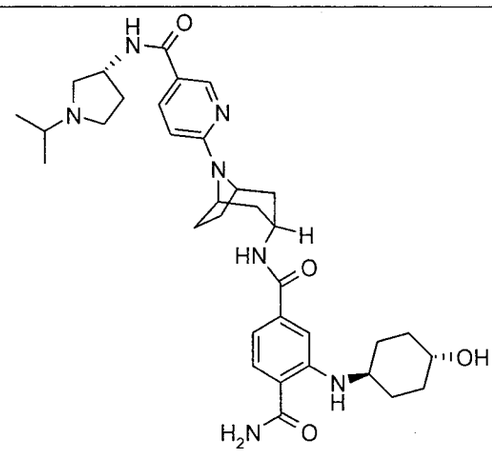
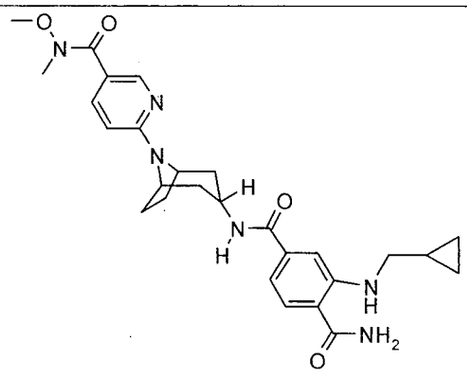
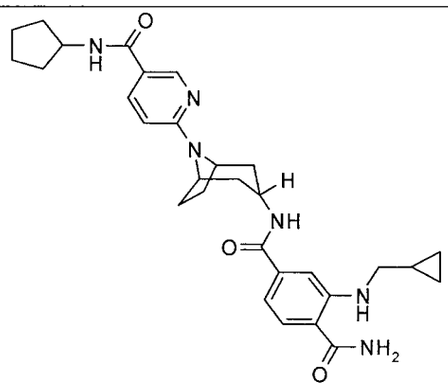
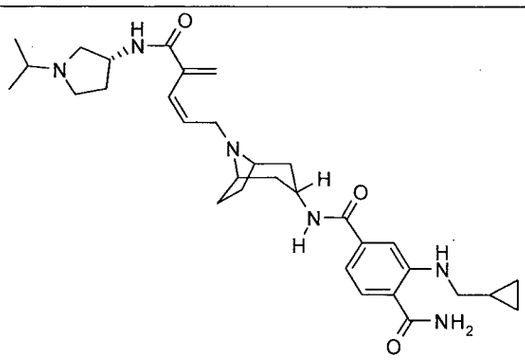
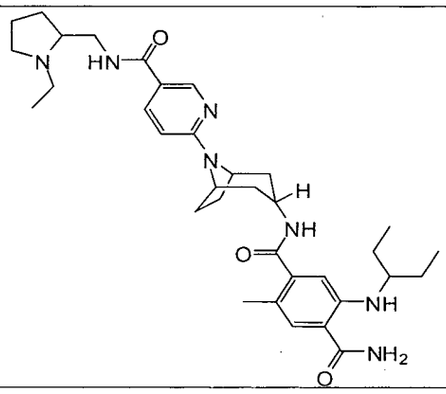
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-yodo-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = D**
	2,6-dimetil-N1-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida **ACTIVIDAD = B**
	N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[2-(metilsulfonil)etil]amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-[(4-trans-hidroxiciclohexil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(4-trans-hidroxiciclohexil)amino]-N4-{8-[5-({[1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-[(ciclopropilmetil)amino]-N4-[8-(5-{[metil(metiloxi)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida **ACTIVIDAD = C**
	N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil)amino]-N4-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	5-[(1-etilpropil)amino]-N-{8-[5-({[(1-etilpirrolidin-2-il)metil]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**

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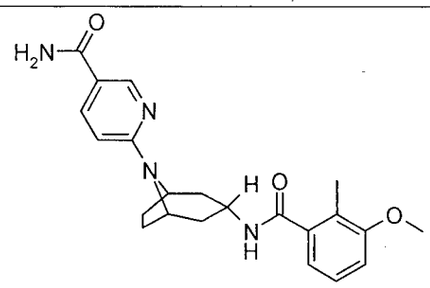
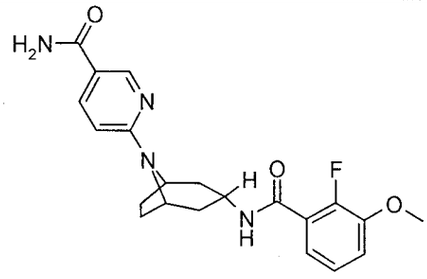
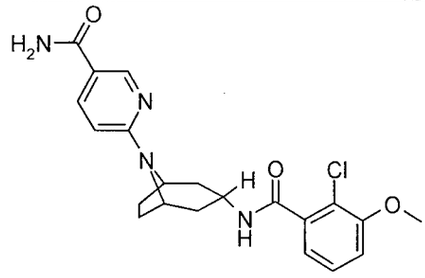
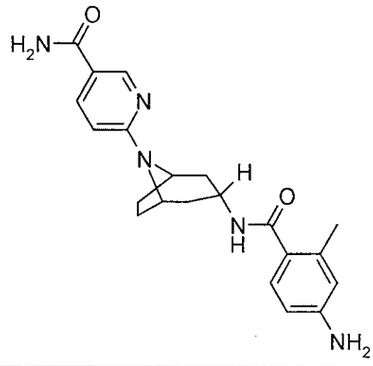
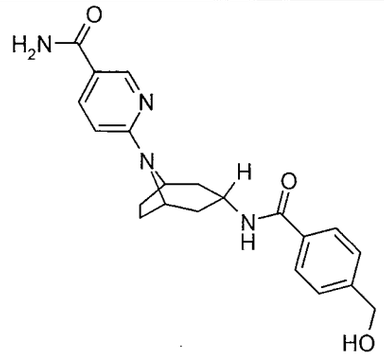
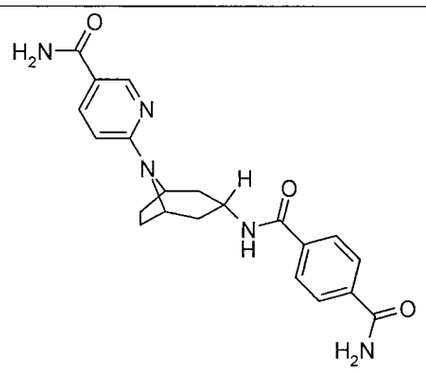
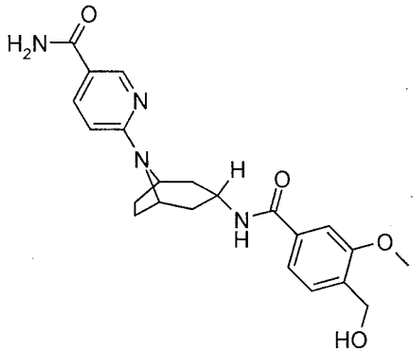
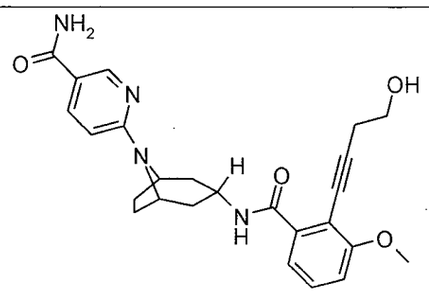
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-fluoro-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[2-cloro-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	6-(3-endo-{[(4-amino-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida **ACTIVIDAD = D**

648.

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = C**
	6-[3-endo-({[4-(hidroximetil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	6-[3-endo-({[2-(4-hidroxibut-1-in-1-il)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**

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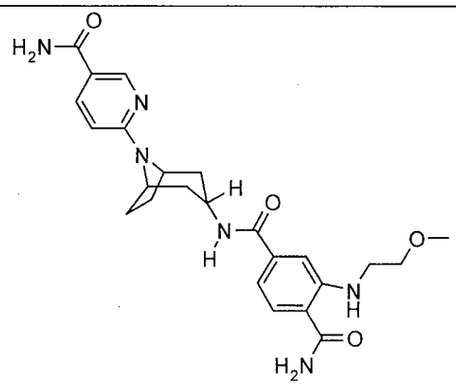
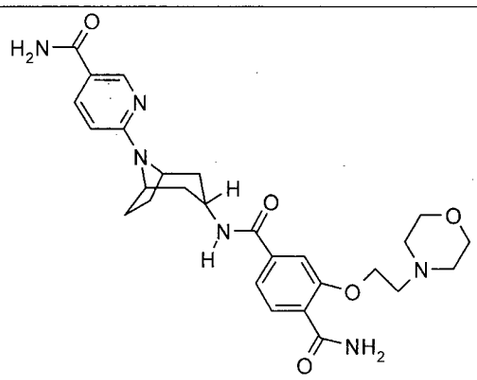
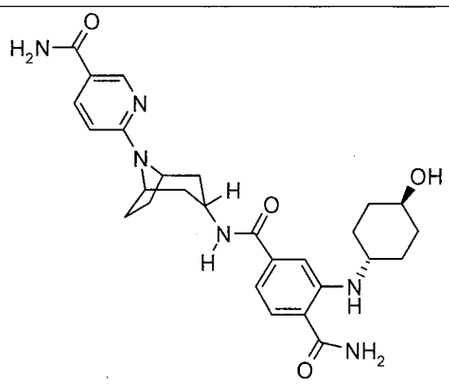
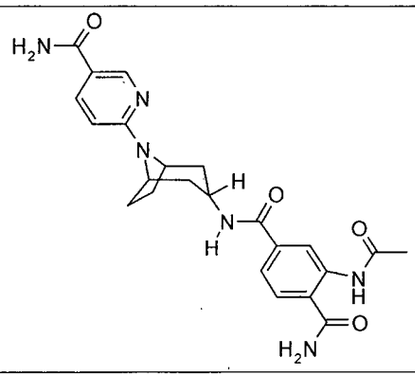
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[2-(metiloxi)etil]amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(2-morfolin-4-iletil)oxibencen-1,4-dicarboxilato de **ACTIVIDAD = C**
	N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(4-hidroxiciclohexil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-(acetilamino)-N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = C**

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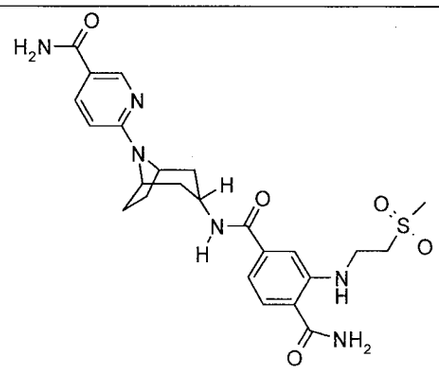
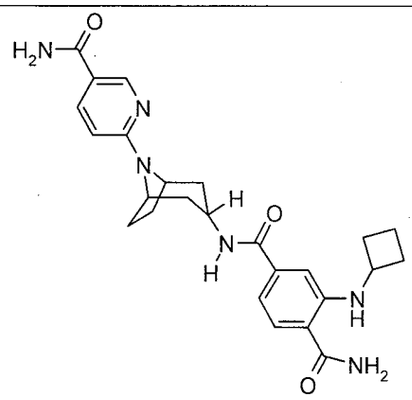
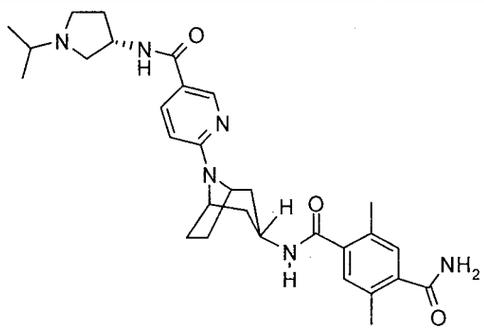
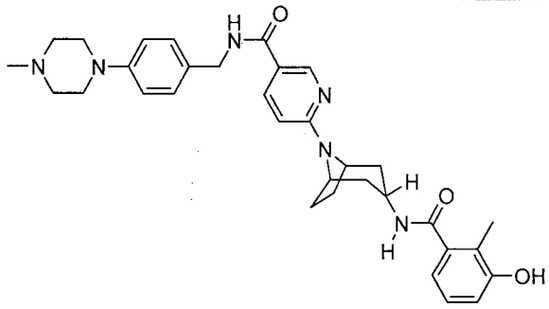
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[2-(metilsulfonil)etil]amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(ciclobutilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2,5-dimetil-N-{8-[5-({[(3S)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	6-(3-endo-{[(3-hidroxi-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida **ACTIVIDAD = A**

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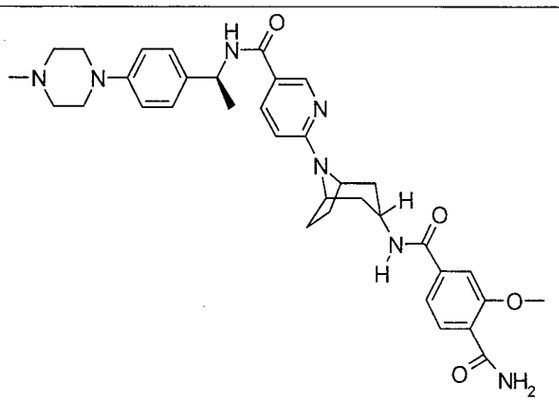
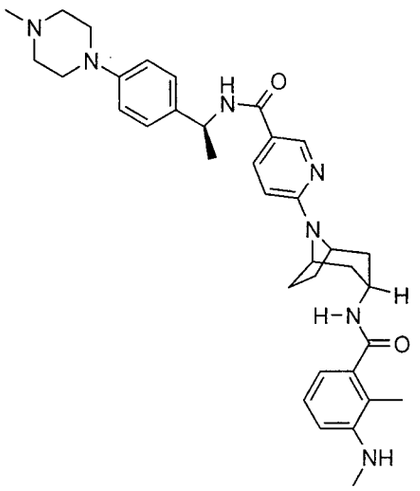
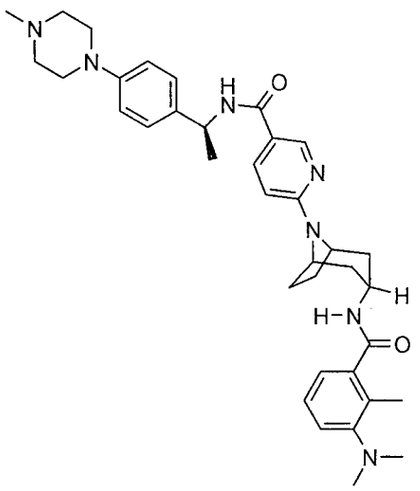
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-(metiloxi)-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-metil-3-(metilamino)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[3-(dimetilamino)-2-metilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida **ACTIVIDAD = D**

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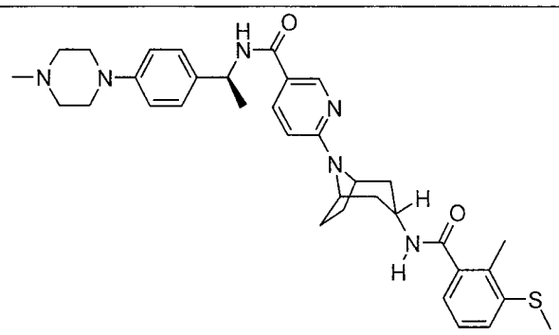
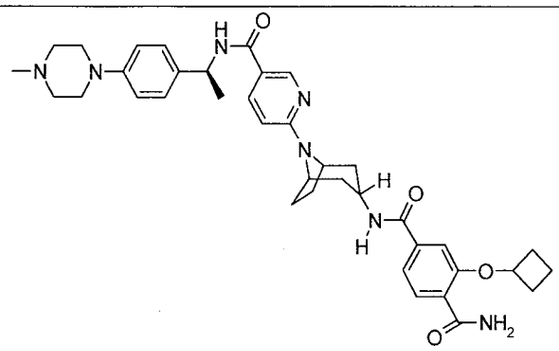
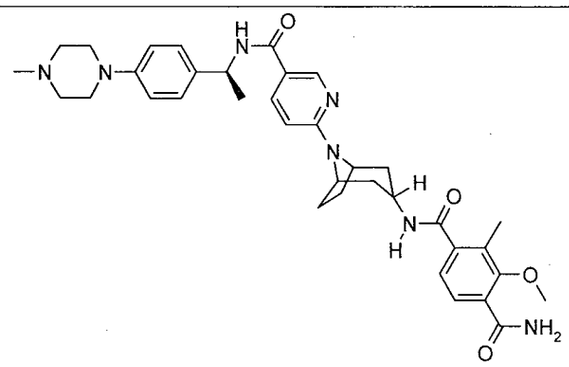
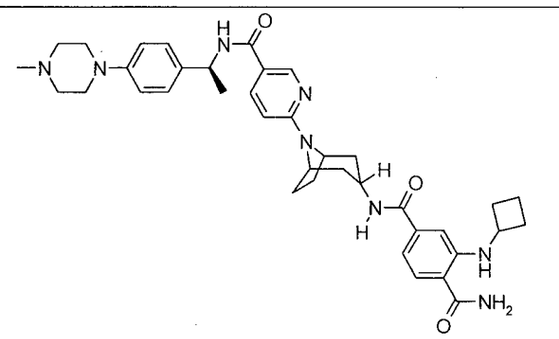
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-metil-3-(metiltio)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida **ACTIVIDAD = B**
	2-(ciclobutiloxi)-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = B**
	2-metil-3-(metiloxi)-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-(ciclobutilamino)-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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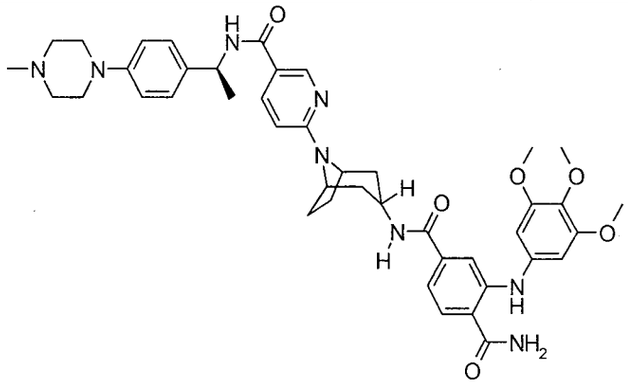
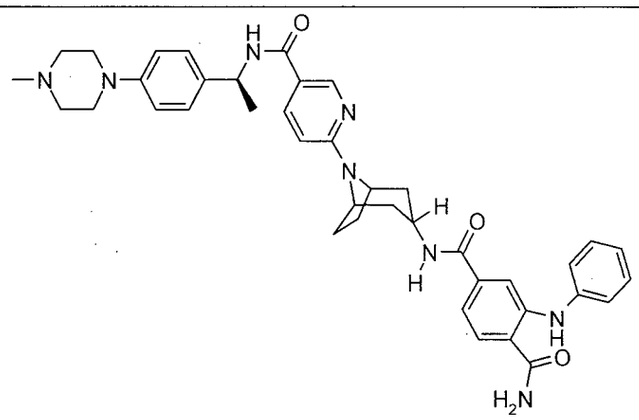
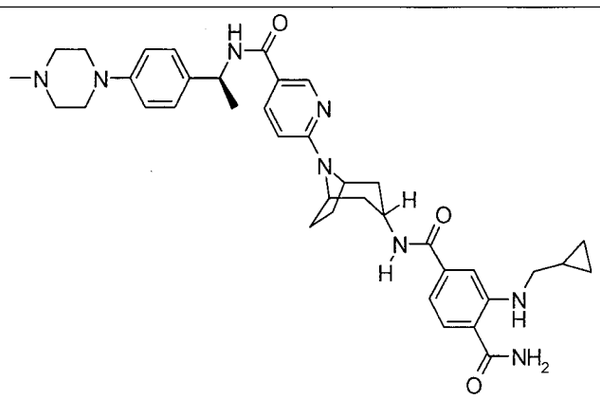
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[3,4,5-tris(metiloxi)fenil]amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-(fenilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil)amino]-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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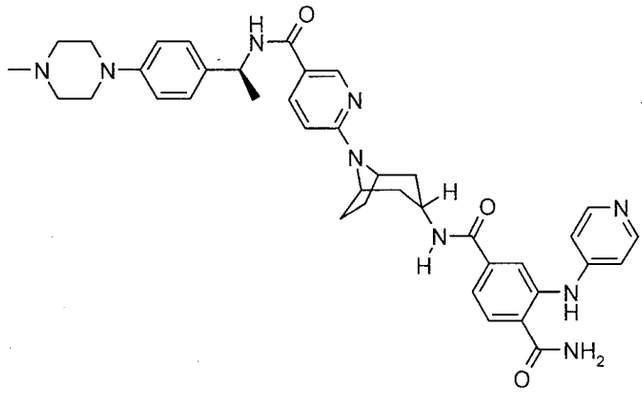
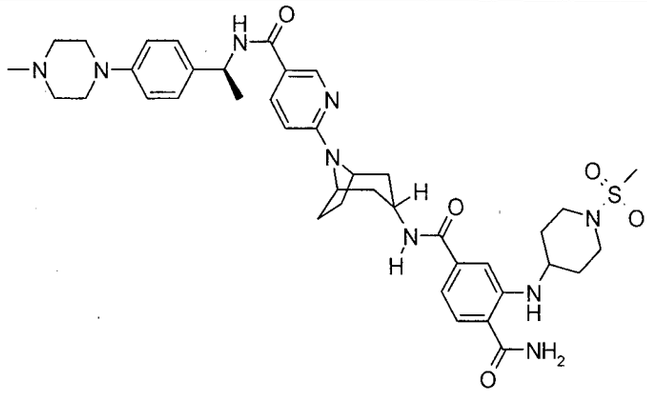
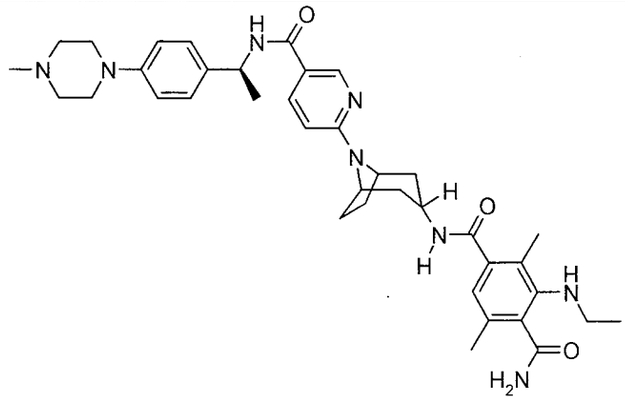
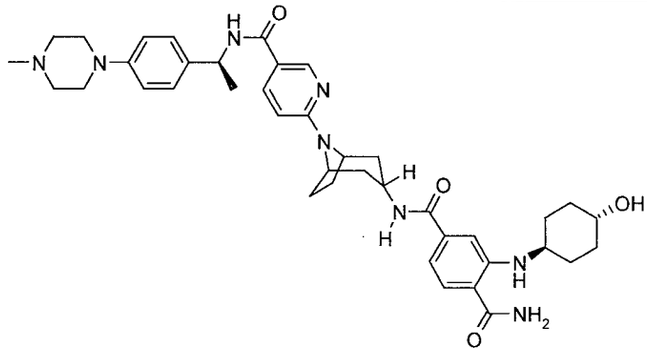
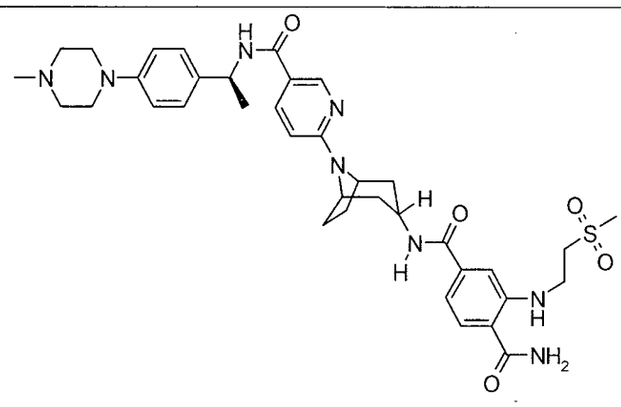
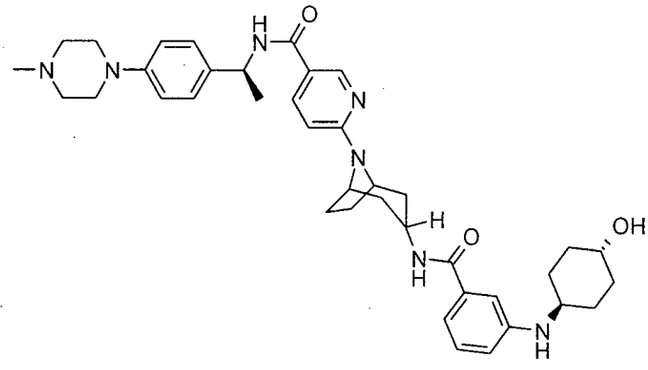
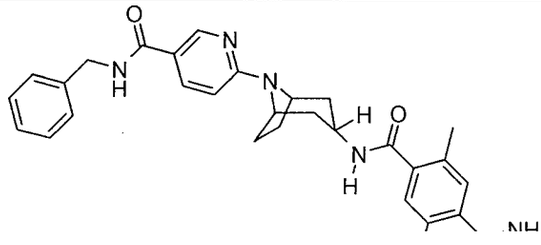
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-(piridin-4-ilamino)bencen-1,4-dicarboxilato de **ACTIVIDAD = A**
	N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[1-(metilsulfonil)piperidin-4-il]amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	3-(etilamino)-2,5-dimetil-N1-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = D**

6 SS

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-[(4-hidroxiciclohexil)amino]-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[2-(metilsulfonil)etil]amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	6-{3-endo-[({3-[(4-hidroxiciclohexil)amino]fenil}carbonil)amino]-8-azabiciclo[3.2.1]oct-8-il}-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida **ACTIVIDAD = D**
	2,5-dimetil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida

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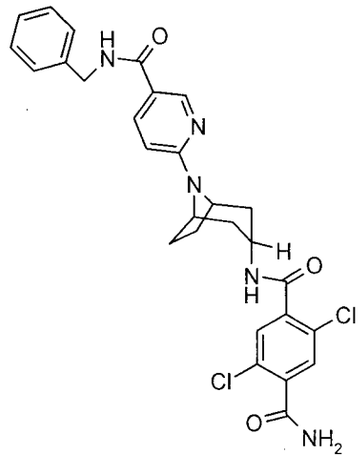
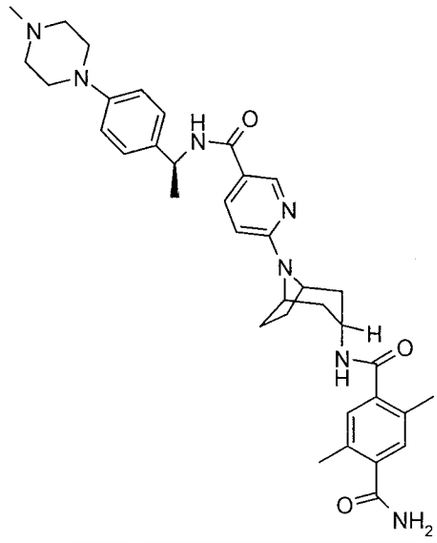
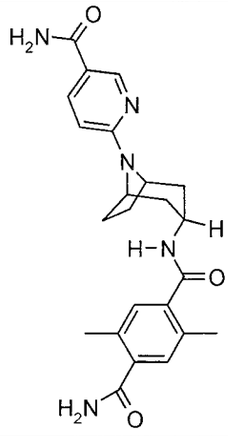
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2,5-dicloro-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2,5-dimetil-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida **ACTIVIDAD = A**

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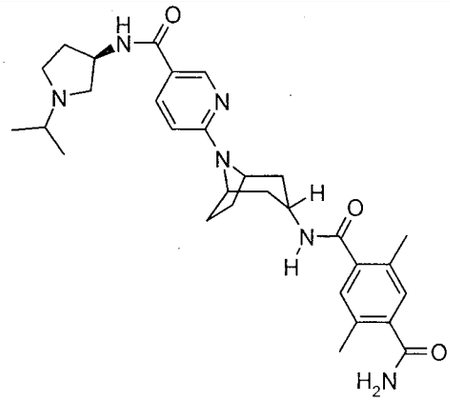
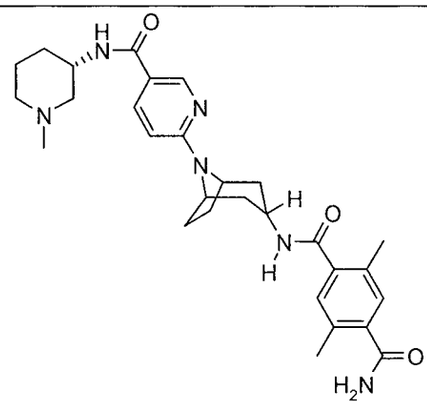
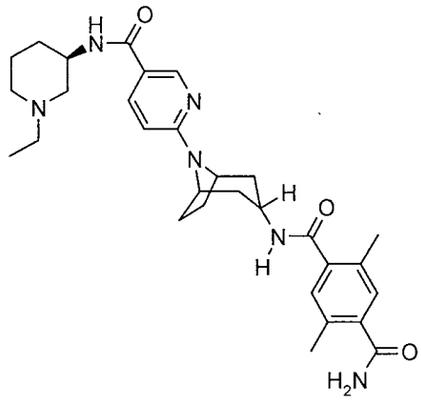
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2,5-dimetil-N-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2,5-dimetil-N-{8-[5-({[(3S)-1-metilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-({[(3R)-1-etilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida **ACTIVIDAD = A**

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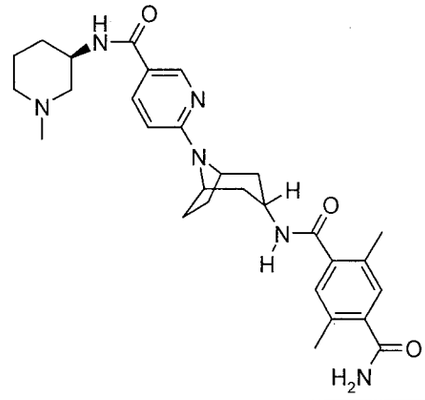
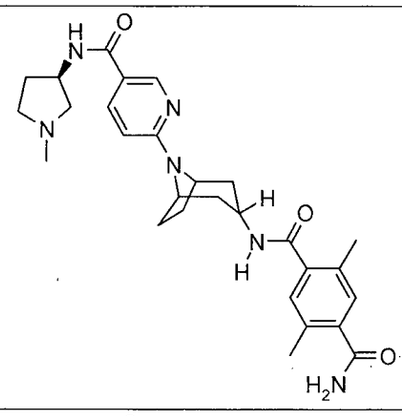
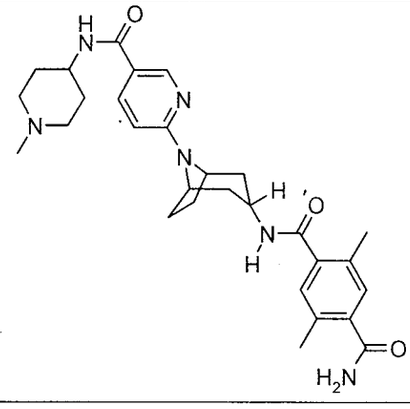
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2,5-dimetil-N-{8-[5-({[(3R)-1-metilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2,5-dimetil-N-{8-[5-({[(3R)-1-metilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = B**
	2,5-dimetil-N-[8-(5-{[(1-metilpiperidin-4-il)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida **ACTIVIDAD = B**

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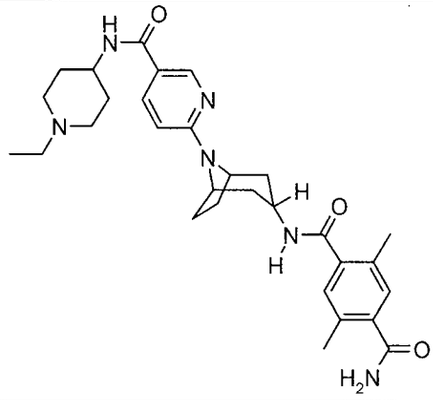
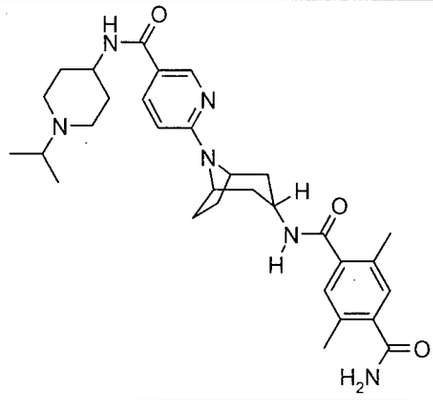
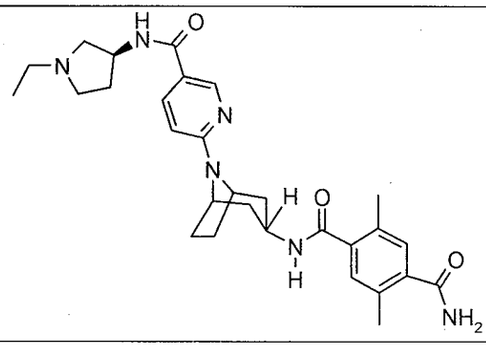
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[8-(5-{[(1-etilpiperidin-4-il)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2,5-dimetilbencen-1,4-dicarboxamida **ACTIVIDAD = B**
	2,5-dimetil-N-{8-[5-({[1-(1-metiletil)piperidin-4-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = B**
	N-{8-[5-({[(3S)-1-etilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida **ACTIVIDAD = A**

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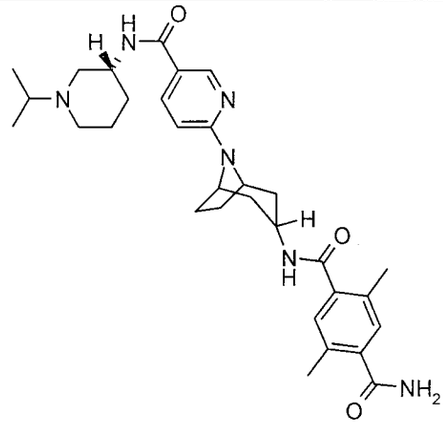
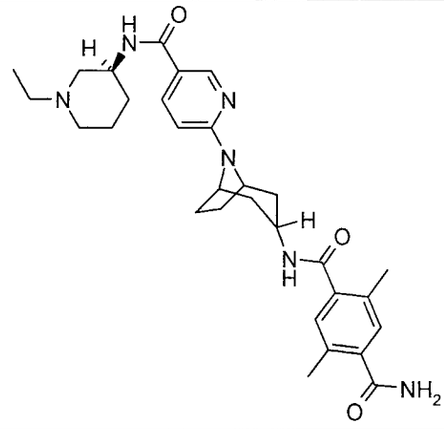
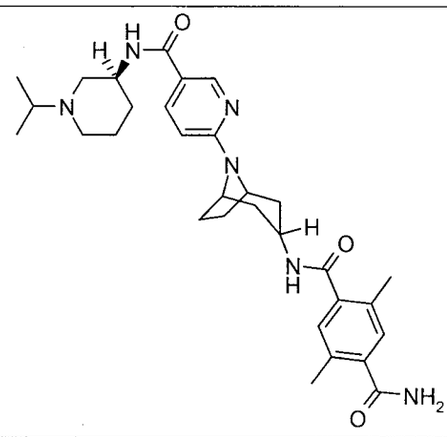
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2,5-dimetil-N-{8-[5-({[(3R)-1-(1-metiletil)piperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-({[(3S)-1-etilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida **ACTIVIDAD = B**
	2,5-dimetil-N-{8-[5-({[(3S)-1-(1-metiletil)piperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = B**

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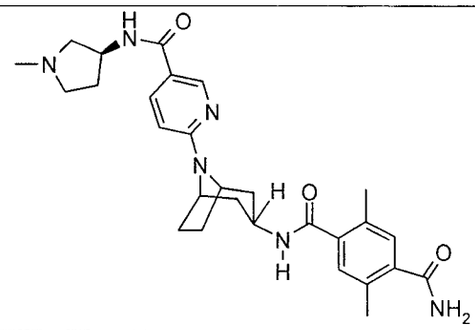
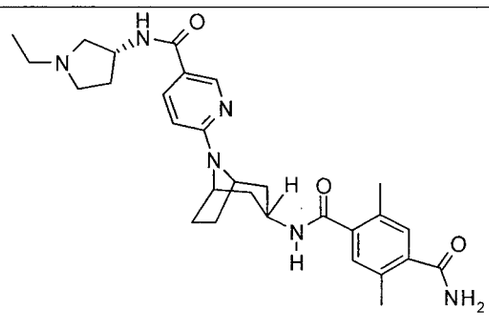
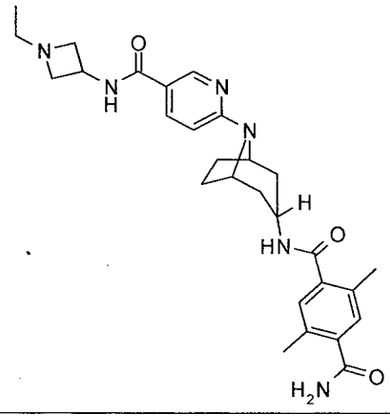
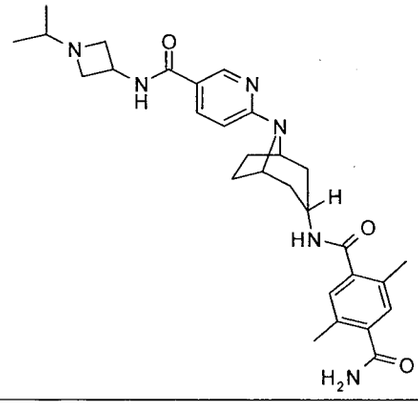
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2,5-dimetil-N-{8-[5-({[(3S)-1-metilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-({[(3R)-1-etilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-[8-(5-{[(1-etilazetidin-3-il)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2,5-dimetilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2,5-dimetil-N-{8-[5-({[1-(1-metiletil)azetidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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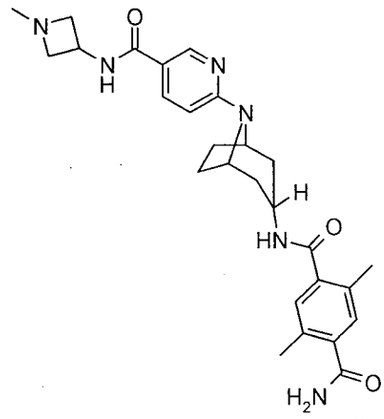
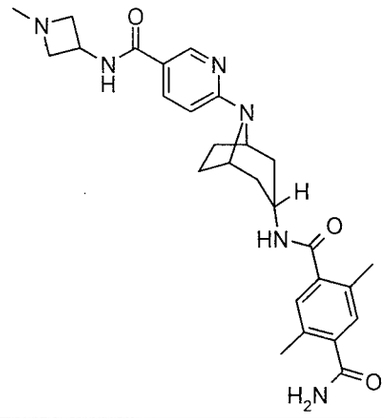
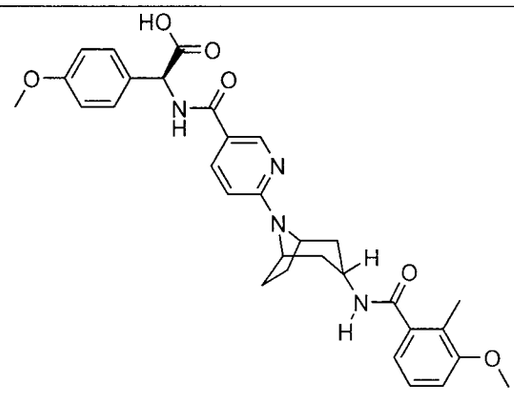
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2,5-dimetil-N-[8-(5-{[(1-metilazetidin-3-il)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	(2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoato de metilo **ACTIVIDAD = C**
	Ácido (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoico **ACTIVIDAD = C**

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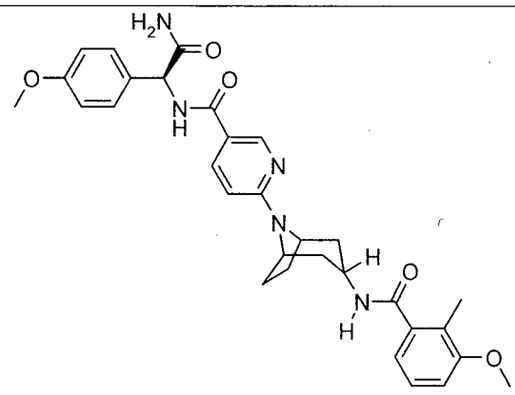
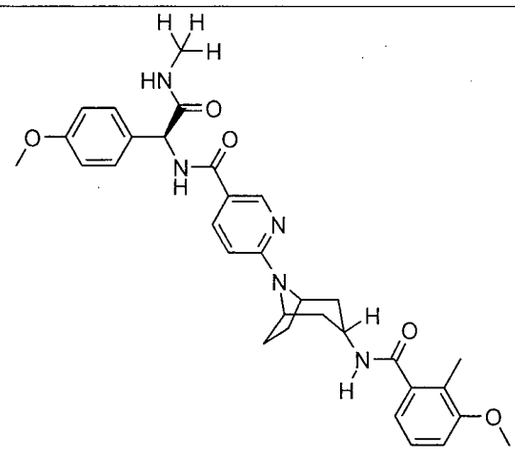
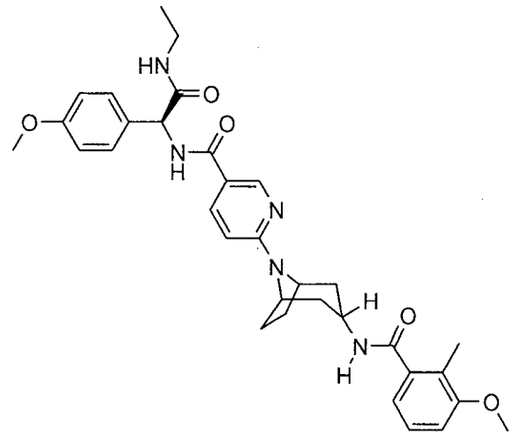
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{(1S)-2-amino-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-{(1S)-2-(metilamino)-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	N-{(1S)-2-(etilamino)-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**

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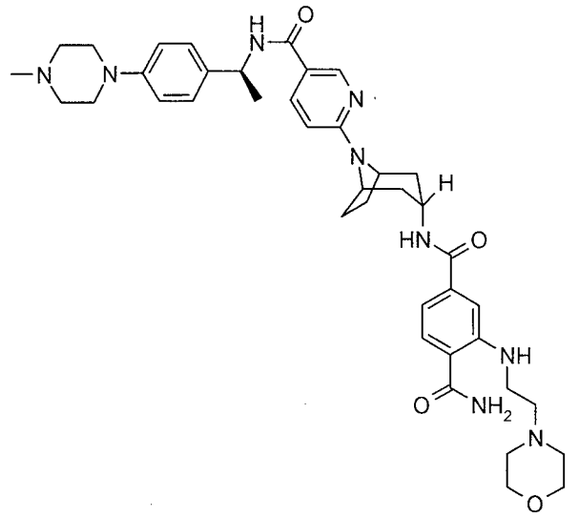
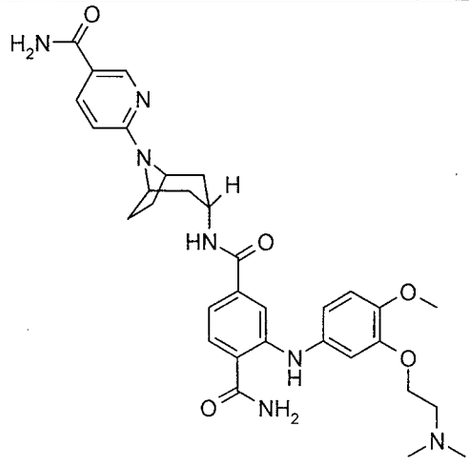
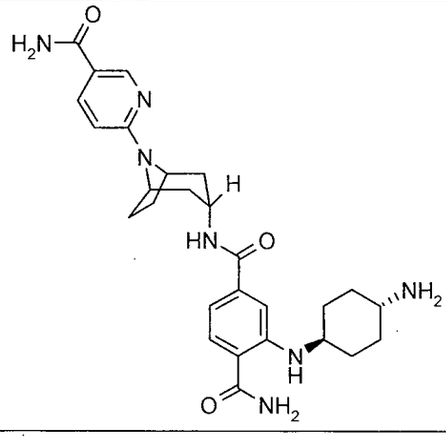
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-[(2-morfolin-4-iletil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(trans-4-aminociclohexil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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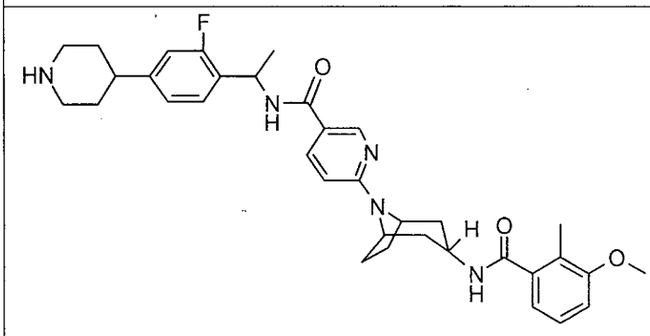
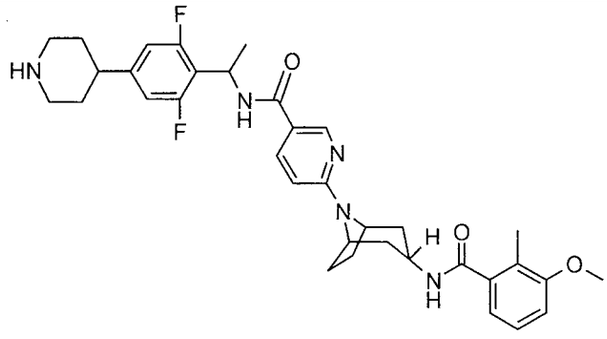
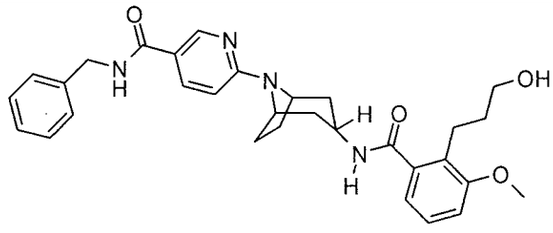
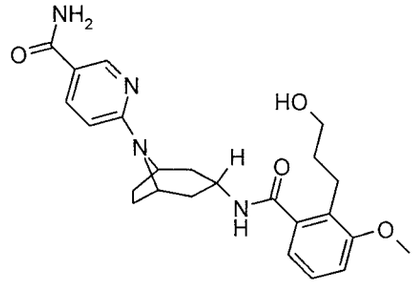
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[1-(2-fluoro-4-piperidin-4-ilfenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = A**
	N-[1-(2,6-difluoro-4-piperidin-4-ilfenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**
	6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = A**
	6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = C**

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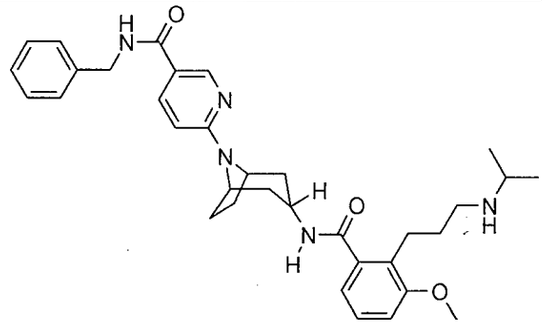
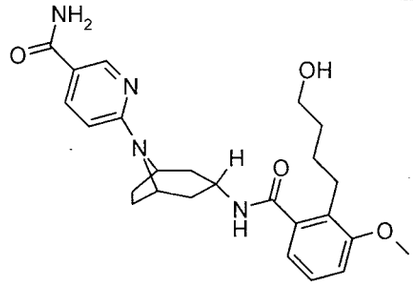
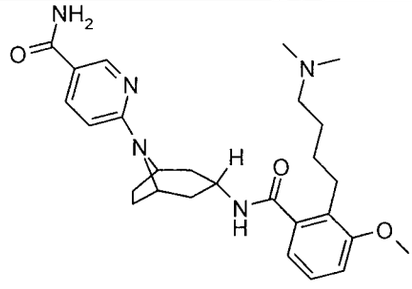
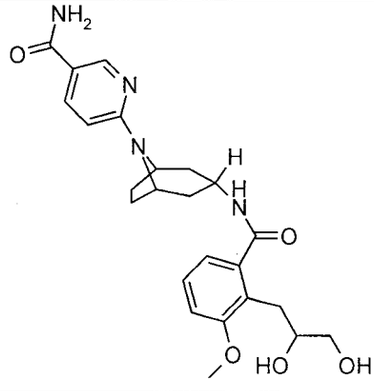
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[2-{3-[(1-metiletil)amino]propil}-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-(4-hidroxibutil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = B**
	6-{3-endo-[({2-[4-(dimetilamino)butil]-3-(metiloxi)fenil}carbonil)amino]-8-azabiciclo[3.2.1]oct-8-il}piridin-3-carboxamida **ACTIVIDAD = C**
	6-[3-endo-({[2-(2,3-dihidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida **ACTIVIDAD = D**

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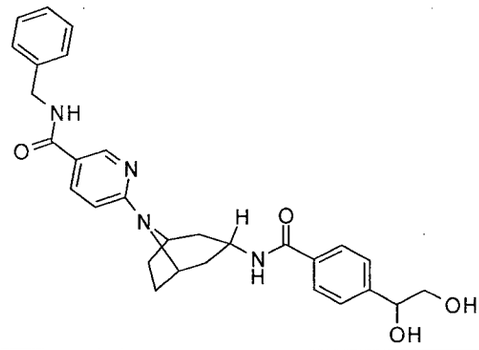
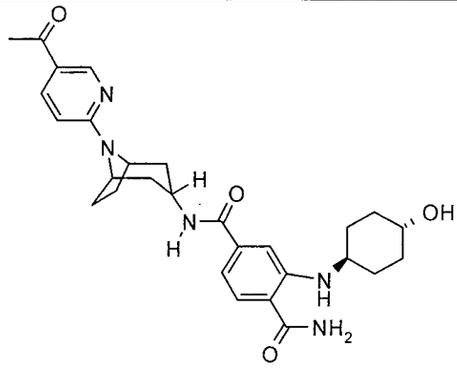
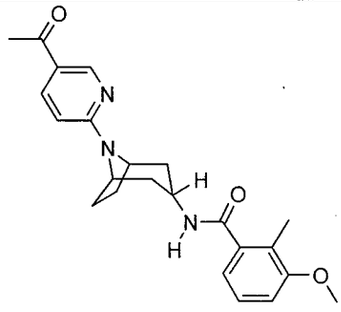
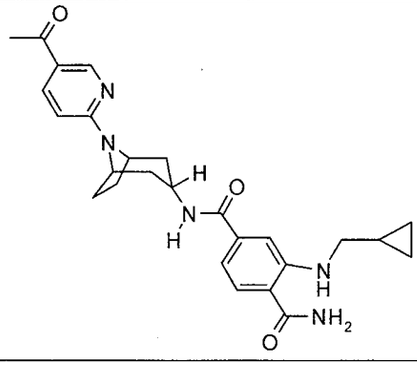
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	6-[3-endo-({[4-(1,2-dihidroxietil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida **ACTIVIDAD = C**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(trans-4-hidroxiciclohexil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-metil-3-(metiloxi)benzamida **ACTIVIDAD = B**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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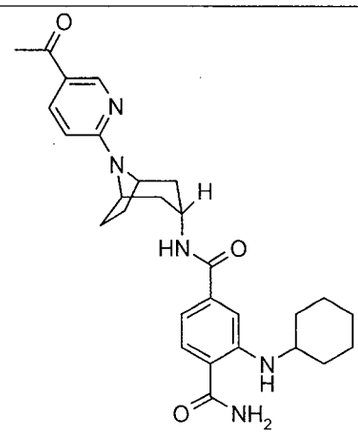
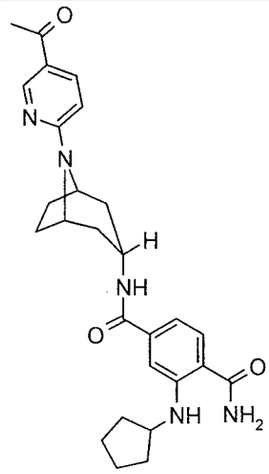
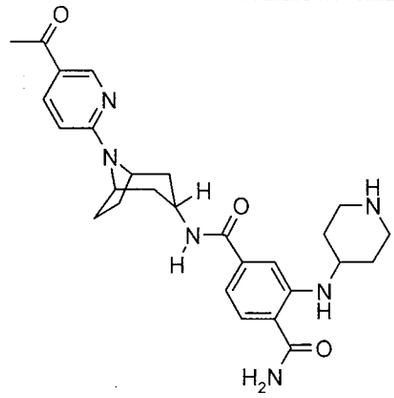
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(ciclohexilamino) bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(ciclopentilamino) bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(piperidin-4-ilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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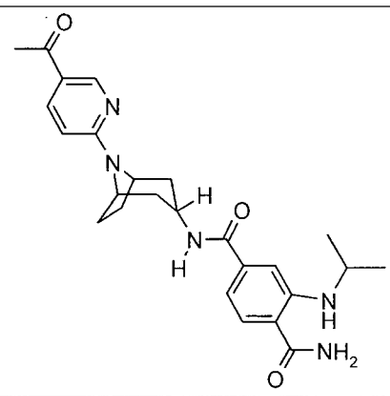
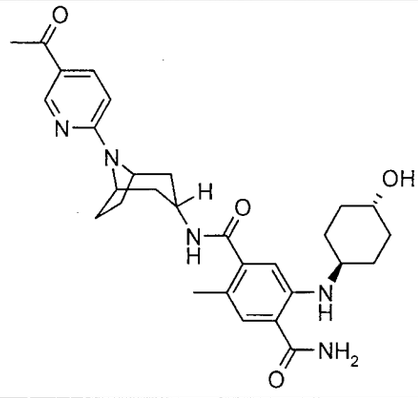
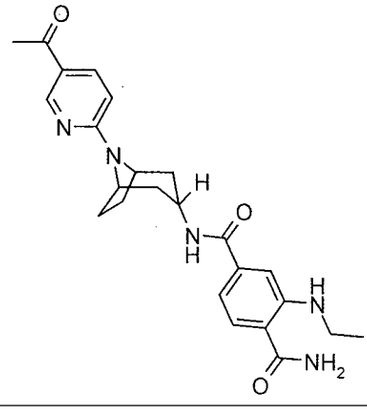
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-metiletil)amino]benceno-1,4-dicarboxamida **ACTIVIDAD = A**
	N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-5-[(trans-4-hidroxiciclohexil)amino]-2-metilbenceno-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(etilamino)benceno-1,4-dicarboxamida **ACTIVIDAD = A**

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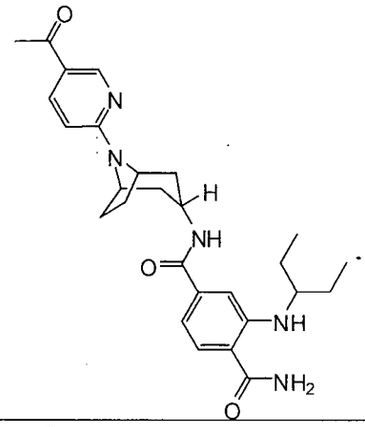
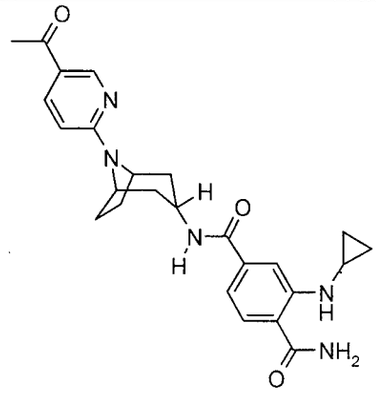
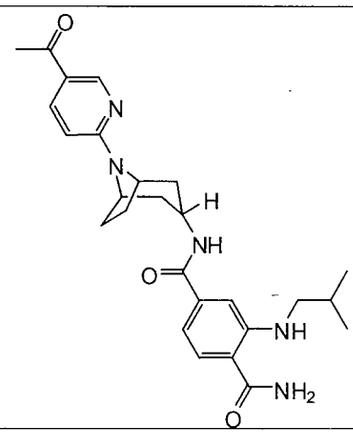
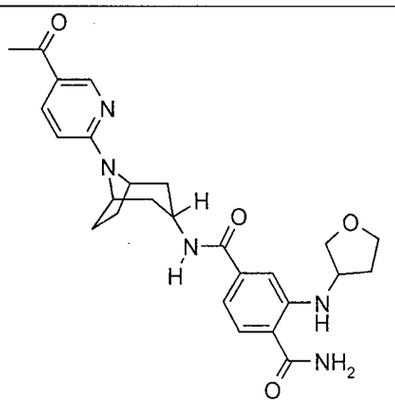
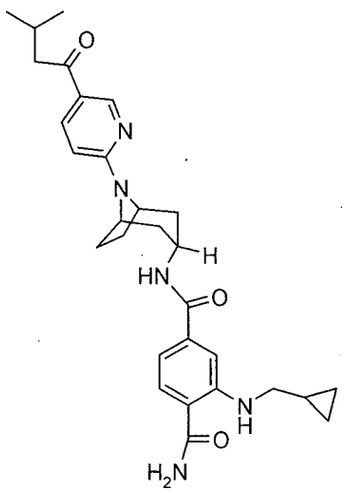
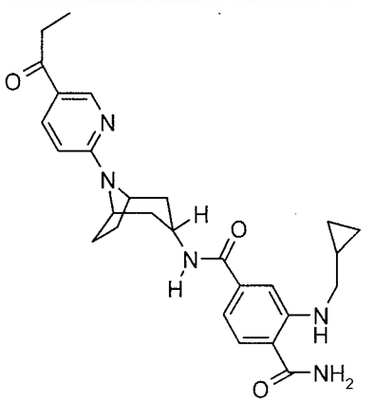
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-etilpropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(ciclopropilamino) bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2-metilpropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**

67 L

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(tetrahidrofuran-3-ilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-metilbutanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = C**
	2-[(ciclopropilmetil)amino]-N4-[8-(5-propanoilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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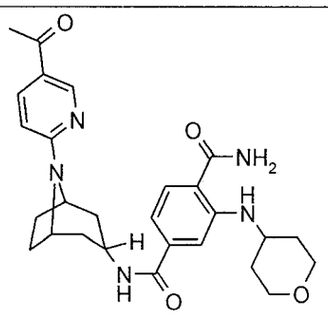
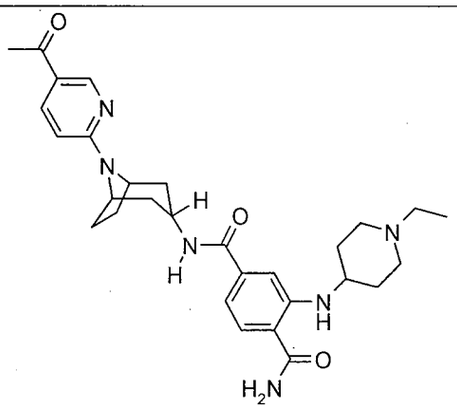
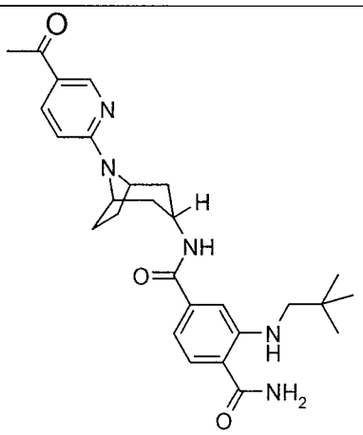
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(tetrahidro-2H-pyran-4-ilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-etilpiperidin-4-il)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = B**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2-dimetilpropil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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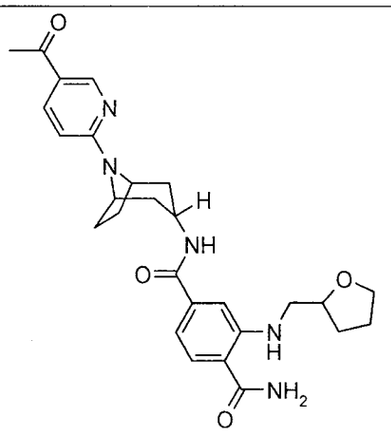
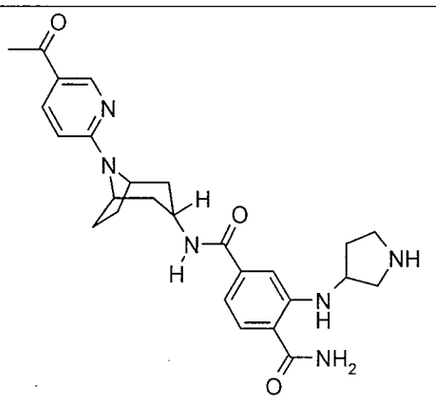
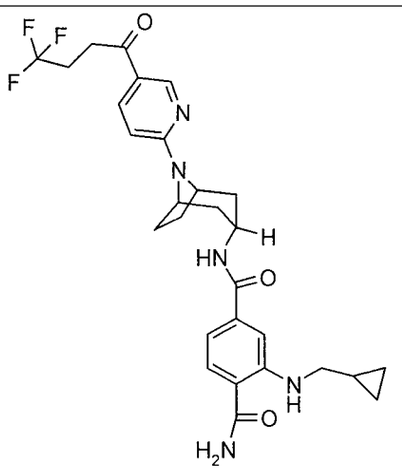
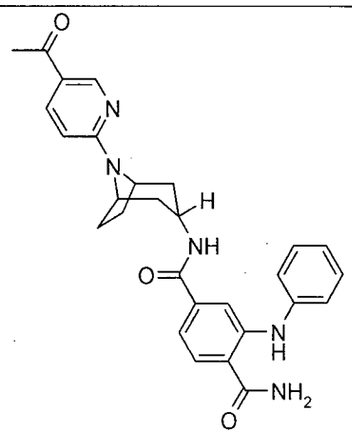
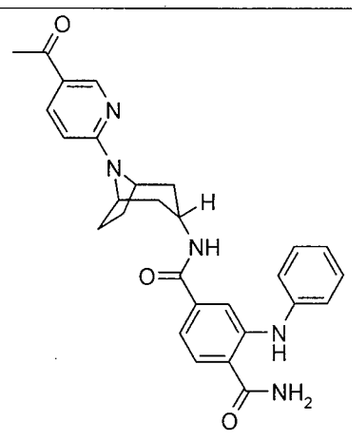
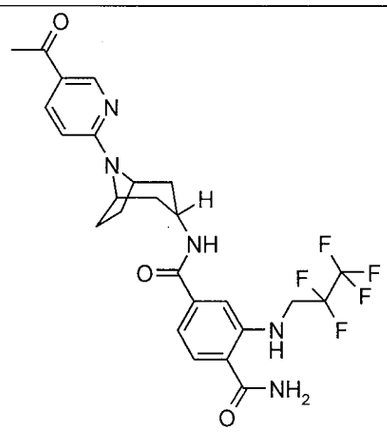
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(tetrahidrofuran-2-ilmetil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(pirrolidin-3-ilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil)amino]-N4-{8-[5-(4,4,4-trifluorobutanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = D**

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(fenilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2-aminoetil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2,3,3,3-pentafluoropropil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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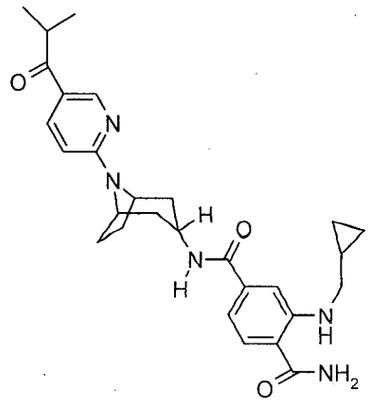
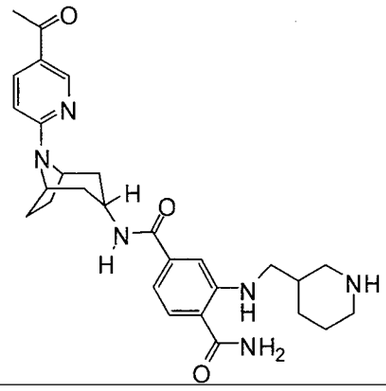
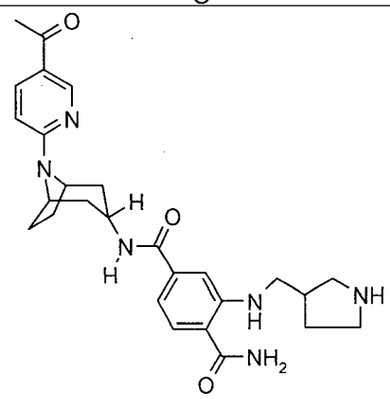
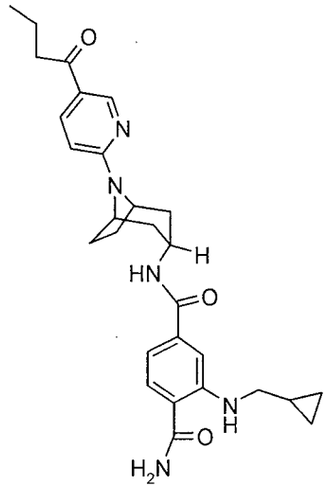
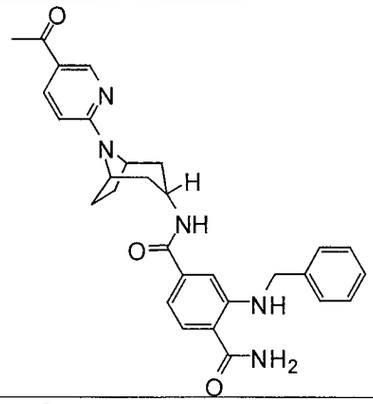
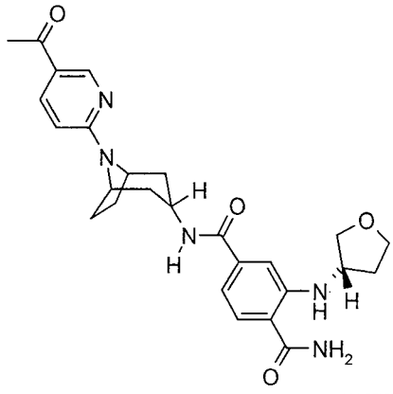
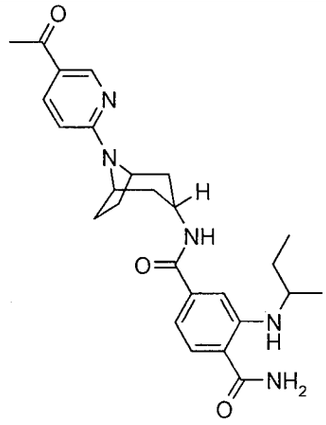
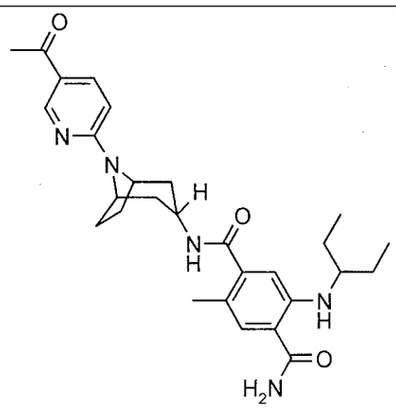
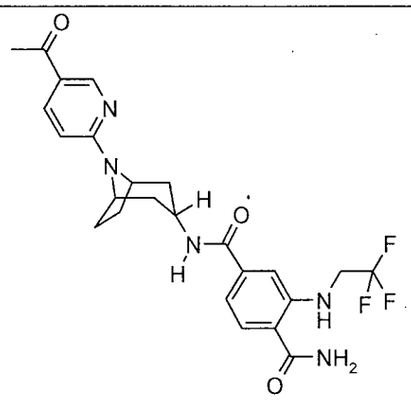
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-[(ciclopropilmetil) amino]-N4-{8-[5-(2-metilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = C**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(piperidin-3-ilmetil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(pirrolidin-3-ilmetil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

676.

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-butanoylpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(ciclopropilmetil) amino]bencen-1,4-dicarboxamida **ACTIVIDAD = B**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(fenilmetil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = B**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(3S)-tetrahidrofuran-3-ilamino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

677

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-metilpropil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-5-[(1-etilpropil)amino]-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2,2-trifluoroetil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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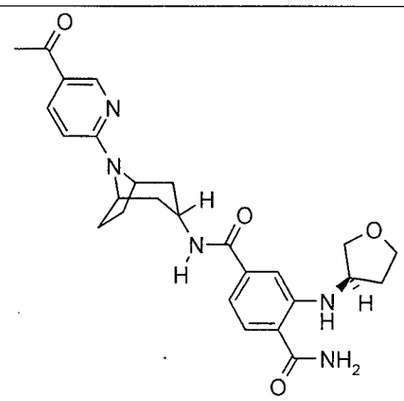
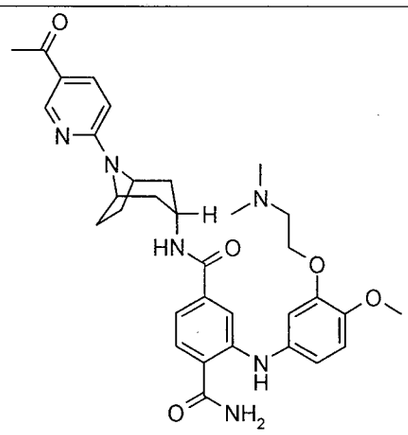
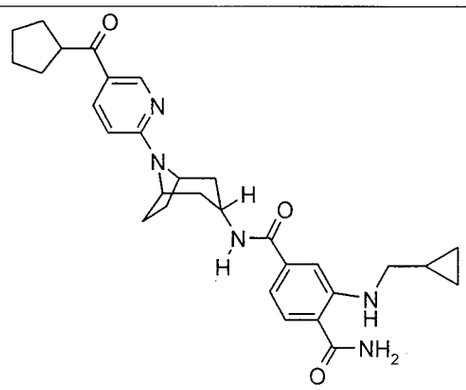
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(3R)-tetrahidrofuran-3-ilamino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(ciclopentilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = D**

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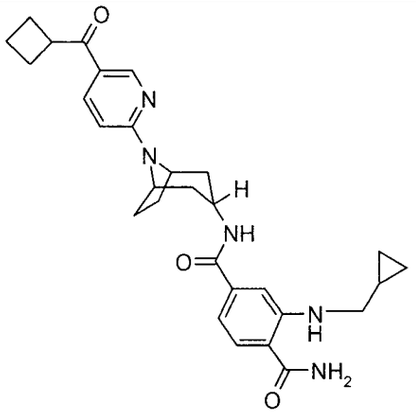
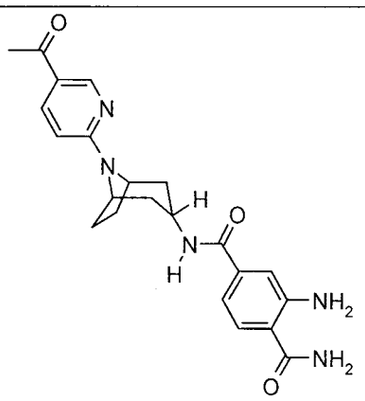
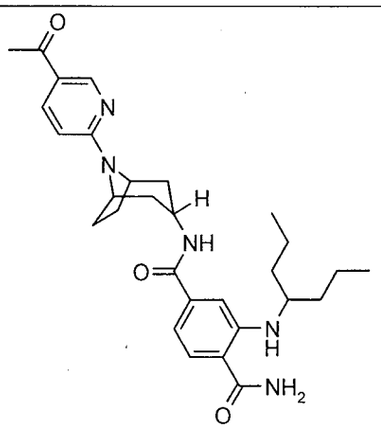
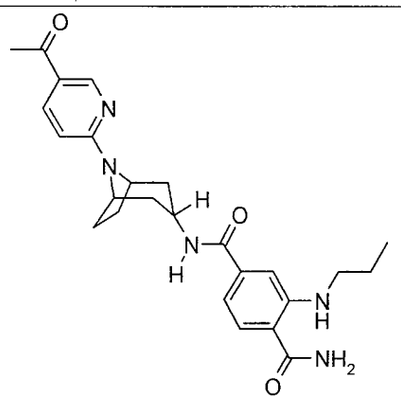
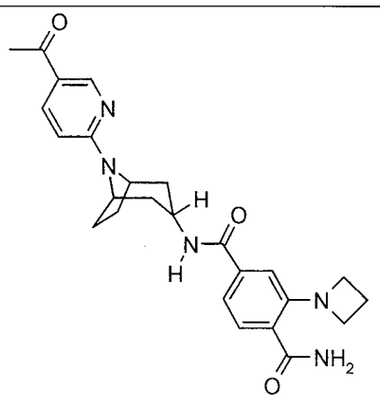
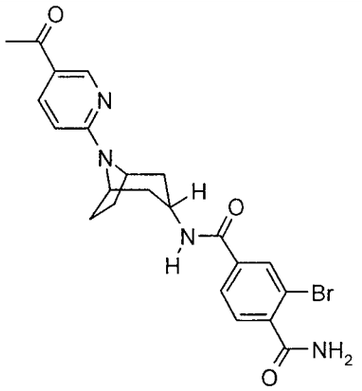
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-{8-[5-(ciclobutilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil) amino]bencen-1,4-dicarboxamida **ACTIVIDAD = C**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-aminobencen-1,4-dicarboxamida **ACTIVIDAD = B**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-propilbutil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(propilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-azetidin-1-ilbencen-1,4-dicarboxamida **ACTIVIDAD = D**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-bromobencen-1,4-dicarboxamida **ACTIVIDAD = A**

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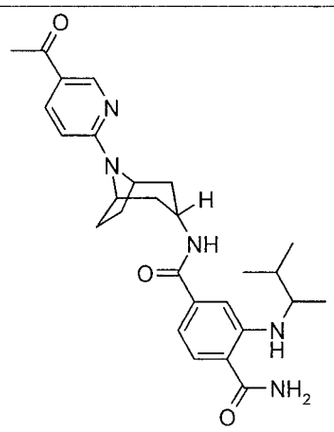
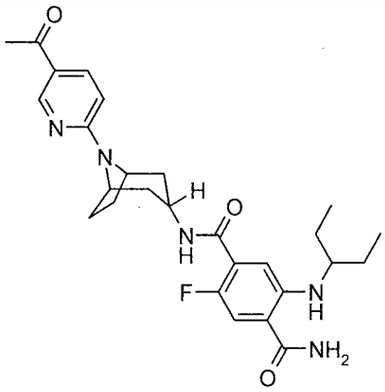
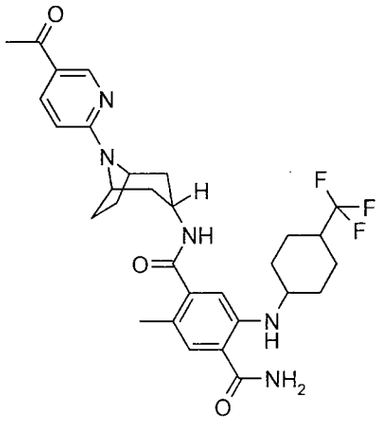
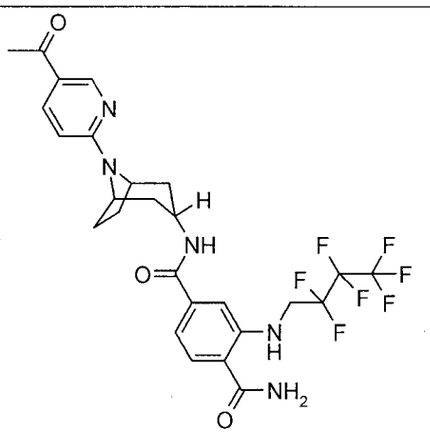
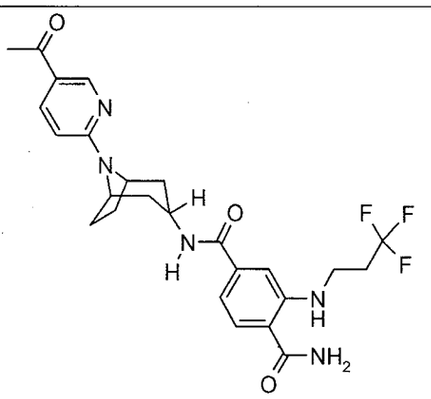
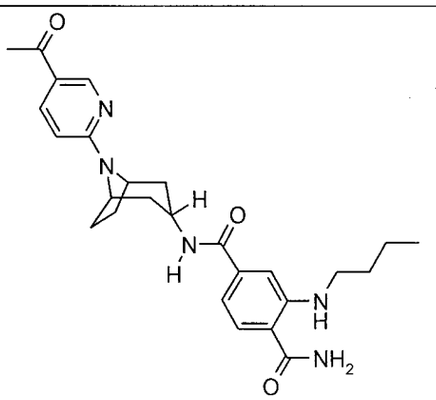
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1,2-dimetilpropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-5-[(1-etilpropil)amino]-2-fluorobencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-metil-5-{[4-(trifluorometil) ciclohexil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**

682

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2,3,3,4,4,4-heptafluorobutil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = B**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(3,3,3-trifluoropropil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(butilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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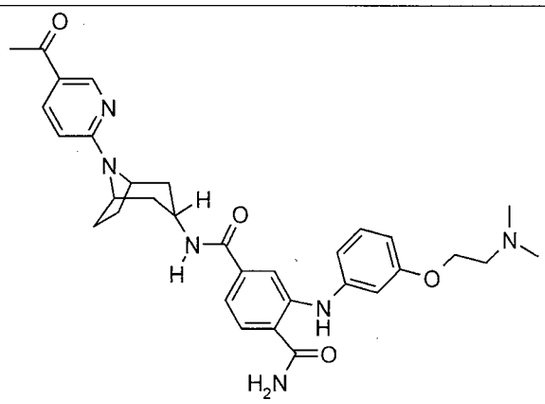
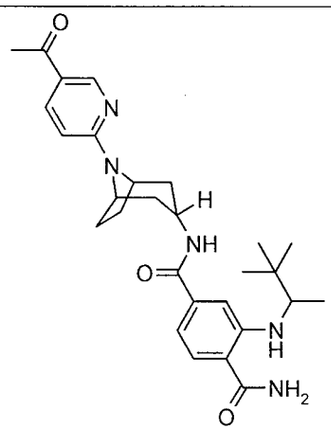
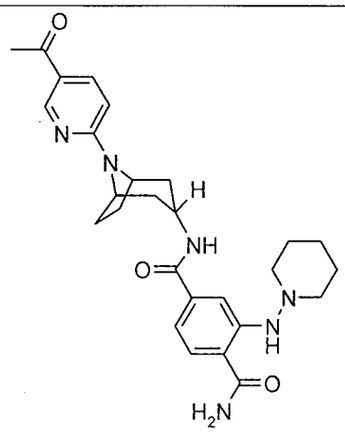
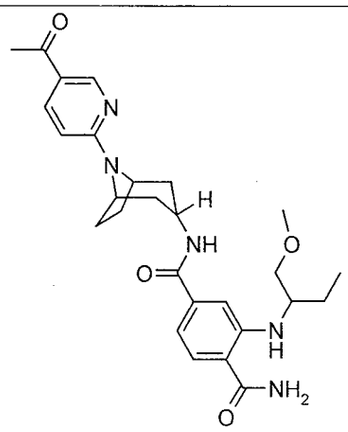
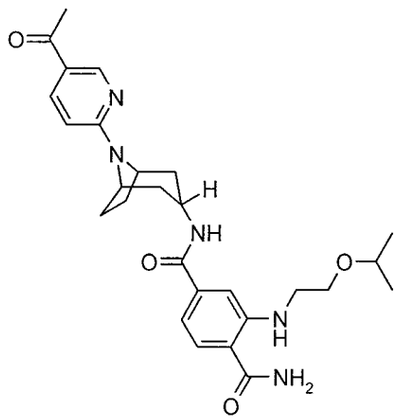
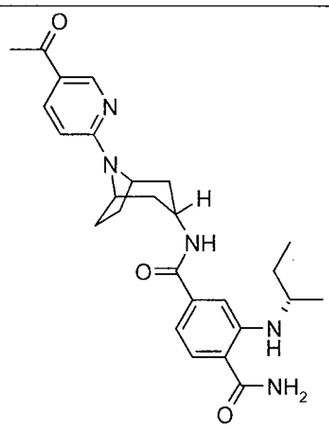
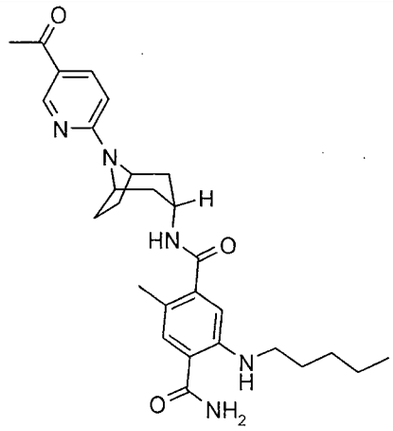
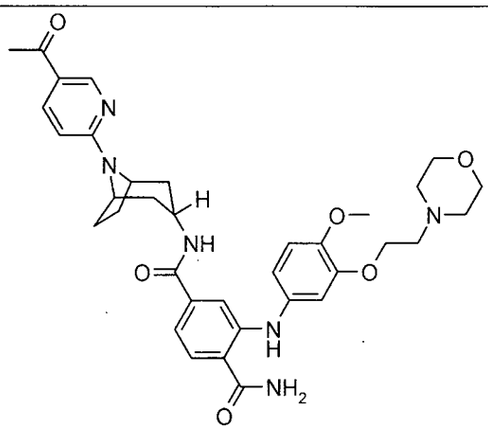
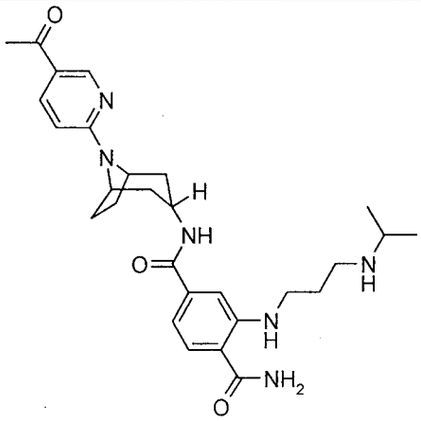
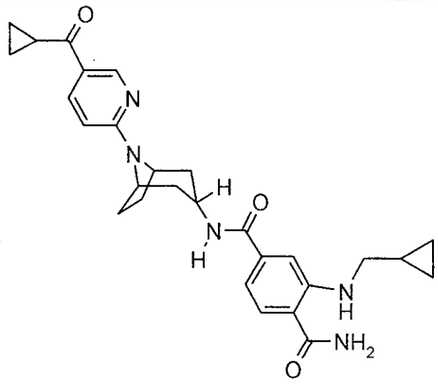
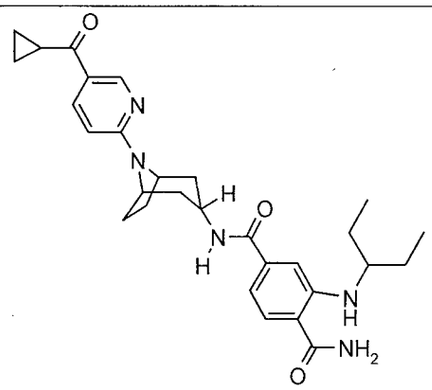
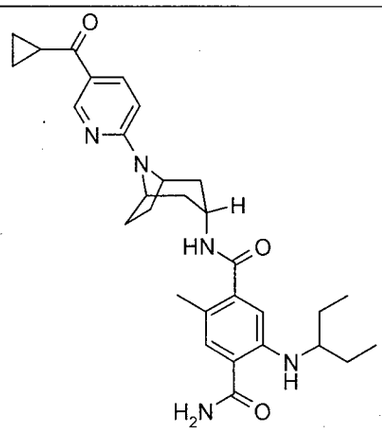
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(3-{[2-(dimetilamino)etil]oxi}fenil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1,2,2-trimetilpropil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(piperidin-1-ilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**

684

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({1-[(metiloxi)metil]propil}amino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({2-[(1-metiletil)oxi]etil}amino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-{[(1S)-1-metilpropil]amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**

68S

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-metil-5-(pentilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({4-(metiloxi)-3-[(2-morfolin-4-iletil)oxi]fenil}amino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({3-[(1-metiletil)amino]propil}amino)bencen-1,4-dicarboxamida **ACTIVIDAD = B**

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil) amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(1-etilpropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**

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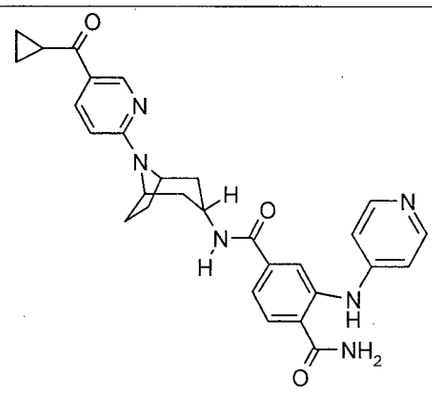
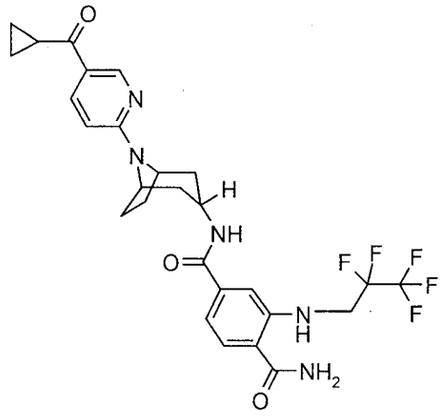
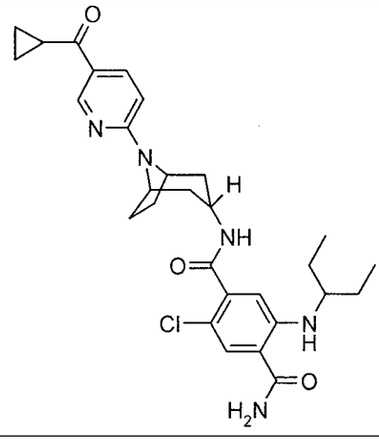
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(piridin-4-ilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(2,2,3,3,3-pentafluoropropil) amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-cloro-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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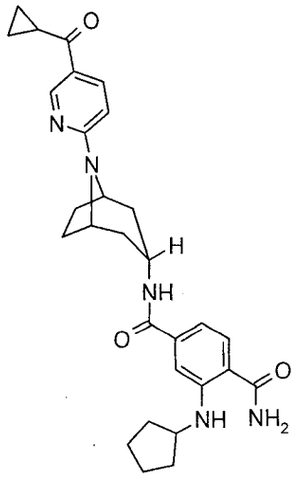
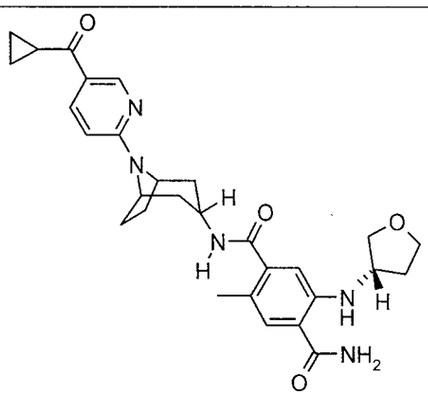
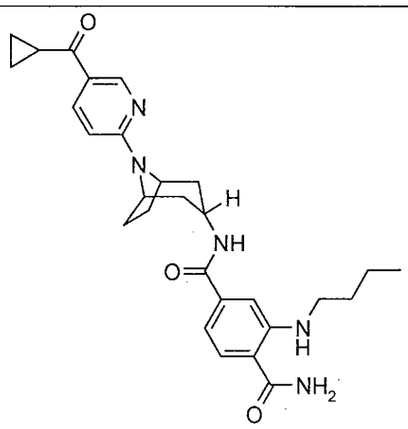
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-(ciclopentilamino)-N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(3S)-tetrahidrofuran-3-ilamino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-(butilamino)-N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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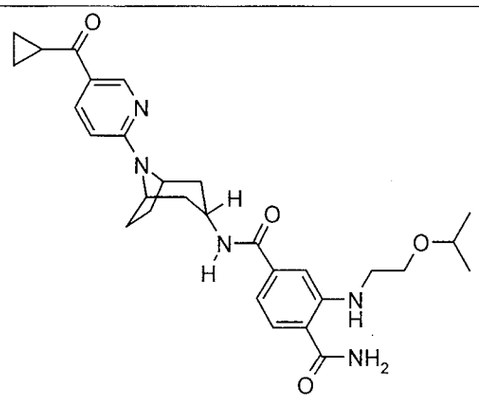
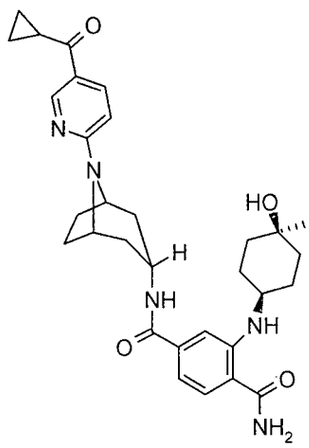
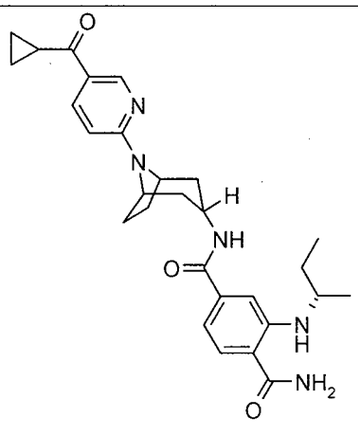
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-({2-[(1-metiletil)oxi]etil} amino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(cis-4-hidroxi-4-metilciclohexil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1S)-1-metilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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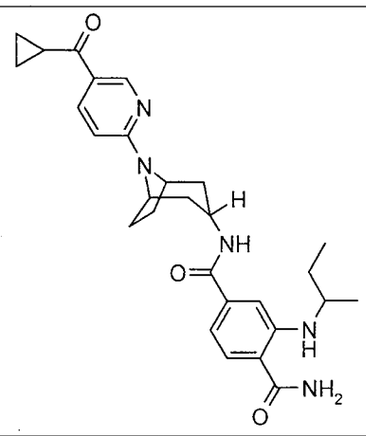
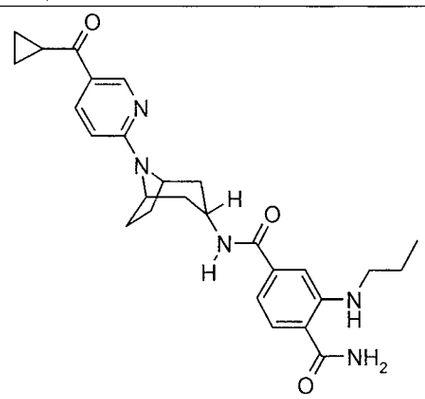
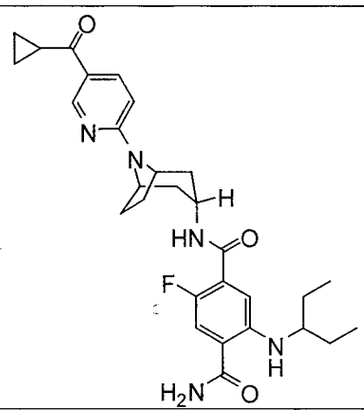
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(1-metilpropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(propilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]-2-fluorobencen-1,4-dicarboxamida **ACTIVIDAD = A**

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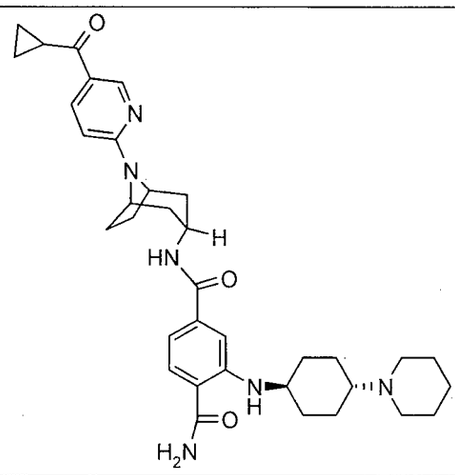
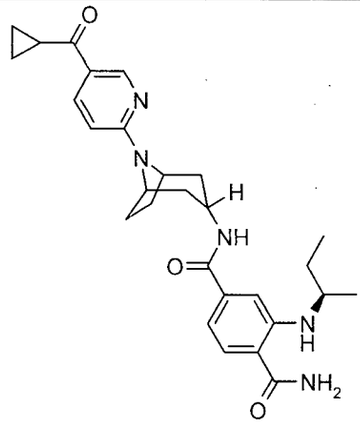
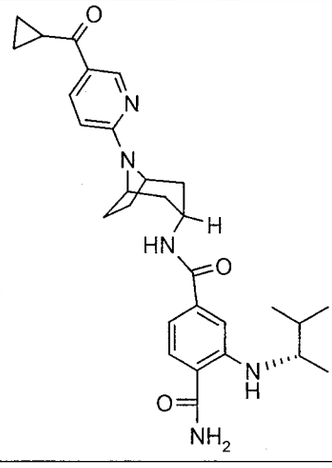
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(trans-4-piperidin-1-ilciclohexil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1R)-1-metilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1S)-1,2-dimetilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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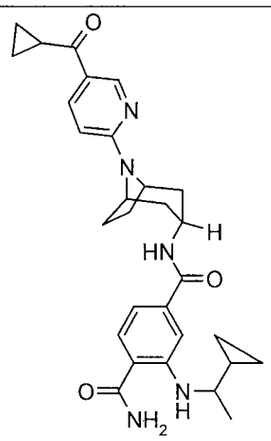
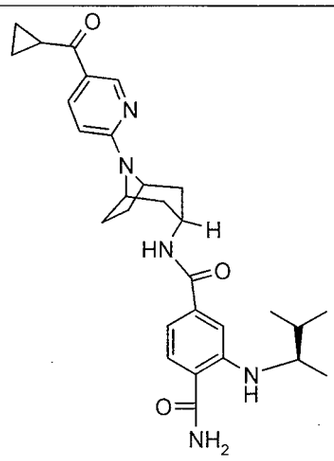
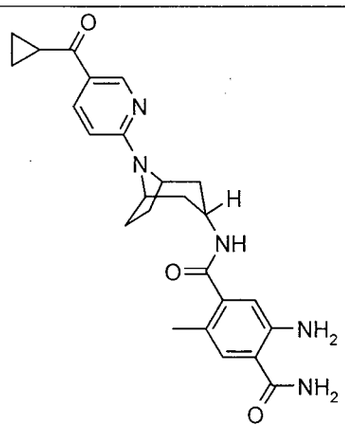
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(1-ciclopropiletil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1R)-1,2-dimetilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	5-amino-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**

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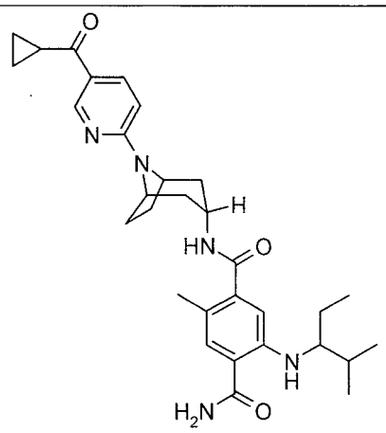
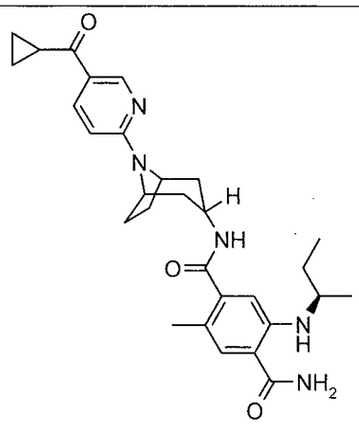
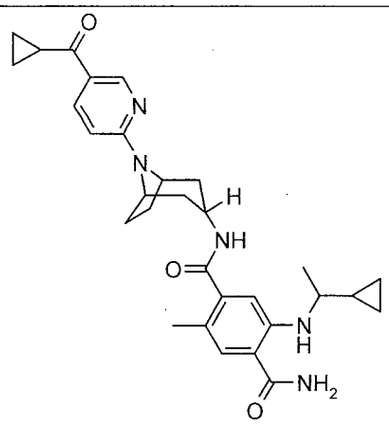
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etil-2-metilpropil)amino]-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[(1R)-1-metilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-ciclopropiletil)amino]-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**

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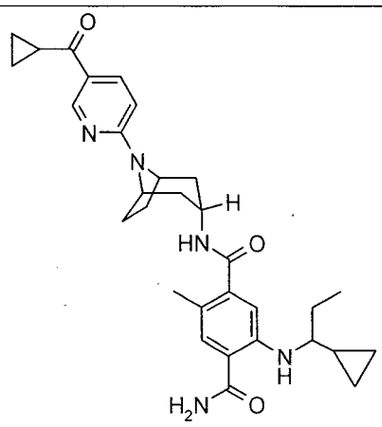
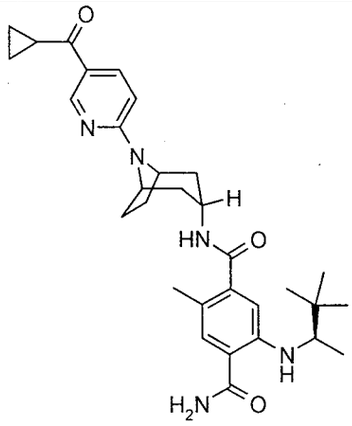
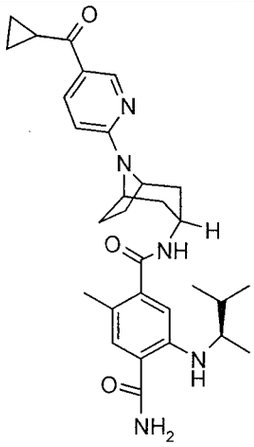
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-ciclopropilpropil) amino]-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[(1R)-1,2,2-trimetilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1R)-1,2-dimetilpropil]amino}-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**

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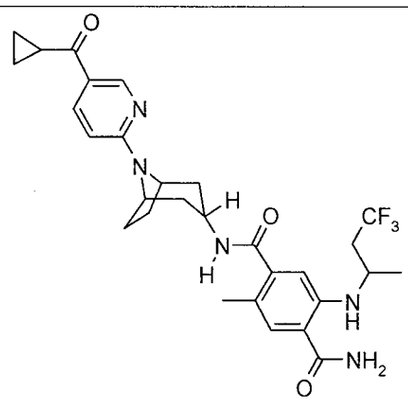
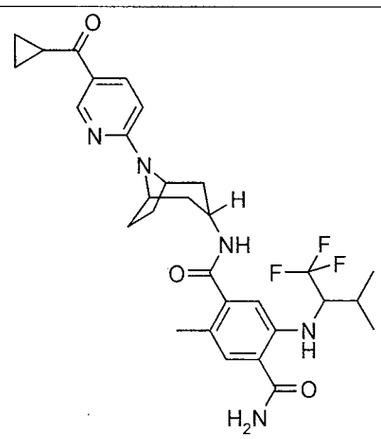
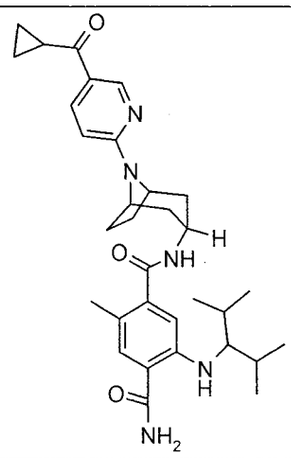
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(3,3,3-trifluoro-1-metilpropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[2-metil-1-(trifluorometil)propil]amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[2-metil-1-(1-metiletil)propil]amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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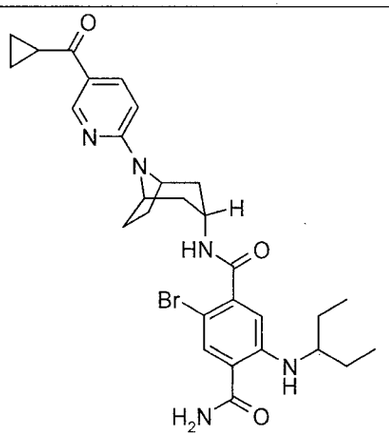
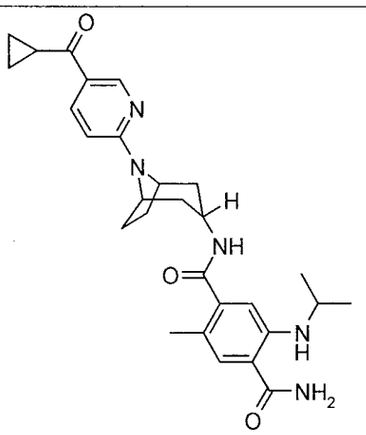
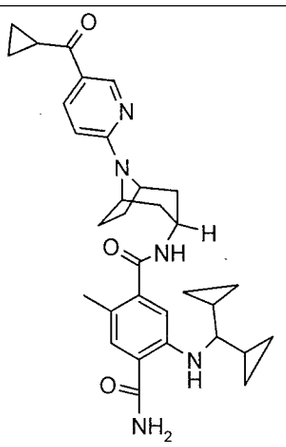
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(1-metiletil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(dicicloprópilmetil) amino]-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**

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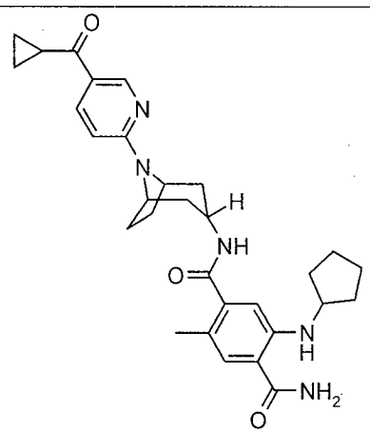
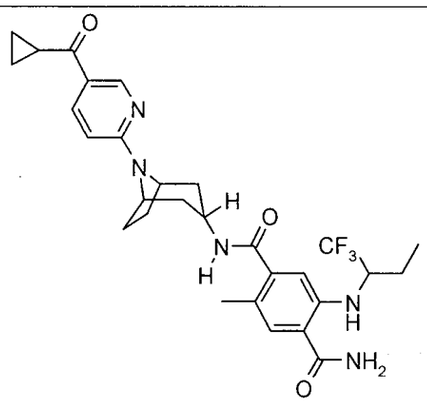
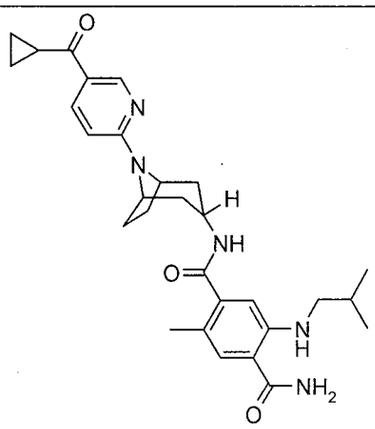
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	5-(ciclopentilamino)-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[1-(trifluorometil)propil]amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(2-metilpropil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

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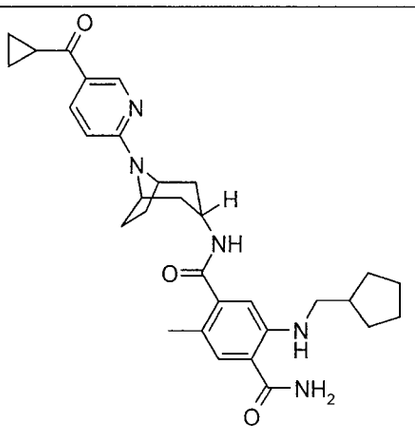
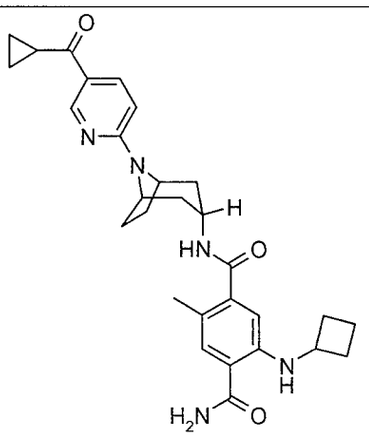
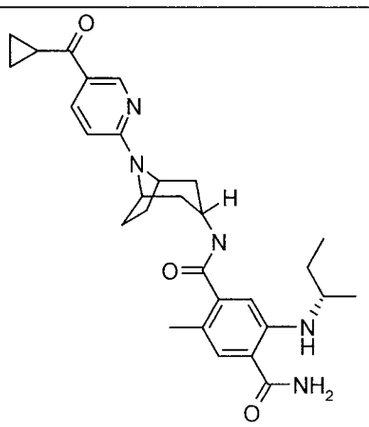
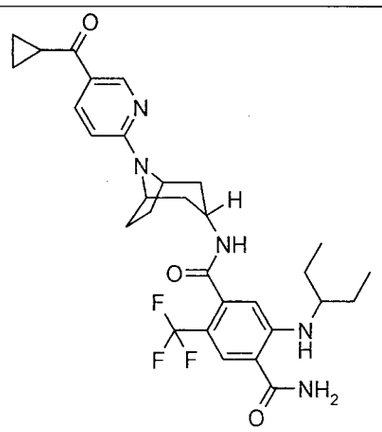
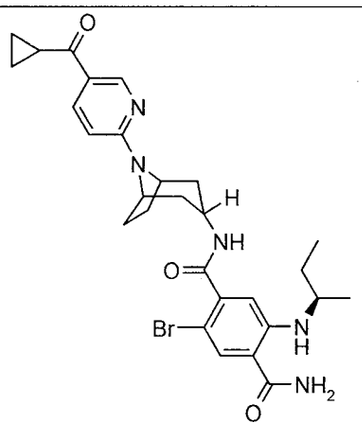
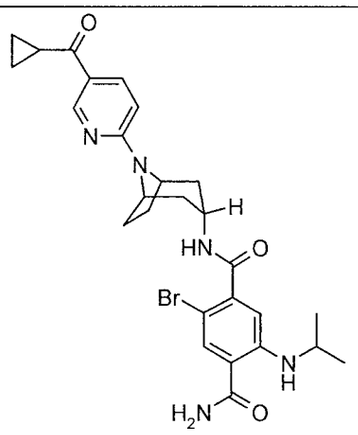
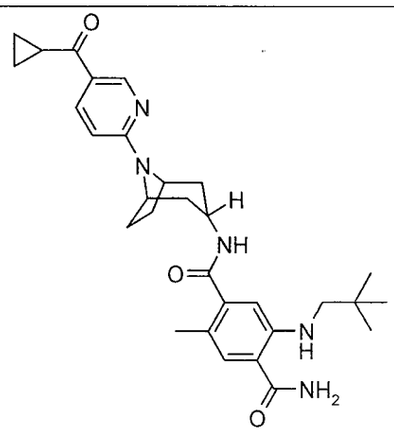
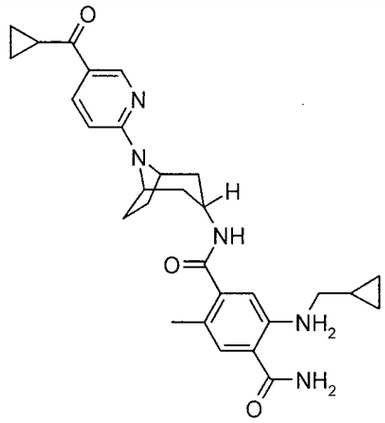
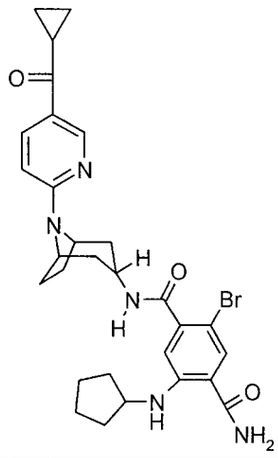
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	5-[(ciclopentilmetil) amino]-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	5-(ciclobutilamino)-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[(1S)-1-metilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**

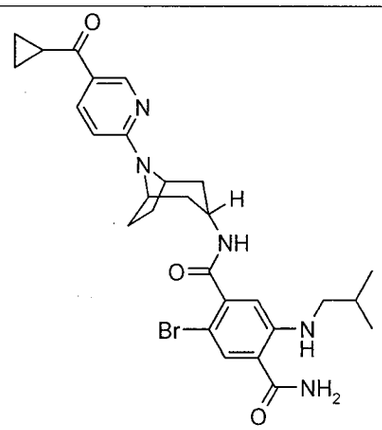
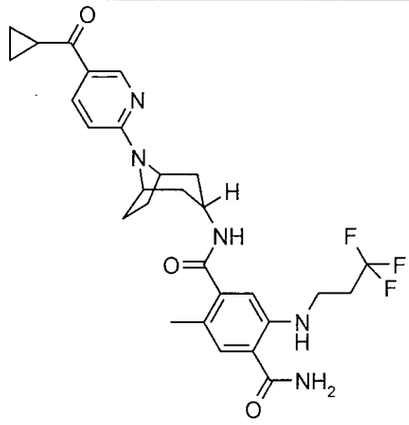
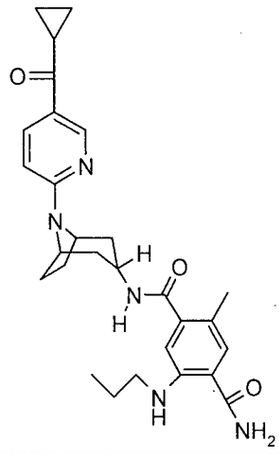
699

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]-2-(trifluorometil)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1R)-1-metilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-metiletil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

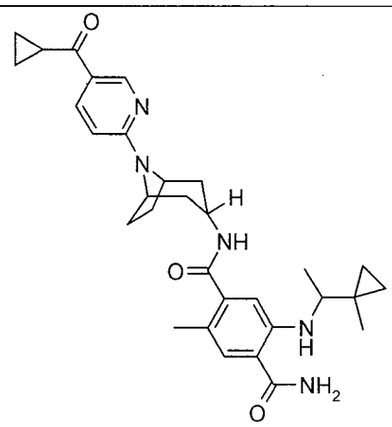
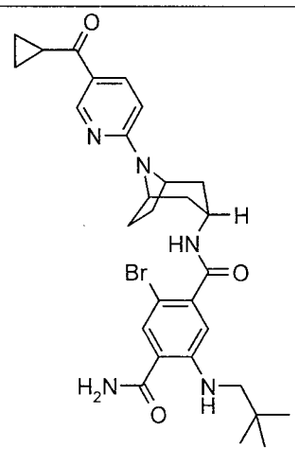
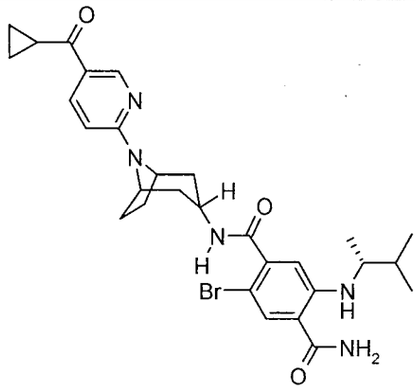
700

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(2,2-dimetilpropil)amino]-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(ciclopropilmetil) amino]-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-bromo-5-(ciclopentilamino)-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**

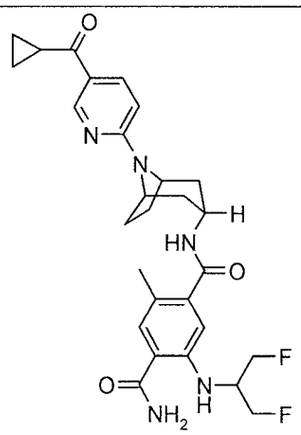
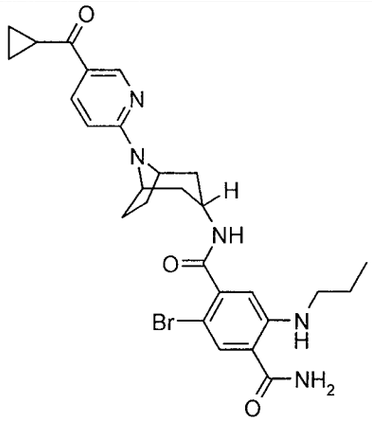
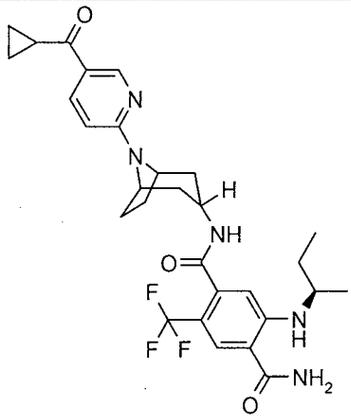
701

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(2-metilpropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabicíclo[3.2.1]oct-3-endo-il}-2-metil-5-[(3,3,3-trifluoropropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-(propilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**

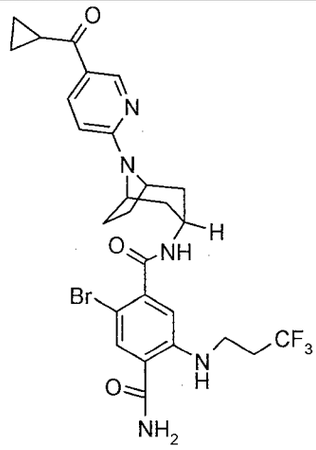
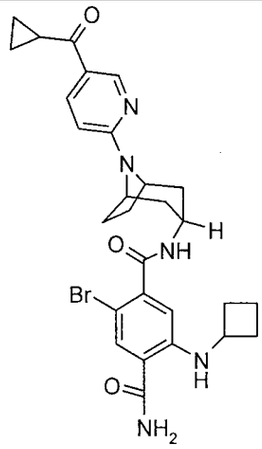
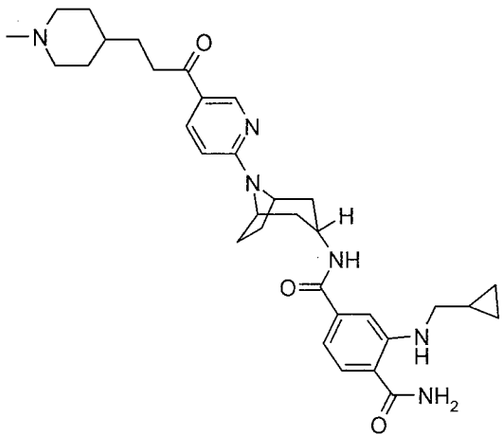
762

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[1-(1-metilciclopropil)etil] amino}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(2,2-dimetilpropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1R)-1,2-dimetilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**

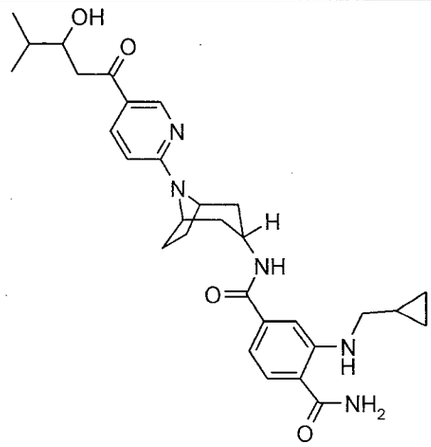
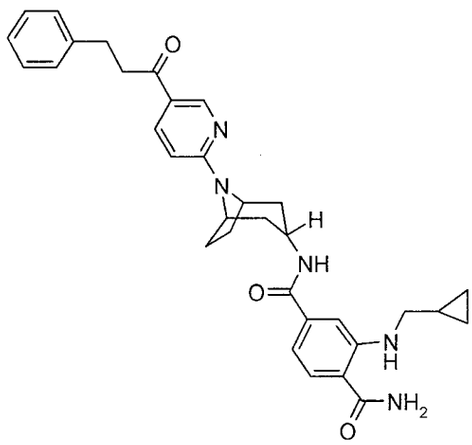
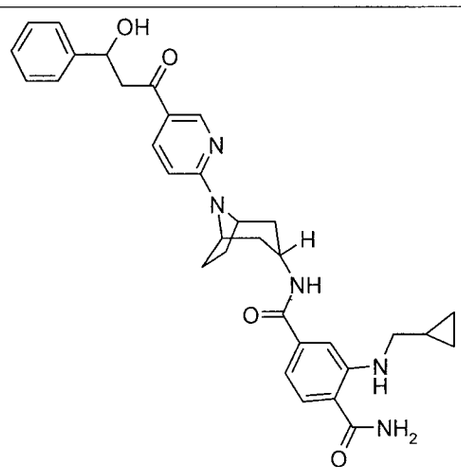
703.

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[2-fluoro-1-(fluorometil)etil] amino}-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-(propilamino)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1R)-1-metilpropil]amino}-2-(trifluorometil)bencen-1,4-dicarboxamida **ACTIVIDAD = A**

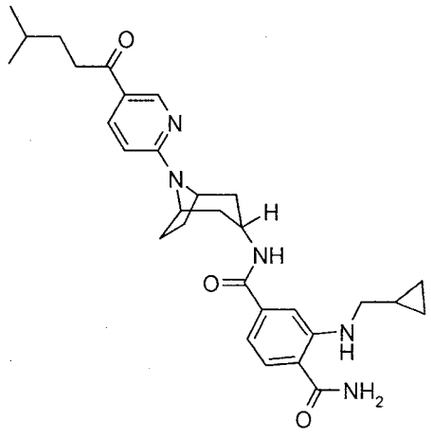
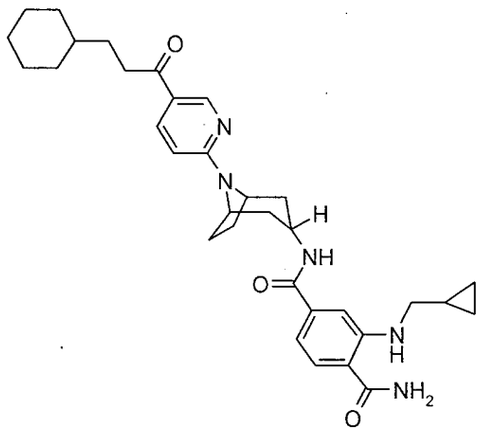
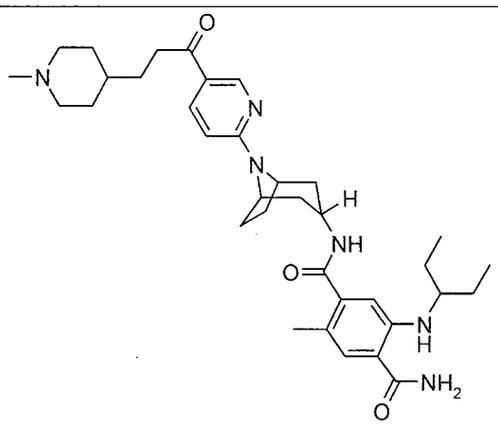
704

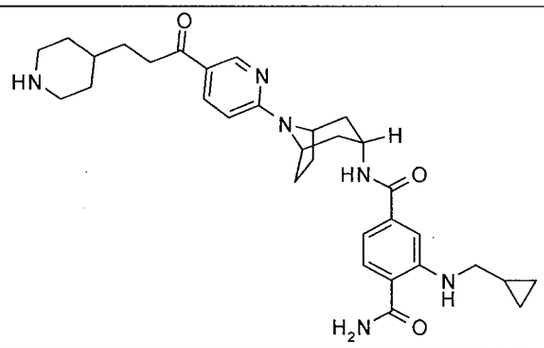
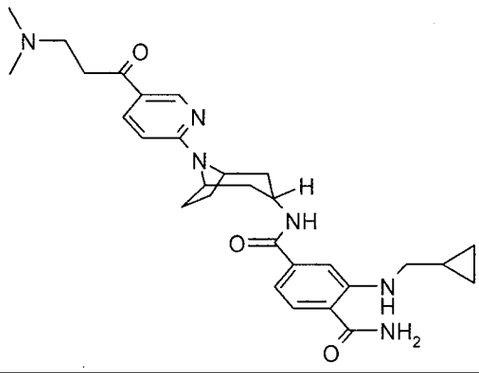
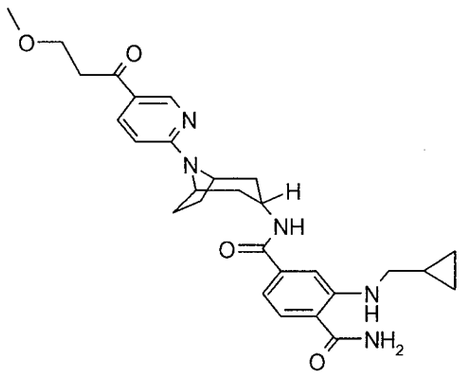
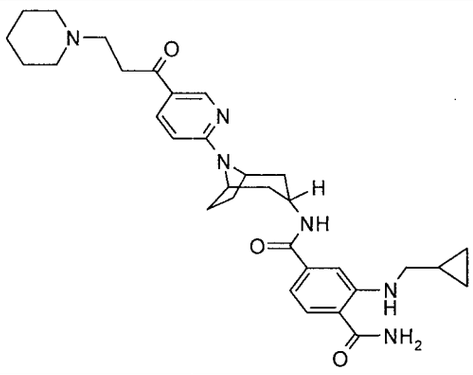
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(3,3,3-trifluoropropil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-bromo-5-(ciclobutilamino)-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil) amino]-N4-(8-{5-[3-(1-metilpiperidin-4-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**

705

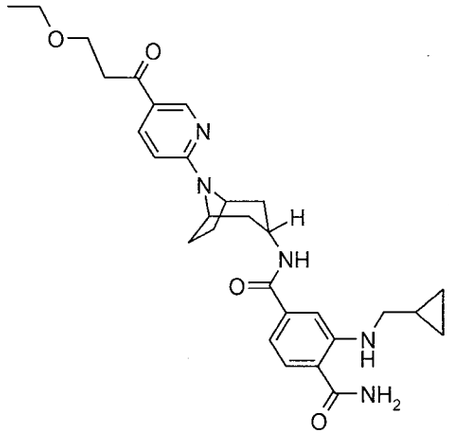
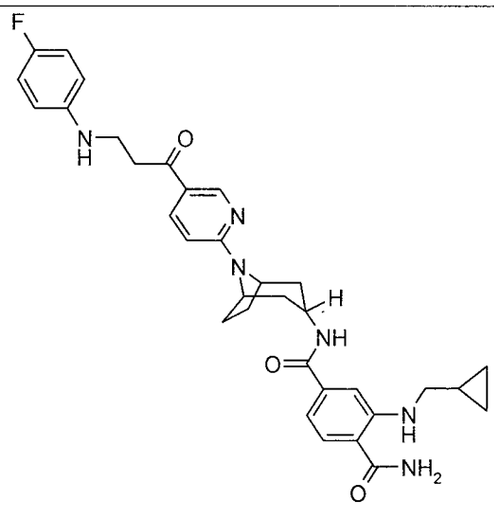
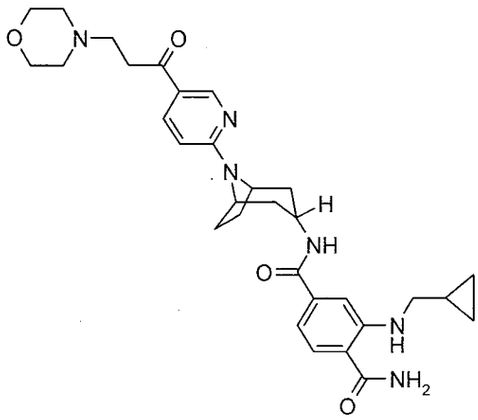
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-[(ciclopropilmetil) amino]-N4-{8-[5-(3-hidroxi-4-metilpentanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil) amino]-N4-{8-[5-(3-fenilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = D**
	2-[(ciclopropilmetil) amino]-N4-{8-[5-(3-hidroxi-3-fenilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = B**

706

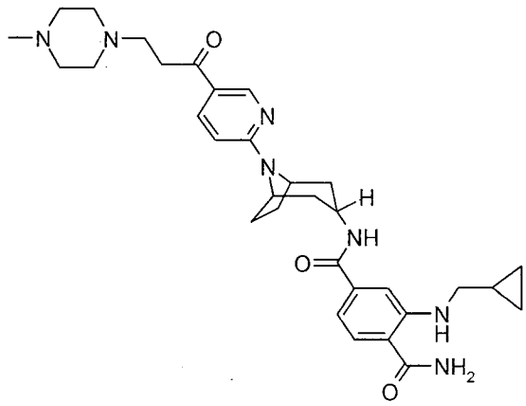
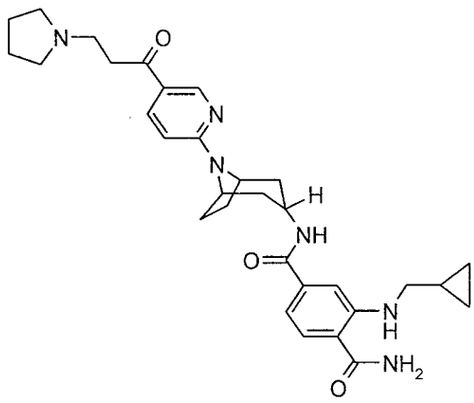
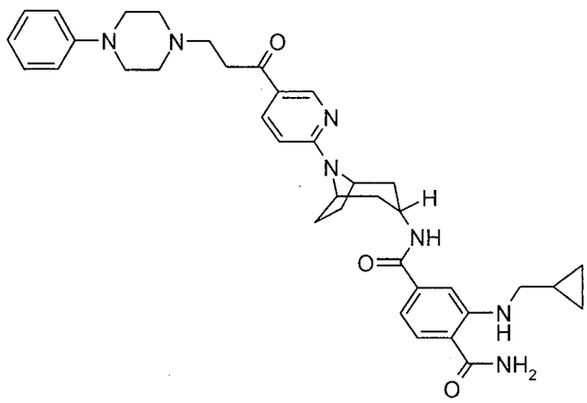
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-[(ciclopropilmetil) amino]-N4-{8-[5-(4-metilpentanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N4-{8-[5-(3-ciclohexilpropanoil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil) amino]bencen-1,4-dicarboxamida **ACTIVIDAD = C**
	5-[(1-etilpropil)amino]-2-metil-N-(8-{5-[3-(1-metilpiperidin-4-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-[(ciclopropilmetil) amino]-N4-{8-[5-(3-piperidin-4-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil) amino]-N4-{8-[5-(N,N-dimetil-beta-alanil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil) amino]-N4-(8-{5-[3-(metiloxi)propanoil] piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil) amino]-N4-{8-[5-(3-piperidin-1-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**

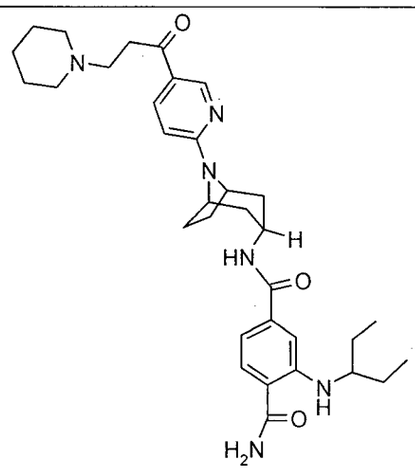
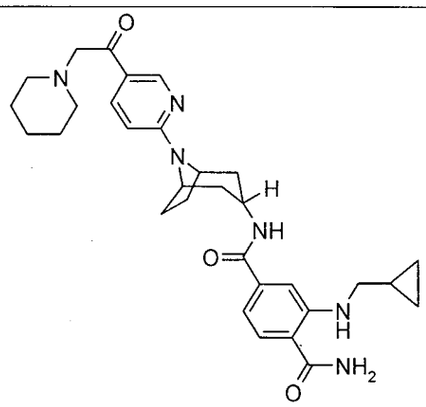
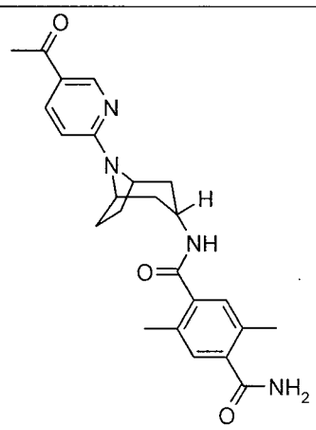
708

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-[(ciclopropilmetil) amino]-N4-(8-{5-[3-(etiloxi)propanoil] piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil) amino]-N4-(8-{5-[N-(4-fluorofenil)-beta-alanyl]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = D**
	2-[(ciclopropilmetil) amino]-N4-{8-[5-(3-morfolin-4-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**

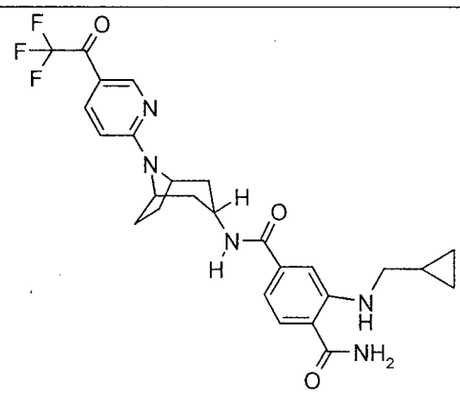
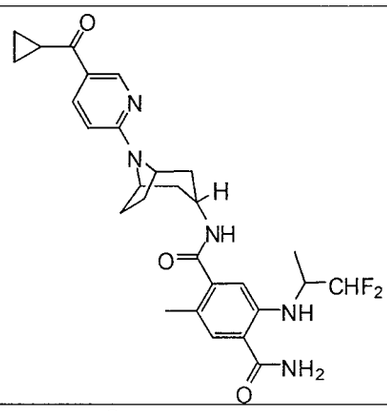
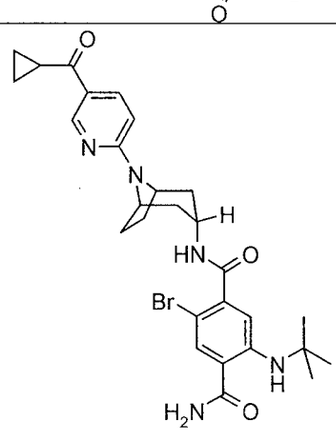
709

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-[(ciclopropilmetil) amino]-N4-(8-{5-[3-(4-metilpiperazin-1-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil) amino]-N4-{8-[5-(3-pirrolidin-1-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil) amino]-N4-(8-{5-[3-(4-fenilpiperazin-1-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida **ACTIVIDAD = B**

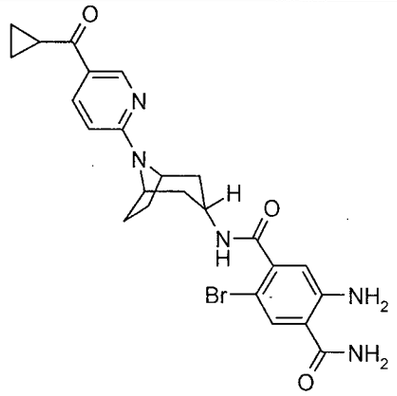
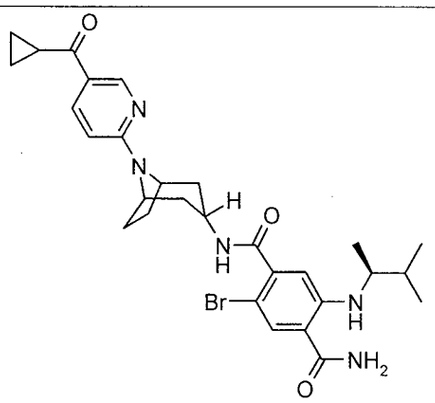
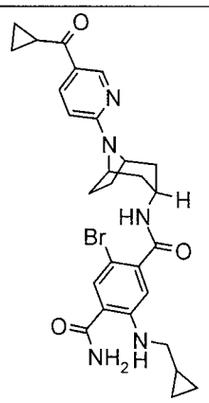
710.

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-[(1-etilpropil)amino]-N4-{8-[5-(3-piperidin-1-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-[(ciclopropilmetil)amino]-N4-{8-[5-(piperidin-1-ilacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = D**
	N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2,5-dimetilbencen-1,4-dicarboxamida **ACTIVIDAD = A**

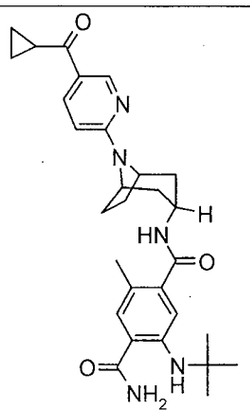
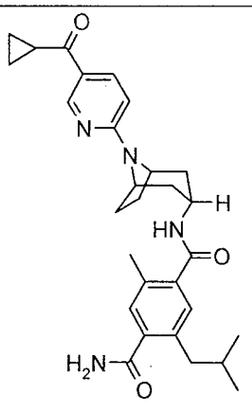
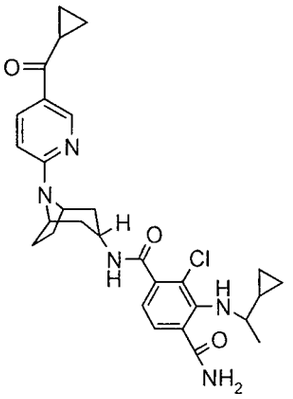
711

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	2-[(ciclopropilmetil) amino]-N4-{8-[5-(trifluoroacetil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = D**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(2,2-difluoro-1-metiletil)amino]-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1,1-dimetiletil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**

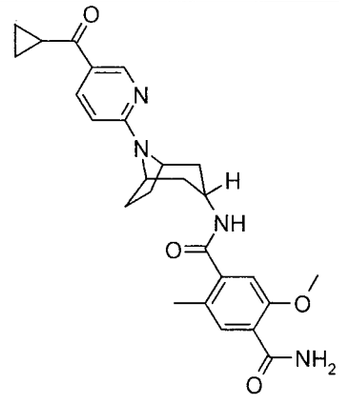
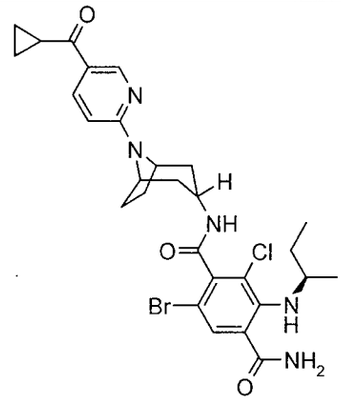
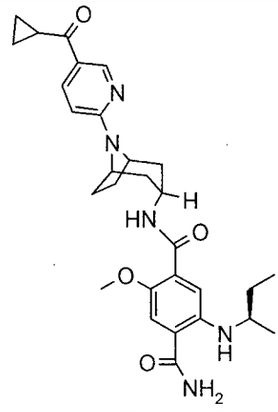
712

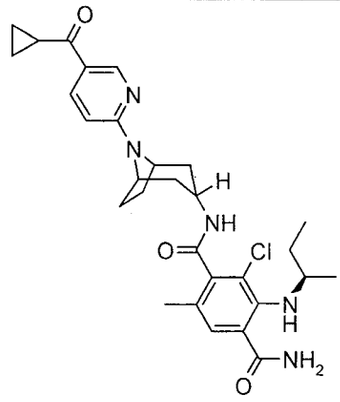
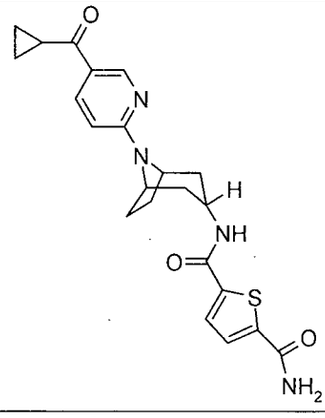
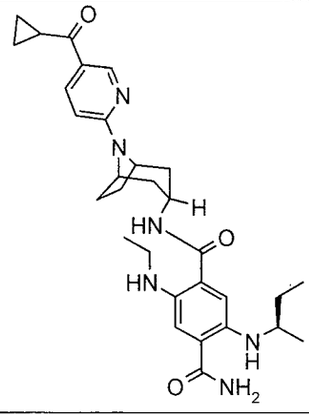
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	5-amino-2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1S)-1,2-dimetilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-bromo-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida **ACTIVIDAD = A**

713

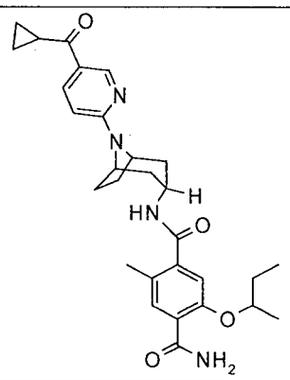
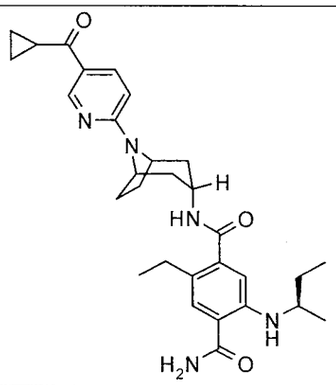
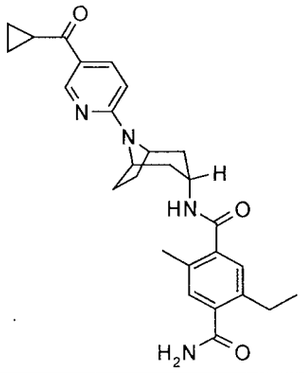
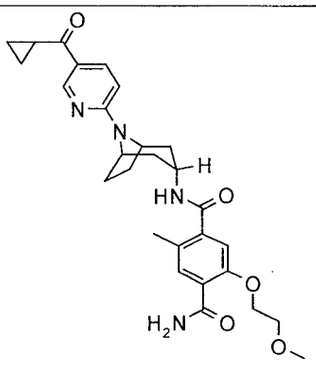
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1,1-dimetiletil)amino]-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-(2-metilpropil)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	2-cloro-N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-3-[(1-ciclopropiletil)amino] bencen-1,4-dicarboxamida **ACTIVIDAD = A**

714

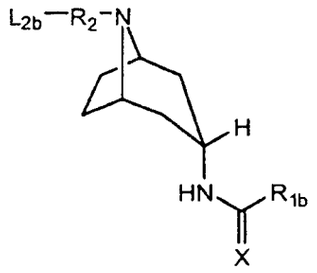
ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-(metiloxi)bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	5-bromo-3-cloro-N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1R)-1-metilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(metiloxi)-5-{[(1R)-1-metilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	3-cloro-N4-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-metil-2-{[(1R)-1-metilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}thiophene-2,5-dicarboxamida **ACTIVIDAD = C**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(etilamino)-5-{[(1R)-1-metilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = D**

726

ESTRUCTURA	NOMBRE Y ACTIVIDAD
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(1-metilpropil)oxi] bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-etil-5-{[(1R)-1-metilpropil]amino} bencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-etil-2-metilbencen-1,4-dicarboxamida **ACTIVIDAD = A**
	N-{8-[5-(ciclopropilcarbonil) piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[2-(metiloxi)etil]oxi} bencen-1,4-dicarboxamida **ACTIVIDAD = B**

[0082] Otro aspecto de la descripción se refiere a un compuesto de conformidad con la Fórmula II:



II

o una sal del mismo farmacéuticamente aceptable, en donde:

R_{1b} se selecciona a partir de heteroarilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de $-NH_2$, halógeno, fenilo y alquilo;

R_2 es un fenilo o un heteroarilo que puede contener 1, 2 o 3 heteroátomos, en donde el arilo o heteroarilo puede ser sustituido con 1, 2 o 3 grupos seleccionados a partir de alquilo, -OH, alcoxi, y halógeno;

R_{3b} se selecciona a partir de hidrógeno, $-CF_3$, $-NH_2$, -OH, alquilo opcionalmente sustituido con 1, 2 o 3 R_{5b}, alcoxi, dialquilaminoalquilo, cicloalquilo opcionalmente sustituido con arilalcoxi, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo, alcoxi, dialquilaminoalcoxi y heterocicloalquilo opcionalmente sustituido con alquilo o arilo, alquenilo, alquinilo, heterocicloalquilo opcionalmente sustituido con un grupo seleccionado a partir de alquilo, -C(O)O-alquilo y

718.

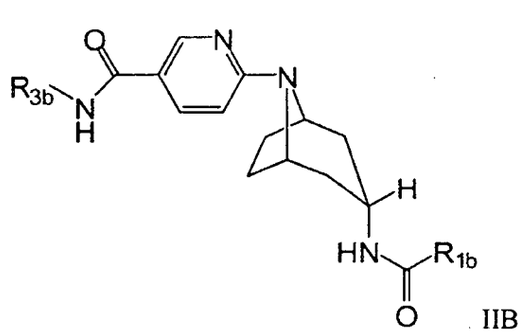
arilalquilo, arilalquilo opcionalmente sustituido con alquilheterocicloalquilo en cualquier posición del anillo del grupo arilo, y heteroarilo;

R_{5b} se selecciona a partir de halógeno, cicloalquilo, heteroarilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo y alcoxi, alquiltio, heterocicloalquilo opcionalmente sustituido con 1, 2, o 3 grupos seleccionados a partir de alquilo, halógeno, fenilo y oxo, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo, alcoxi, dialquilaminoalcoxi y heterocicloalquilo opcionalmente sustituido con alquilo, alcoxi, dialquilamino, -OH, $-C(O)-NH_2$, $-C(O)-O-CH_3$, -C(O)-N(H)alquilo (C_1-C_3), heteroarilamino opcionalmente sustituido con halógeno y $-OCF_3$;

L_{2b} es $-C(O)-NH-R_{3b}$, -CN o $-C(O)-R_{3b}$; y

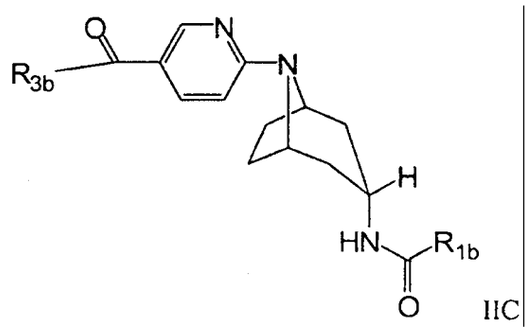
X es O u S.

[0083] Otra modalidad del compuesto de Fórmula II es un compuesto de conformidad con la Fórmula IIB o IIC:



IIB

719



IIC

en donde R_{1b} es como se define en el compuesto de Fórmula II; y R_{3b} se selecciona a partir de alquilo opcionalmente sustituido con 1, 2 o 3 halógenos, cicloalquilo y hidrógeno.

[0084] En otra modalidad del compuesto de Fórmula II, R_{3b} se selecciona a partir de H, cicloalquilo, y alquilo (C_1-C_6) opcionalmente sustituido con uno o más halógenos.

[0085] En otra modalidad de la Fórmula II, IIB o IIC, R_{3b} es metilo.

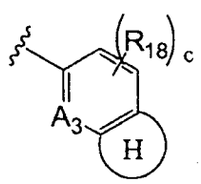
[0086] En otra modalidad de la Fórmula II, IIB o IIC, R_{3b} es ciclopropilo.

[0087] En otra modalidad del compuesto de Fórmula II, IIB o IIC, R_{3b} es $-CH_2CF_3$.

[0088] En otra modalidad del compuesto de Fórmula II, IIB o IIC, R_{3b} es 1-metiletilo.

[0089] En otra modalidad del compuesto de Fórmula II, IIB o IIC, R_{1b} es

720.



(O)

en donde:

A_3 es =N- o =CH-;

cada R_{18} es independientemente seleccionado a partir de $-NH_2$, halógeno y alquilo;

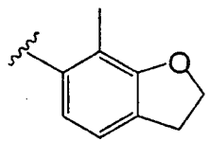
el anillo (H) es un anillo heterocíclico de 5 o 6 elementos fusionado a los dos átomos de carbono a los cuales el anillo (H) está unido, en donde el anillo (H) contiene 1, 2 o 3 heteroátomos seleccionados a partir de N, O u S; y

c es 0, 1 o 2.

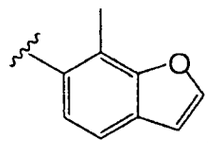
[0090] En otras modalidades del compuesto de Fórmula II, IIB o IIC, R_{1b} es de la Fórmula (O) y se selecciona a partir de 1H-bencimidazol opcionalmente sustituido con 1 o 2 grupos metilo, 1H-indol opcionalmente sustituido con 1 o 2 grupos metilo, benzofurano, 3,4-dihidro-2H-cromenilo opcionalmente sustituido con 1 o 2 grupos metilo, 2,3-dihidrobenzofuranilo opcionalmente sustituido con 1 o 2 grupos metilo, 2,3-dihidro-1,4-benzodioxin-6-ilo opcionalmente sustituido con 1 o 2 grupos metilo, 1H-1,2,3-benzotriazol opcionalmente sustituido con 1, 2 o 3 grupos metilo, 9H-purin-9-ilo opcionalmente sustituido con 1 o 2 grupos seleccionados a partir de halógeno y amino, 1,3-

benzotiazol opcionalmente sustituido con 1 o 2 grupos metilo, y 2,3-dihidro-1-benzofurano opcionalmente sustituido con 1 o 2 grupos metilo.

[0091] En otras modalidades del compuesto de Fórmula II, IIB o IIC, R_{1b} es

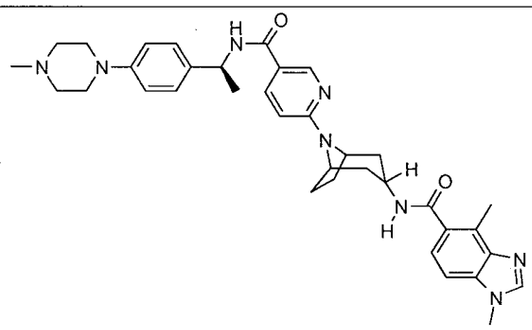
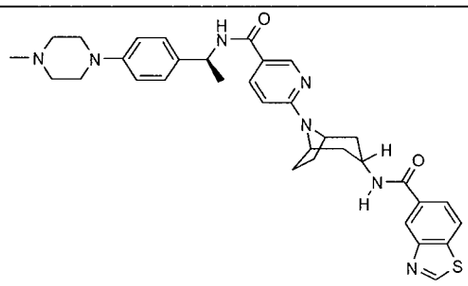


o

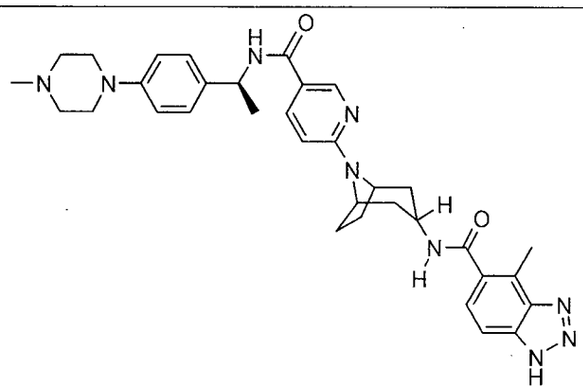
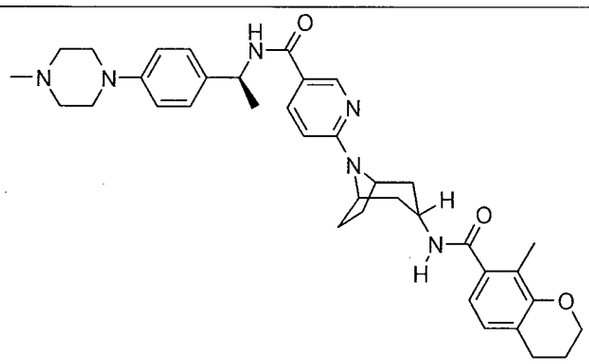
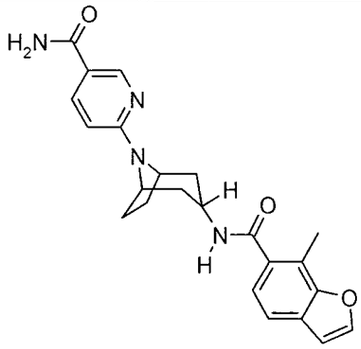
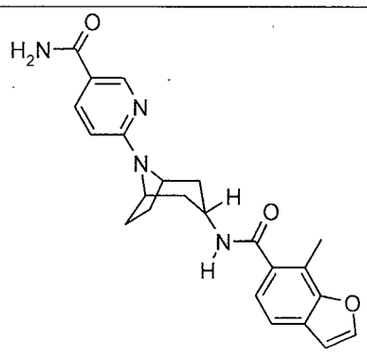


[0092] En otra modalidad, el compuesto de Fórmula II se selecciona a partir de uno de los siguientes compuestos de la Tabla II, o una sal farmacéuticamente aceptable de cualquiera de los compuestos en la Tabla II:

TABLA II

ESTRUCTURA	NOMBRE
	1,4-dimetil-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1H-bencimidazol-5-carboxamida
	N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1,3-benzotiazol-5-carboxamida

722

ESTRUCTURA	NOMBRE
	4-metil-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1H-1,2,3-benzotriazol-5-carboxamida
	6-(3-endo-{[(8-metil-3,4-dihidro-2H-cromen-7-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida
	6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida
	6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida

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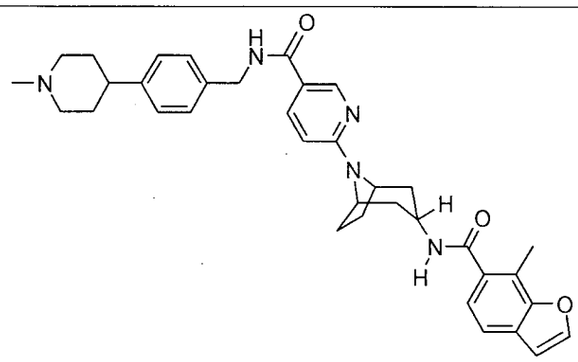
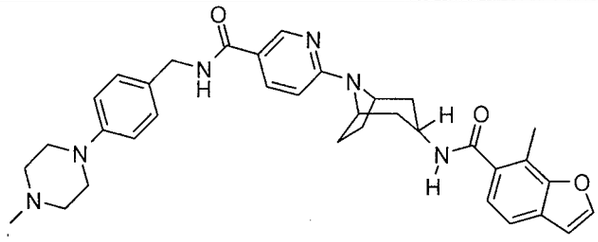
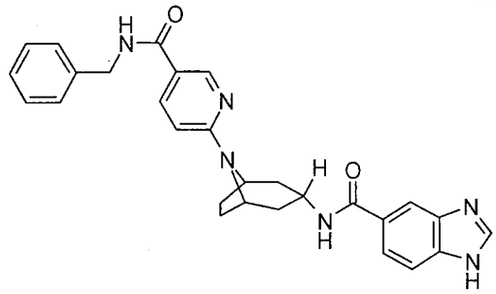
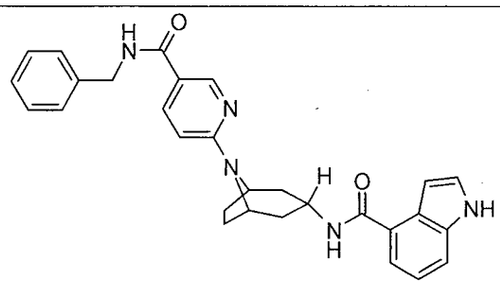
ESTRUCTURA	NOMBRE
	6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(1-metilpiperidin-4-il)fenil]metil}piridin-3-carboxamida
	6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida
	N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-bencimidazol-5-carboxamida
	N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-indol-4-carboxamida

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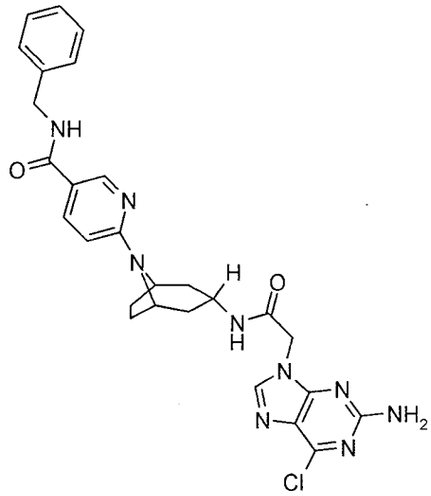
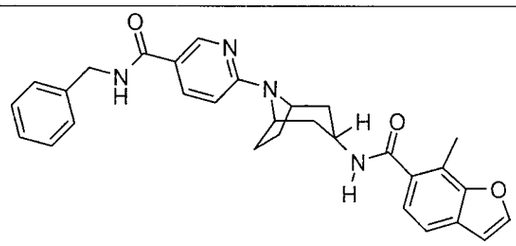
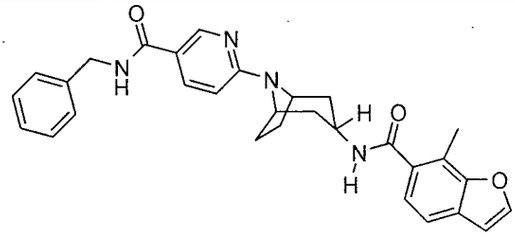
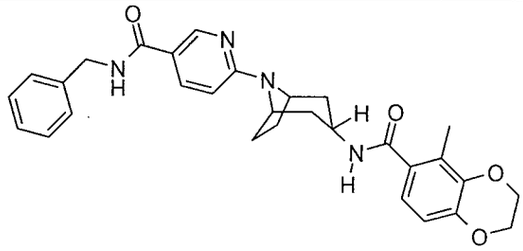
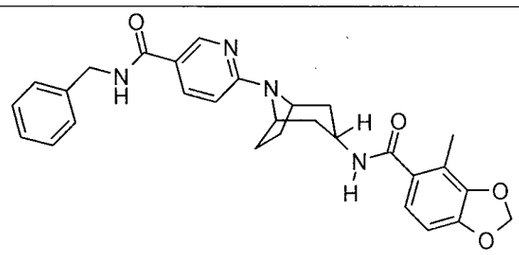
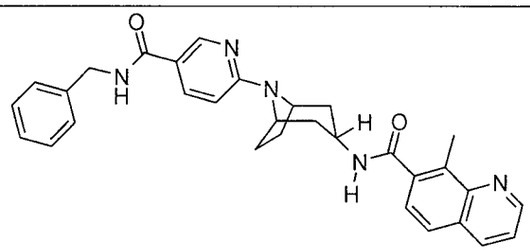
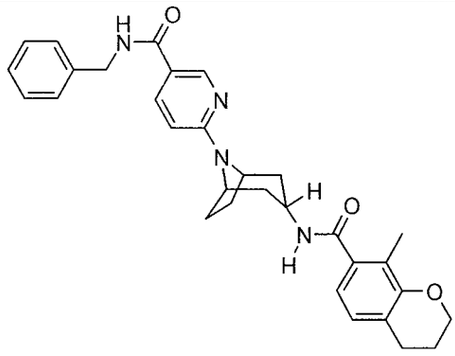
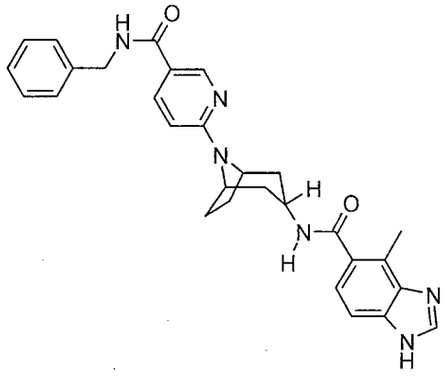
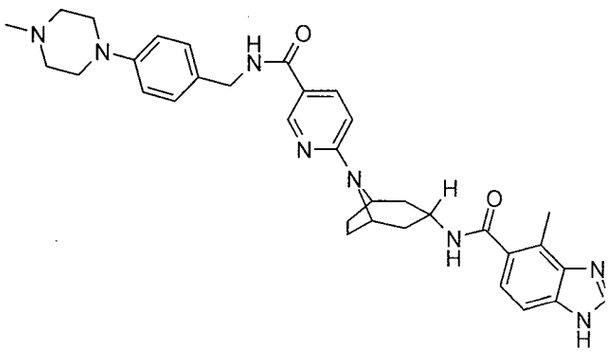
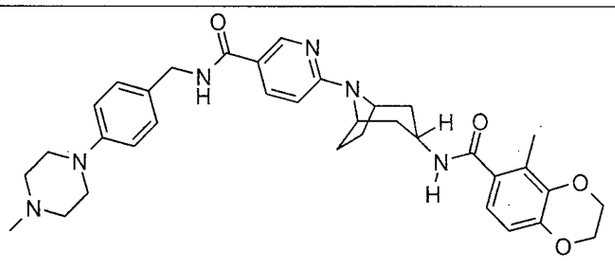
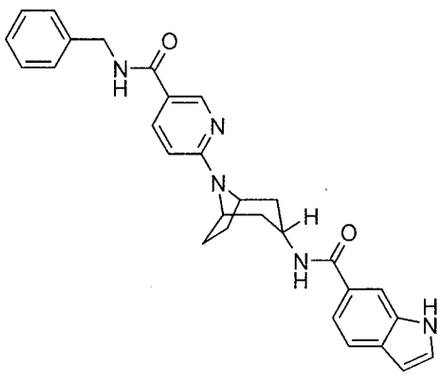
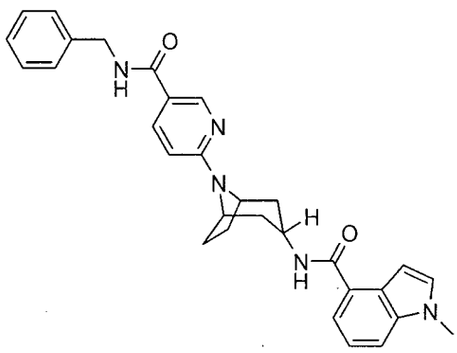
ESTRUCTURA	NOMBRE
	6-(3-endo-{[(2-amino-6-cloro-9H-purin-9-il)acetil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida
	6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida
	6-(3-endo-{[(5-metil-2,3-dihidro-1,4-benzodioxin-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida

725.

ESTRUCTURA	NOMBRE
	6-(3-endo-{[(4-metil-1,3-benzodioxol-5-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida
	8-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]quinolin-7-carboxamida
	6-(3-endo-{[(8-metil-3,4-dihidro-2H-cromen-7-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida
	4-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-bencimidazol-5-carboxamida

726.

ESTRUCTURA	NOMBRE
	4-metil-N-(8-{5-[({[4-(4-metilpiperazin-1-il)fenil]metil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1H-bencimidazol-5-carboxamida
	6-(3-endo-{[(5-metil-2,3-dihidro-1,4-benzodioxin-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida
	N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-indol-6-carboxamida
	1-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-indol-4-carboxamida

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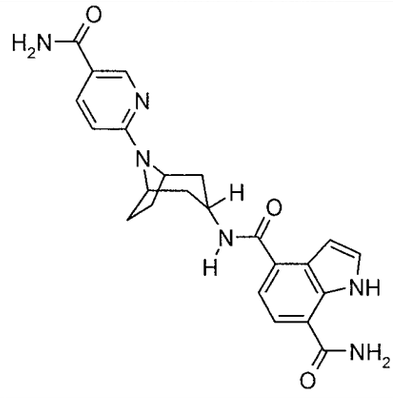
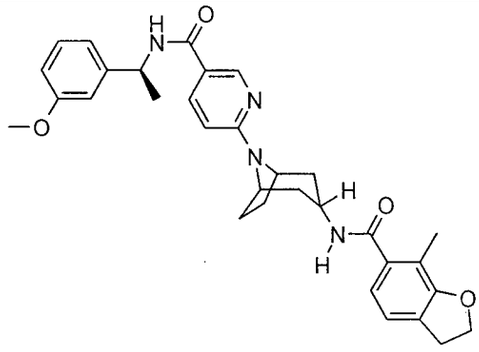
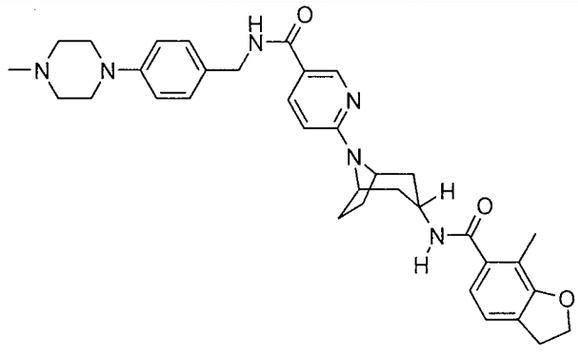
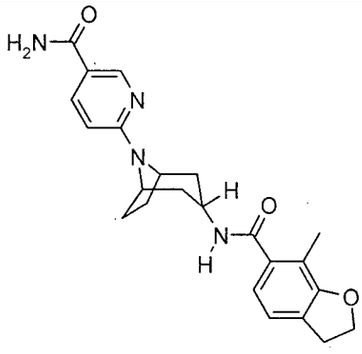
ESTRUCTURA	NOMBRE
	N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-1H-indol-4,7-dicarboxamida
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[3-(metiloxi)fenil]etil}piridin-3-carboxamida
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida

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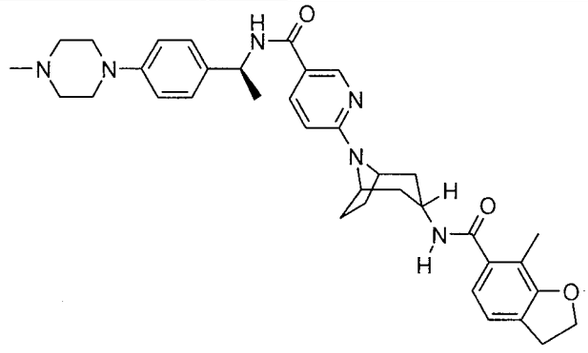
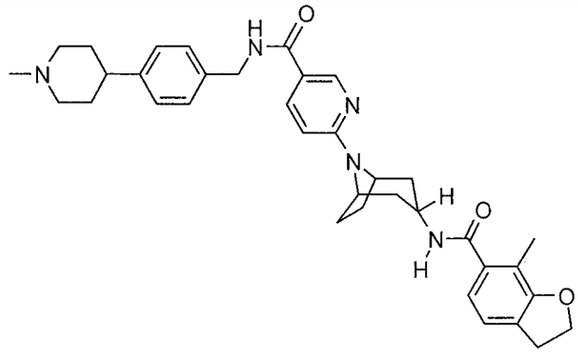
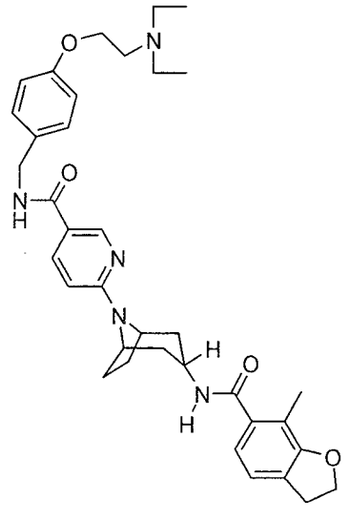
ESTRUCTURA	NOMBRE
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(1-metilpiperidin-4-il)fenil]metil}piridin-3-carboxamida
	N-[(4-{[2-(dietilamino)etil]oxi}fenil)metil]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida

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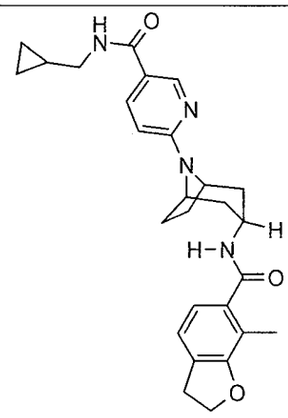
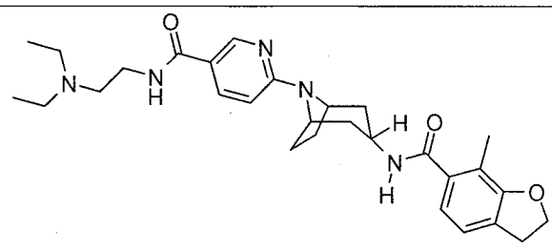
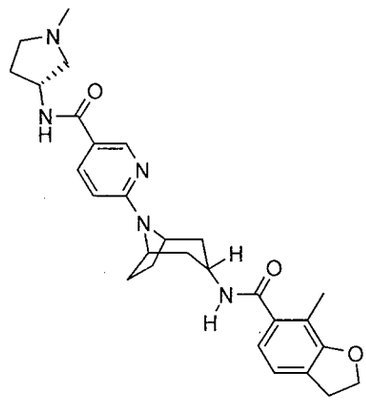
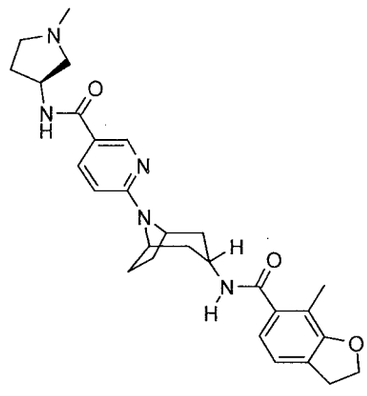
ESTRUCTURA	NOMBRE
	N-(ciclopropilmetil)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida
	N-[2-(dietilamino)etil]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-metilpirrolidin-3-il]piridin-3-carboxamida
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-metilpirrolidin-3-il]piridin-3-carboxamida

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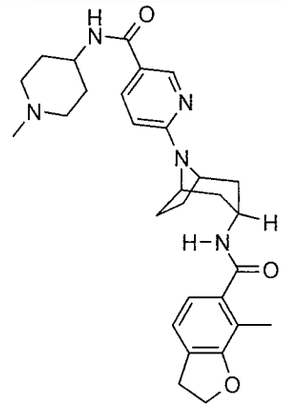
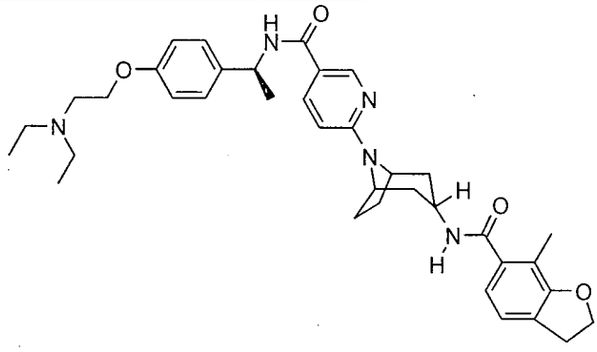
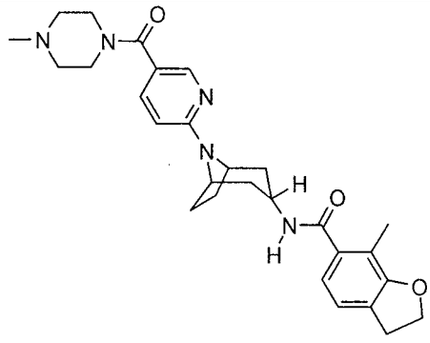
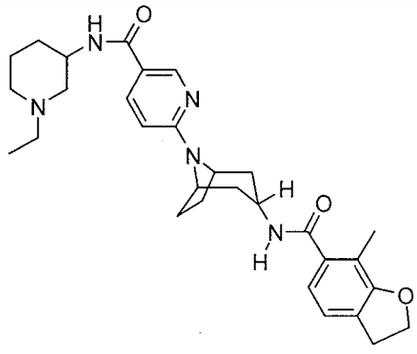
ESTRUCTURA	NOMBRE
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(1-metilpiperidin-4-il)piridin-3-carboxamida
	N-[(1S)-1-(4-{[2-(dietilamino)etil]oxi}fenil)etil]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida
	7-metil-N-(8-{5-[(4-metilpiperazin-1-il)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2,3-dihidro-1-benzofuran-6-carboxamida
	N-(1-etilpiperidin-3-il)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida

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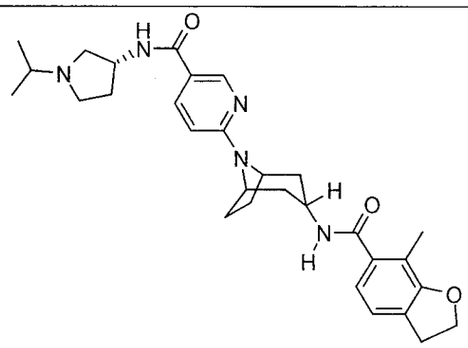
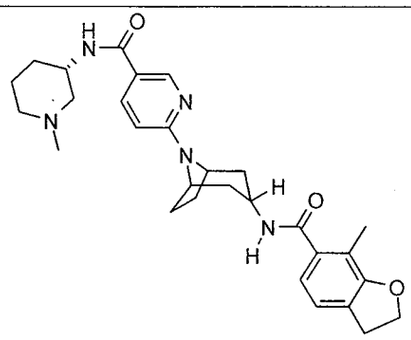
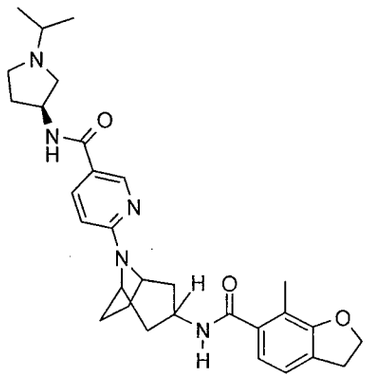
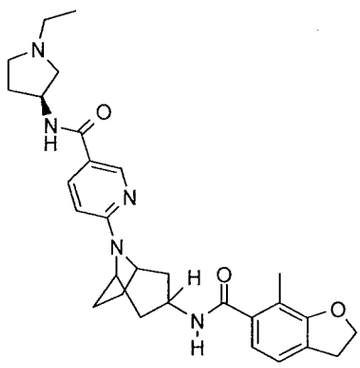
ESTRUCTURA	NOMBRE
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-(1-metiletil)pirrolidin-3-il]piridin-3-carboxamida
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-metilpiperidin-3-il]piridin-3-carboxamida
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-(1-metiletil)pirrolidin-3-il]piridin-3-carboxamida
	N-[(3S)-1-etilpirrolidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida

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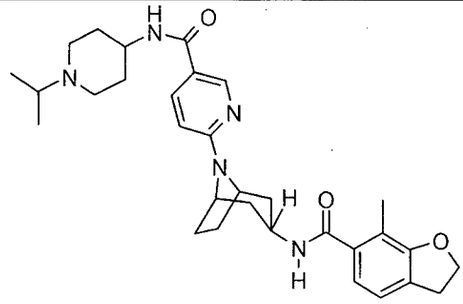
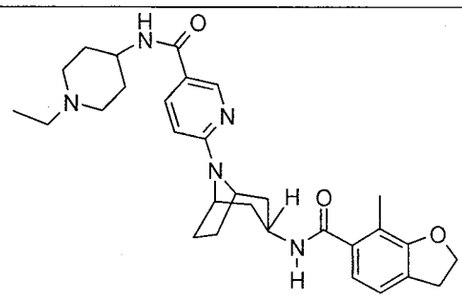
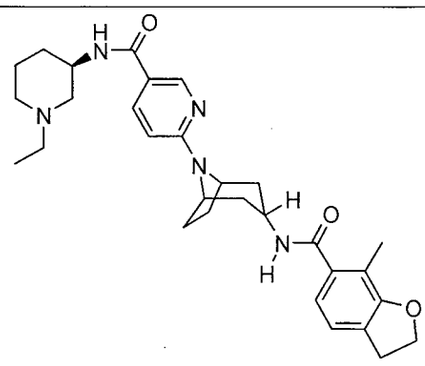
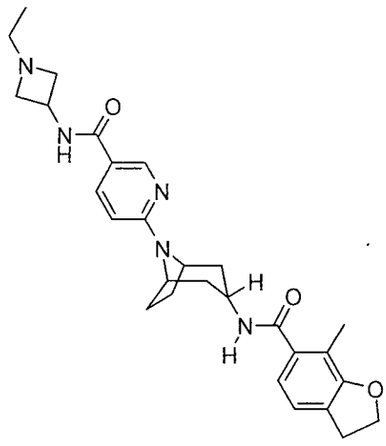
ESTRUCTURA	NOMBRE
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[1-(1-metiletil)piperidin-4-il]piridin-3-carboxamida
	N-(1-etilpiperidin-4-il)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida
	N-[(3R)-1-etilpiperidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida
	N-(1-etilazetidin-3-il)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida

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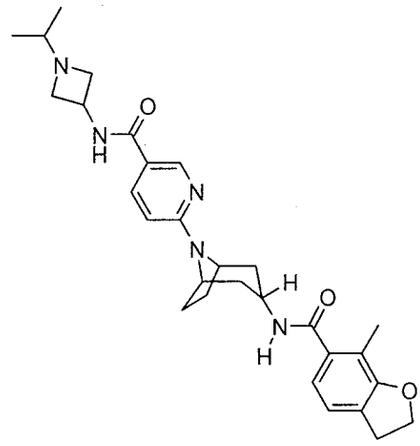
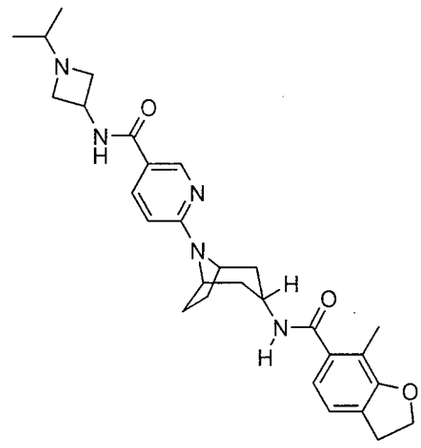
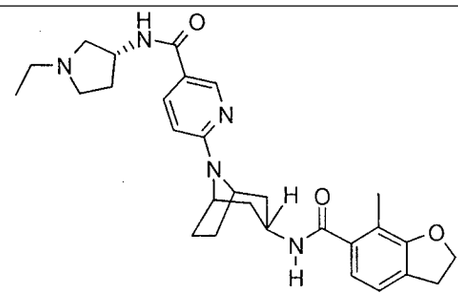
ESTRUCTURA	NOMBRE
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[1-(1-metiletil)azetidin-3-il]piridin-3-carboxamida
	N-(1-metilazetidin-3-il)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida
	N-[(3R)-1-etilpirrolidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida

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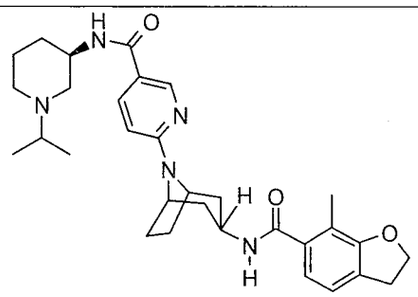
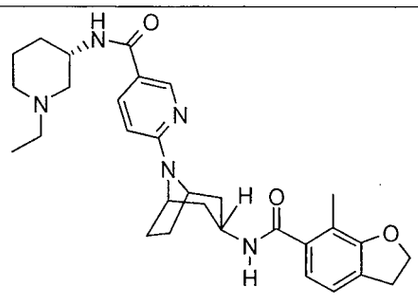
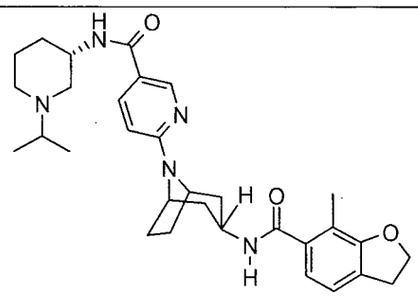
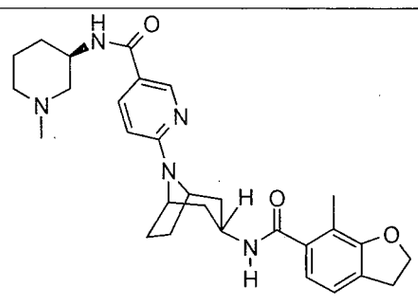
ESTRUCTURA	NOMBRE
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-(1-metiletil)piperidin-3-il]piridin-3-carboxamida
	N-[(3S)-1-etilpiperidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-(1-metiletil)piperidin-3-il]piridin-3-carboxamida
	6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-metilpiperidin-3-il]piridin-3-carboxamida

[0093] Los compuestos en las Tablas I y II son nombrados de conformidad con la aplicación sistemática de las reglas de nomenclatura acordadas por la Unión Internacional de Química Aplicada y Pura (IUPAC), Unión Internacional de

Bioquímica y Biología Molecular (IUBMB), y el Servicio de Resúmenes Químicos (CAS). Los nombres se generaron usando software nombrado ACD/Labs de liberación 8.00, versión de producto 8.08.

[0094] La actividad para cada uno de los compuestos en la Tabla I es representada por las letras A, B, C y D. Estas letras son listadas después de cada uno de los compuestos en la Tabla I, en la misma hilera como cada uno de los compuestos. La actividad que se asocia con cada una de estas letras se define abajo:

A significa valores IC_{50} de HSP90 de menos de 500 nM.

B significa valores IC_{50} de HSP90 que varían desde 500 nM hasta 999 nM.

C significa valores IC_{50} de HSP90 que varían desde 1000 nM hasta 1999 nM.

D significa valores IC_{50} de HSP90 que varían desde 2000 nM hasta 10,000 nM.

[0095] La expresión y actividad de HSP90, es frecuentemente regulada descendentemente en células tumorales [5-8] y es particularmente asociada con prognosis pobre en cáncer de mama [9, 10]. Además, la HSP90 en células tumorales, parece existir en un estado hiperactivado con actividad de ATPase elevada, la cual es altamente sensible a inhibición de HSP90, comparada con la forma ampliamente

latente encontrada en células normales [11]. Este estado hiperactivado sugiere que los inhibidores de HSP90 pueden selectivamente, dirigir células tumorales con relativamente bajo impacto en tejidos normales. Muchas proteínas cliente de HSP90, están involucradas en varios aspectos de crecimiento y progreso de tumor [6, 7, 12, 13]. La HSP90 promueve el plegado y/o estabilización de muchas proteínas oncogénicas que confieren crecimiento autónomo en las células (por ejemplo, EGFR y ErbB2 [14-17], B-Raf [18, 19] y receptores de la hormona esteroide [20]) y también regula múltiples proteínas que promueven la supervivencia de células tumorales (por ejemplo, receptor IGF 1 [21], PDK1 y Akt [22, 23], RIP [24], IκB [24, 25] y survivina [26]). La HSP90 también promueve el progreso del ciclo celular aberrante estabilizando Cdk4, Cdk6 y ciclina D [27], Cdk2, y Plk1 [28, 29]. Contrariamente, los inhibidores de HSP90 pueden regular descendentemente la cinasa Chk1 de punto de verificación del ciclo celular y sensibilizar tumores a varias formas de quimioterapia [30, 31]. La inhibición de HSP90 puede también, despuntar la angiogénesis del tumor, puesto que las tirosinas cinasas del receptor del factor de crecimiento endotelial (VEGF) y del factor inducible de hipoxia (HIF-1α), son clientes HSP90 [32]. El receptor de tirosina cinasa Met, el cual estimula la movilidad, migración e invasión celular, también es regulado descendentemente en respuesta a la

inhibición de HSP90, tanto directamente como vía inhibición de HIF-1α [33, 34]. A parte de su papel como una chaperona celular, la HSP90α también ha sido implicada en la degradación de matriz extracelular e invasión de células tumorales, vía activación (y posiblemente estabilización) de la metaloproteinasa de matriz MMP2 [35, 36]. La depleción o inhibición de HSP90 promueve la erosión del telómero y apoptosis [37], y también puede permitir la evolución de fenotipos heterogéneos, metastásicos y resistentes al fármaco, permitiendo la propagación de mutaciones metastables [38, 39]. La HSP90 ha sido implicada en la activación de la respuesta de proteína no desplegada (UPR, [40, 41]). La falla de la UPR (por ejemplo, vía inhibición de HSP90), conduce a una señal de estrés ER y apoptosis. Por lo tanto, los inhibidores de HSP90 pueden promover la muerte de células tumorales indirectamente interrumpiendo la UPR, así como también dirigiendo directamente factores pro-supervivencia objetivos.

[0096] Además del cáncer, varias otras enfermedades pueden ser susceptibles al tratamiento usando inhibidores de HSP90. Existen datos sustanciales que soportan un papel para inhibidores de HSP90 en el tratamiento de enfermedades neurodegenerativas e infecciosas. Otras indicaciones no oncológicas para HSP90 incluyen, enfermedades inflamatorias, trastornos autoinmunes, apoplejía, isquemia, trastornos

cardiacos, sepsis, trastornos fibrogenéticos (por ejemplo, escleroderma, poliomiositis, lupus sistémico, artritis reumatoide, cirrosis hepática, formación queloide, nefritis intersticial, fibrosis quística y fibrosis pulmonar) y enfermedades metabólicas.

[0097] Varias enfermedades neurodegenerativas ("taupatías"), que incluyen enfermedad de Alzheimer (AD) y demencia lobar frontotemporal, son caracterizadas por acumulación de formas hiperfosforiladas o mutadas de la proteína Tau asociada al microtúbulo [42]. Los inhibidores HSP90 pueden ser capaces de degradar vía proteínas Tau aberrantes vía dos mecanismos complementarios. Primero, la HSP90 parece estabilizar p35 (una proteína neuronal involucrada en la fosforilación Tau aberrante) y proteína Tau mutante (pero no del tipo nativo) [43]. Segundo, la inhibición de HSP90 induce expresión de HSP70, la cual puede promover el pliegue productivo de Tau [44] y/o degradación selectiva de proteínas Tau aberrantes [45]. Sin embargo, la HSP90 aislada a partir del tejido cerebral afectado por AD, muestra afinidad marcadamente superior para un inhibidor HSP90 comparado con HSP90 a partir de tejido cerebral normal [45], concordante con una observación similar en células tumorales [11].

[0098] La expresión de HSP90 en el organismo hospedero ha sido implicada en mediar tanto la infección como

replicación de un amplio intervalo de patógenos virales, que incluyen virus de ARN de cepa negativa y virus de la influenza [46-48], hepatitis B [49], hepatitis C [50, 51] y virus del herpes simple tipo 1 [52]. De manera importante, la inhibición farmacológica de HSP90 se encontró por impartir la replicación de ARN sin selección para la emergencia de mutantes resistentes a fármaco [53]. La HSP90 también promueve el crecimiento y supervivencia de levadura patogénica, aunque en este caso, está involucrada la enzima fúngica endógena. La geldanamicina incrementa la susceptibilidad de especies de Candida y Aspergillus a otros antibióticos [54], y un anticuerpo dirigido contra la levadura de HSP90 (Mycograb), fue recientemente mostrado por mejorar significantemente la actividad de anfotericina B en un estudio clínico de doble ciego, aleatorizado [55]. La HSP90 fúngica también puede ayudar a promover la resistencia del fármaco [54]. La inhibición de HSP90 también mostró recientemente aliviar el daño pulmonar e inflamación en un modelo de ratón de sepsis aguda [56], sugiriendo un papel más amplio para inhibidores de HSP90 en el tratamiento de enfermedades inflamatorias e infecciosas.

[0099] La benzoquinona ansamicina geldanamicina, se identificó como un inhibidor de HSP90 [57], y varios análogos de geldanamicina han sido evaluados como agentes anticancerígenos en ensayos clínicos, con alguna evidencia de

actividad. Sin embargo, la formulación y administración de estos agentes permanecen sin cambio. Un inhibidor oralmente disponible de HSP90 podrá tener amplia utilidad en el tratamiento de un amplio intervalo de malignidades y potencialmente otras enfermedades.

[00100] Los inhibidores de HSP90 han sido reportados por mostrar efectos sinergísticos en el crecimiento y supervivencia de células tumorales cuando se combinan con varios quimioterapéuticos. Ejemplos incluyen, inhibidores de HSP90 en combinación con inhibidores de proteosoma (por ejemplo, bortezomib) en mieloma múltiple, EGFR (por ejemplo, Iressa) o PI3K (por ejemplo, LY294002) inhibidores en glioma maligno, agentes que dañan el ADN (por ejemplo, etopósido o cisplatino) en leucemia y tumores pediátricos, y radiación en varios tumores que incluyen, cervical, próstata, glioma y pancreático. Mientras la sinergia observada puede ser hipotetizada por ser debido a pérdida de estabilidad de proteínas cliente HSP90 específicas, puede también ser debido a pérdida de capacidad amortiguadora en estrés general de la célula.

[00101] Adicionalmente, varias proteínas mutantes resistentes al fármaco han sido mostradas por ser dependientes de HSP90 por su estabilización y actividad, allanando el camino en pruebas in vivo de estudios de concepto y diseños de ensayos clínicos para uso de

inhibidores de HSP90 contra ciertos tumores resistentes al fármaco. Ejemplos incluyen, mutaciones c-KIT resistentes a imatinib en GIST (tumor estromal gastrointestinal), mutantes de EGFR resistentes a gefitinib y erlotinib (L858R/T790M) en NSCL, y mutantes BCR-ABL(T315I) resistentes a imatinib en CML. En efecto, el inhibidor HSP90 relacionado con 17-AAG IPI-504, fue concedido recientemente al estado de fármaco huérfano para GIST después que se observó una alta velocidad de respuesta en pacientes GIST resistentes a Gleevec enrolados en el ensayo Fase I.

[00102] Adicionalmente, la inhibición de HSP90 puede ser en parte, responsable de la actividad anti-tumoral del inhibidor de desacetilasa histona recientemente aprobado por la FDA Vorinostat (ácido hidroxámico suberoanilido, o SAHA). La actividad de HSP90 ha sido reportada por ser negativamente regulada a través de la acetilación directa de la chaperona, y los inhibidores de HDAC son mostrados por resultar en la acumulación de proteína HSP90 acetilada, inactiva, y degradación incrementada de proteínas cliente HSP90, implicando la función HDAC en el control positivo de la función de HSP90. Por lo tanto, el mecanismo de acción clínico de inhibidores de HDAC solos o en combinación, puede en ciertos casos, ser debido a la inhibición de la función de HSP90.

[00103] La expresión de HSP90 en el organismo

hospedero ha sido implicada en mediar tanto la infección como replicación de un amplio intervalo de patógenos virales. Los inhibidores de HSP90 geldanamicina y radicicol, imparten la replicación del virus de ARN de cepa negativa y virus de la influenza desestabilizando la polimerasa de ARN viral, y la geldanamicina también puede inhibir la replicación del virus de la hepatitis C. La HSP90 también dirige el repliegue y localización intracelular de la polimerasa de ADN a partir del virus del herpes simple tipo 1 y es requerida para la actividad de transcriptasa inversa de hepatitis B. La inhibición farmacológica de HSP90 se encontró por impartir la replicación de virus de ARN en animales infectados y cultivos celulares, sin selección para la emergencia de mutantes resistentes a fármaco. Sin embargo, la HSP90 puede ser ampliamente implicada en el desarrollo de resistencia al fármaco en microorganismos, como se discute abajo.

[00104] La HSP90 también promueve el crecimiento y supervivencia de levadura patogénica, aunque en este caso, está involucrada la enzima fúngica endógena. La geldanamicina incrementa la susceptibilidad de especies de Candida y Aspergillus a otros antibióticos, y un anticuerpo dirigido contra la levadura HSP90 (Mycograb) fue recientemente mostrado por mejorar significantemente la actividad de anfotericina B en un estudio clínico de doble ciego, aleatorizado. Como en el caso de células tumorales, la HSP90

puede actuar vía mecanismos múltiples, pero quizás más notable es el potencial para HSP90 fúngicas para promover la resistencia al fármaco. La HSP90 endógena puede soportar la expresión de proteínas mutantes que confieren resistencia al fármaco, y los inhibidores de HSP90 parecen inhibir la resistencia al fármaco bajo condiciones de selección agudas, pero tienen menos efecto en la resistencia que es adquirida por selección más gradual en la presencia de antibióticos. De este modo, los inhibidores de HSP90 pueden tener utilidad temprana en el tratamiento de infecciones fúngicas, antes de que las mutaciones de resistencia tenga una oportunidad de emerger. De manera intrigante, los efectos inductores de resistencia al fármaco de HSP90 son mediados por calcineurina, la cual también está implicada en tanto resistencia a la actividad de ciclosporina A como geldanamicina en el parásito malarial Plasmodium falciparum.

[00105] La inhibición de HSP90 también mostró recientemente aliviar el daño pulmonar e inflamación en un modelo de ratón de sepsis aguda, sugiriendo un papel más amplio para inhibidores de HSP90 en el tratamiento de enfermedades inflamatorias e infecciosas.

[00106] Además del cáncer, varias otras enfermedades pueden ser susceptibles a tratamiento usando inhibidores de HSP90. Estas incluyen trastornos neurodegenerativos y enfermedades infecciosas. Varias enfermedades

neurodegenerativas, que incluyen enfermedad de Alzheimer (AD) y demencia lobar frontotemporal, son caracterizadas por acumulación de formas hiperfosforiladas o mutadas de la proteína Tau asociada al microtúbulo. Estas proteínas Tau patogénicas forman agregados intracelulares conocidos como ovillos neurofibrilares, los cuales han sido propuestos por tener un papel causativo en la enfermedad, pero pueden representar alternativamente, un mecanismo protector celular contra la forma soluble, tóxica, de Tau. La degradación selectiva de proteínas Tau aberrantes puede por lo tanto, representar una nueva estrategia terapéutica. Los inhibidores de HSP90 pueden lograr esta degradación vía dos mecanismos complementarios. Primero, la HSP90 parece estabilizar p35 (una proteína neuronal involucrada en la fosforilación Tau aberrante) y proteína Tau mutante (pero no del tipo nativo): la actividad de estas proteínas patogénicas podrá por lo tanto, ser reducida por inhibición de HSP90. Segundo, la inhibición de HSP90 induce expresión de HSP70, la cual puede promover el pliegue productivo de Tau y/o degradación selectiva de proteínas Tau aberrantes. Sin embargo, la HSP90 aislada a partir del tejido cerebral afectado por AD, muestra afinidad marcadamente superior para un inhibidor HSP90 comparado con HSP90 a partir de tejido cerebral normal, concordante con una observación similar en células tumorales.

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[00108] Otra modalidad de la descripción se refiere a una composición farmacéutica que comprende el compuesto de Fórmula I, IB, IC, ID, IE, o una sal del mismo farmacéuticamente aceptable, y un portador, excipiente o diluyente farmacéuticamente aceptable.

[00109] Otra modalidad de la descripción se refiere a un método para inhibir HSP90 en una célula, que comprende contactar la célula, en la cual se desea la inhibición de HSP90, con el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable.

[00110] Otra modalidad de la descripción se refiere a un método para inhibir HSP90 en una célula, que comprende contactar una célula en la cual se desea la inhibición de HSP90 con una composición farmacéutica, que comprende el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, y un portador, excipiente o diluyente farmacéuticamente aceptable.

[00111] Otra modalidad de la descripción se refiere a un método para tratar una enfermedad o condición que involucra HSP90, que comprende administrar a un animal, en necesidad del tratamiento, el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable.

[00112] Otra modalidad de la descripción se refiere a un método para tratar una enfermedad o condición que involucra HSP90, que comprende administrar a un animal, en necesidad

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del tratamiento, una composición farmacéutica que comprende el compuesto de Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, y un portador, excipiente o diluyente farmacéuticamente aceptable. En una modalidad adicional, la enfermedad o condición siendo tratada es cáncer.

[00113] En otra modalidad, se contempla que los compuestos que inhiben HSP90 de la Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, pueden ser usados para tratar una o más enfermedades o condiciones seleccionadas a partir de cáncer de mama, CML, carcinoma colorrectal, glioma, melanoma, mieloma múltiple, cáncer de pulmón de células no pequeñas, cáncer de ovario, cáncer de próstata, carcinoma de células renales, carcinoma de pulmón de células pequeñas, y UPR (respuesta de proteína no plegada).

[00114] En otra modalidad, se contempla que los compuestos que inhiben HSP90 de la Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, pueden ser usados para tratar una o más enfermedades o condiciones seleccionadas a partir de enfermedades neurodegenerativas, enfermedades infecciosas, enfermedades inflamatorias, trastornos autoinmunes, apoplejía, isquemia, trastornos cardiacos, sepsis, trastornos fibrogenéticos (por ejemplo, escleroderma, poliomiositis, lupus sistémico, artritis reumatoide, cirrosis hepática, formación queloide, nefritis intersticial, fibrosis quística y fibrosis pulmonar) y enfermedades metabólicas.

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[00115] Otra modalidad de la descripción se refiere a una composición farmacéutica que comprende uno o más compuestos a partir de la Tabla I, o una sal del mismo farmacéuticamente aceptable, y un portador, excipiente o diluyente farmacéuticamente aceptable.

[00116] Otra modalidad de la descripción se refiere a un método para inhibir HSP90 en una célula, que comprende contactar la célula, en la cual se desea la inhibición de HSP90, con uno o más compuestos a partir de la Tabla I, o una sal del mismo farmacéuticamente aceptable.

[00117] Otra modalidad de la descripción se refiere a un método para inhibir HSP90 en una célula, que comprende contactar una célula en la cual se desea la inhibición de HSP90 con una composición farmacéutica, que comprende uno o más compuestos a partir de la Tabla I, o una sal del mismo farmacéuticamente aceptable, y un portador, excipiente o diluyente farmacéuticamente aceptable.

[00118] Otra modalidad de la descripción se refiere a un método para tratar una enfermedad o condición que involucra HSP90, que comprende administrar a un animal, en necesidad del tratamiento, uno o más compuestos a partir de la Tabla I, o una sal del mismo farmacéuticamente aceptable.

[00119] Otra modalidad de la descripción se refiere a un método para tratar una enfermedad o condición que involucra HSP90, que comprende administrar a un animal, en necesidad

del tratamiento, una composición farmacéutica que comprende uno o más compuestos a partir de la Tabla I, o una sal del mismo farmacéuticamente aceptable, y un portador, excipiente o diluyente farmacéuticamente aceptable. En una modalidad adicional, la enfermedad o condición siendo tratada es cáncer.

[00120] En otra modalidad, se contempla que los compuestos que inhiben HSP90 a partir de la Tabla I, o una sal del mismo farmacéuticamente aceptable, pueden tratar una o más indicaciones seleccionadas a partir de cáncer de mama, CML, carcinoma colorrectal, glioma, melanoma, mieloma múltiple, cáncer de pulmón de células no pequeñas, cáncer de ovario, cáncer de próstata, carcinoma de células renales, carcinoma de pulmón de células pequeñas, y UPR (respuesta de proteína no plegada).

[00121] Los compuestos que inhiben HSP90 de uno o más compuestos a partir de la Tabla I, o una sal del mismo farmacéuticamente aceptable, también son contemplados por ser útiles por ser capaz de tratar una o más enfermedades o condiciones seleccionadas a partir de enfermedades neurodegenerativas, enfermedades infecciosas, enfermedades inflamatorias, trastornos autoinmunes, apoplejía, isquemia, trastornos cardiacos, sepsis, trastornos fibrogenéticos (por ejemplo, escleroderma, poliomiositis, lupus sistémico, artritis reumatoide, cirrosis hepática, formación queloide,

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nefritis intersticial, fibrosis quística y fibrosis pulmonar) y enfermedades metabólicas.

[00122] Varias enfermedades neurodegenerativas ("taupatías"), que incluyen enfermedad de Alzheimer (AD) y demencia lobar frontotemporal, son caracterizadas por acumulación de formas hiperfosforiladas o mutadas de la proteína Tau asociada al microtúbulo. Se contempla que los compuestos que inhiben HSP90 descritos en la presente, pueden degradarse vía proteínas Tau aberrantes vía dos mecanismos complementarios. Primero, HSP90 parece estabilizar p35 (una proteína neuronal involucrada en la fosforilación Tau aberrante) y proteína Tau mutante (pero no del tipo nativo). Segundo, la inhibición de HSP90 induce expresión de HSP70, la cual puede promover el pliegue productivo de Tau y/o degradación selectiva de proteínas Tau aberrantes.

[00123] También se contempla que los compuestos que inhiben HSP90 descrita en la presente, pueden mediar y tratar la infección a partir de un amplio intervalo de patógenos virales, que incluyen virus de ARN de cepa negativa y virus de la influenza, hepatitis B, hepatitis C y virus del herpes simple tipo 1.

[00124] En otra modalidad, se contempla que los compuestos que inhiben HSP90 de la Fórmula I, IB, IC, ID o IE, o una sal del mismo farmacéuticamente aceptable, pueden ser usados para tratar una enfermedad neurodegenerativa caracterizada por

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acumulación de formas hiperfosforiladas o mutadas de la proteína Tau asociada al microtúbulo.

[00125] En otra modalidad, se contempla que los compuestos que inhiben HSP90 de la Fórmula I, IB, IC, ID, IE, o una sal del mismo farmacéuticamente aceptable, pueden ser usados en un método para degradar proteínas Tau aberrantes en un animal, que comprende administrar un compuesto de conformidad con la reivindicación 1 a dicho animal.

[00126] En otra modalidad, se contempla que uno o más de los compuestos que inhiben HSP90 a partir de la Tabla I, o una sal del mismo farmacéuticamente aceptable, pueden ser usados para tratar una enfermedad neurodegenerativa caracterizada por acumulación de formas hiperfosforiladas o mutadas de la proteína Tau asociada al microtúbulo.

[00127] En otra modalidad, se contempla que uno o más de los compuestos que inhiben HSP90 a partir de la Tabla I, o una sal del mismo farmacéuticamente aceptable, pueden ser usados en un método para degradar proteínas Tau aberrantes en un animal, que comprende administrar un compuesto de conformidad con la reivindicación 1 a dicho animal.

[00128] En otras modalidades, cualquiera de los métodos anteriores para tratar cualquiera de las enfermedades o condiciones descritas en la presente, además comprenden administrar tratamiento por radiación o uno o más agentes terapéuticos seleccionados a partir de Camptotecina,

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Topotecano, 9-Nitrocamptotecina, 9-Aminocamptotecina, Carenitecina, Irinotecano, Etopósido, Fosfato de Etopósido, Tenipósido, Amsacrina, Razoxano, Dexrazoxano, Mecloretamina, Ciclofosfamida, Ifosfamida, Clorambucilo, Melfalano, Tiotepa, Trenimon, Trietilenmelamina, Dianhidrogalactitol, Dibromodulcitol, Busulfan, dimetilsulfato, Cloroetilnitrosourea, Carmustina, Lomustina, Metil-Lomustina, Estreptozotocina, Clorozotocina, Prednimustina, Estramustina, Procarbazina, Dacarbazina, Hexametilmelamina, Pentametilmelamina, Temozolomida, Cisplatino, Carboplatino, Oxaliplatino, Bleomicina, Dactinomicina, Mitramicina, Rapamicina, Mitomicina C, Daunorubicina, Doxorubicina, Epirubicina, Idarubicina, Metotrexato, Edatrexato, Trimetoprim, Nolatrexed, Raltitrexed, Hidroxiurea, 5-fluorouracilo, Ftorafur, Capecitabina, Furtulon, Eniluracilo, ara-C, 5-azacitidina, Gemcitabina, Mercaptopurina, Tioguanina, Petostatina, ADN antisentido, ARN antisentido, un híbrido ARN/antisentido ADN, una ribozima, radiación ultravioleta, Vincristina, Vinblastina, Paclitaxel, Docetaxel, L-Asparaginasa, un inhibidor de cinasa, Imatinib, Mitotano, Aminoglutetimida, Dietilestilbestrol, Etinil estradiol, Tamoxifen, Anastrozol, Propionato de testosterona, Fluoximesterona, Flutamida, Leuprólido, Prednisona, Caproato de hidroxiprogesterona, Acetato de medroxiprogesterona, Acetato de megestrol, Alfa-interferón, e Interleucina.

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Abreviaturas y Definiciones

[00129] Las siguientes abreviaturas y términos tienen los significados indicados a través de ésta:

Abreviatura	Significado
Ac	Acetilo
Br	Amplio
°C	Grados Celsius
c-	Ciclo
CBZ	CarboBenZoxi = benciloxicarbonilo
D	Doblete
Dd	Doblete de doblete
Dt	Doblete de triplete
DIPEA	*N,N*-diisopropiletilamina
DMF	*N,N*-dimetilformamida
DMSO	dimetil sulfóxido
EI	Ionización de Impacto del Electrón
Et	Etilo
G	gramo(s)
GC	Cromatografía de gas
h o hr	Hora(s)
HOAc	Ácido acético
HOBt	Hidroxibenzotriazol
HPLC	Cromatografía líquida de alta presión

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Abreviatura	Significado
L	Litro(s)
M	Molar o molaridad
M	Multiplete
Me	Metilo
Mesilo	Metansulfonilo
Mg	miligramo(s)
MHz	megahertz (frecuencia)
Min	minuto(s)
mL	mililitro(s)
mM	Milimolar
Mmol	milimole(s)
Mol	mole(s)
MS	Análisis espectral de masas
MTBE	Metil t-butil éter
N	normal o normalidad
NBS	*N*-bromosuccinimida
NCS	*N*-clorosuccinimida
nM	Nanomolar
NMO	Óxido de *N*-metilmorfolina
NMR	Espectroscopia de resonancia magnética nuclear
PEG	Polietilenglicol
pEY	Poli-glutamina, tirosina
Ph	Fenilo
PhOH	Fenol
PfP	Pentafluorofenol

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Abreviatura	Significado
PfP	Pentafluorofenol
PfPy	Pentafluoropiridina
PPTS	p-toluensulfonato de piridinio
Py	Piridina
PyBroP	Hexafluoroflosfato de bromo-tris-pirrolidino-fosfonio
Q	Quartete
RT	Temperatura ambiente
Sat.	Saturado
S	Singlete
s-	Secundario
t-	Terciario
t o tr	Triplete
TBDMS	*t*-butildimetilsililo
TES	Trietilsililo
TFA	Ácido trifluoroacético
THF	Tetrahidrofurano
TMOF	Ortoformiato de trimetilo
TMS	Trimetilsililo
Tosyl	*p*-toluensulfonilo
Trt	Trifenilmetilo
uL	microlitro(s)
uM	Micromole(s) o micromolar

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[00130] Como se usa en la presente especificación, las siguientes palabras y fases son en general, propuestas para tener los significados como se expone abajo, excepto en la magnitud que el contexto en el cual son usados, lo indique de otro modo o son expresamente definidos por significar algo diferente.

[00131] El símbolo "-" significa un enlace único, "=" significa un enlace doble, "≡" significa un enlace triple, "----" significa un enlace único o doble. Cuando un grupo es representado removido de su fórmula precursora, el símbolo "∿∿" será usado al final del enlace el cual fue teóricamente desdoblado para separar el grupo de su fórmula estructural precursora.

[00132] Cuando las estructuras químicas son representadas o descritas, a menos que se declare explícitamente de otro modo, todos los carbonos son asumidos por tener sustitución de hidrógeno para conformar a una valencia de cuatro. Por ejemplo, en la estructura en el lado izquierdo del esquema abajo, existen nueve hidrógenos implicados. Los nueve hidrógenos son representados en la estructura del lado derecho. Algunas veces un átomo particular en una estructura como se describe en la fórmula textual por tener un hidrógeno o hidrógenos como sustitución (hidrógeno expresamente definido), por ejemplo, $-CH_2CH_2-$. Se entiende por uno de habilidad ordinaria en la técnica, que las técnicas

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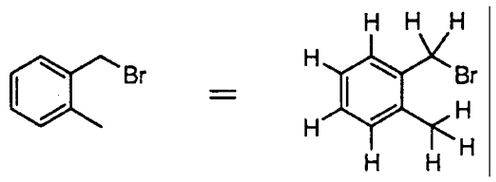
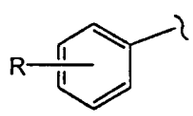
descriptivas mencionadas anteriormente son comunes en las artes químicas para proporcionar brevedad y simplicidad a la descripción de estructuras de otro modo complejas.

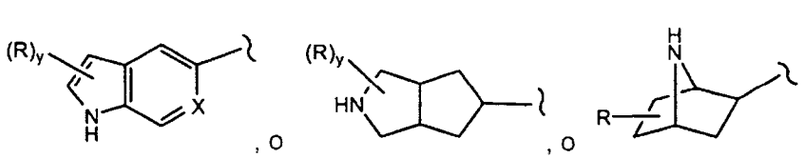


[00133] Si un grupo "R" es representado como "flotante" en un sistema de anillo, como por ejemplo en la fórmula:



después, a menos que se defina de otro modo, un sustituyente "R" puede residir en cualquier átomo del sistema de anillo, asumiendo el reemplazo de un hidrógeno representado, implicado o expresamente definido, a partir de uno de los átomos del anillo, tan pronto como se forma una estructura estale.

[00134] Si un grupo "R" es representado como flotante sobre un sistema de anillo fusionado, como por ejemplo, en las fórmulas:



entonces, a menos que se defina de otro modo, un sustituyente "R" puede residir en cualquier átomo del sistema

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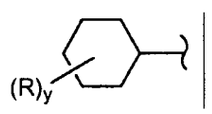
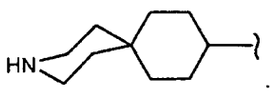
de anillo fusionado, asumiendo el reemplazo de un hidrógeno representado (por ejemplo, el -NH- en la fórmula anterior), hidrógeno implicado (por ejemplo, como en la fórmula anterior, en donde los hidrógenos no son mostrados, sino entendidos por estar presentes), o hidrógeno expresamente definido (por ejemplo, en donde en la fórmula anterior, "X" iguala =CH-) a partir de uno de los átomos del anillo, tan pronto como se forme una estructura estable. En el ejemplo representado, el grupo "R" puede residir en ya sea el anillo de 5 elementos o 6 elementos del sistema de anillo fusionado. En la fórmula representada anteriormente, cuando y es 2 por ejemplo, entonces los dos "R" pueden residir en cualquiera de los dos átomos del sistema de anillo, nuevamente asumiendo que cada uno reemplaza un hidrógeno representado, implicado o expresamente definido en el anillo.

[00135] Cuando un grupo "R" se representa por existir en un sistema de anillo que contiene carbonos saturados, como por ejemplo, en la fórmula:



en donde, en este ejemplo, "y" puede ser más de uno, asumiendo que cada uno reemplaza un hidrógeno actualmente representado, implicado, o expresamente definido en el anillo; después, a menos que se defina de otro modo, en donde la estructura resultante es estable, dos "R" pueden

residir en el mismo carbono. Un ejemplo simple es cuando R es un grupo metilo; puede existir un dimetilo geminal en un carbono del anillo representado (un carbono "anular"). En otro ejemplo, dos R en el mismo carbono, que incluyen tal carbono, pueden formar un anillo, de este modo creando una estructural de anillo espirocíclico (un grupo "espirocíclico") con el anillo representado como por ejemplo, en la fórmula:



[00136] "Administración" y variantes de la misma (por ejemplo "administrar" un compuesto) con referencia a un compuesto de esta descripción (es decir, un compuesto de la Fórmula I, II o III como se describe en la presente), significa introducir el compuesto o un profármaco del compuesto en el sistema del animal en necesidad de tratamiento. Cuando un compuesto de esta descripción o profármaco del mismo, se proporciona en combinación con uno o más de otros agentes activos (por ejemplo, cirugía, radiación y quimioterapia, etc.), "administración" y sus variantes, son cada una entendidas por incluir introducción concurrente y secuencial del compuesto o profármaco del mismo y otros agentes.

[00137] "Alquilo" es propuesto por incluir moléculas que tienen 1-12 carbonos en tamaño del alquilo (C_1-C_{12}), el cual

puede ser de cadena recta o ramificada. Por ejemplo, alquilo puede referirse a un n-hexilo, iso-hexilo, ciclobutiletilo, y similares. Alquilo es propuesto por incluir grupos alquilo inferior desde 1-6 carbonos en tamaño, tal como metilo, etilo, propilo, isopropilo, butilo, s-butilo, t-butilo, isobutilo, pentilo, hexilo y similares. Un residuo alquilo que tiene un número específico de carbonos es nombrado, todos los isómeros geométricos que tienen tal número de carbonos están propuestos por ser abarcados; de este modo, por ejemplo, ya sea "butilo" o "alquilo C_4" significa incluir n-butilo, sec-butilo, isobutilo, t-butilo; y por ejemplo, "propilo" o "alquilo C_3" cada uno incluye n-propilo y isopropilo.

[00138] -alquilo (C_1-C_6) es una subserie de grupos alquilo que son de uno a seis átomos de carbono en longitud, y pueden ser de cadena recta o ramificada.

[00139] -alquilo (C_1-C_3) es una subserie de grupos alquilo que son de uno a seis átomos de carbono en longitud, y puede ser de cadena recta o ramificada.

[00140] "Cicloalquilo" significa un sistema de anillo mono o multicíclico, no aromático, comprende aproximadamente 3 hasta aproximadamente 14 átomos de carbono, que incluyen 5 hasta 10 átomos de carbono, o 5 hasta 7 átomos de carbono en el anillo. Ejemplos no limitantes de cicloalquilos monocíclicos incluyen ciclopropilo, ciclopentilo,

ciclohexilo, cicloheptilo y similares. Ejemplos no limitantes de cicloalquilos múlticiíciclos incluyen 1-decalina, norbornilo, adamantilo y similares. Los cicloalquilos pueden ser sistemas espirocíclicos o sistemas de anillo fusionado o puenteado.

[00141] "Cicloalquilalquilo" significa un grupo "cicloalquilo", como se define en la presente, unido a un grupo "alquilo", como se define en la presente, en donde el alquilo grupo está unido a la porción precursora.

[00142] "Alquilo sustituido con uno o más halo e hidroxi" significa un grupo alquilo sustituido con 1, 2, o 3 hidroxi o 1, 2 o 3 halo.

[00143] "Alquileno" se refiere a un grupo divalente de cadena recta o ramificada que consiste solamente de átomos de carbono e hidrógeno, que no contienen insaturación y que tienen de uno a diez átomos de carbono, por ejemplo, metileno, etileno, propileno, *n*-butileno y similares. Alquileno es una subserie de alquilo, con referencia a los mismos residuos como alquilo, pero que tienen dos puntos de unión y, específicamente, completamente saturados. Ejemplos de alquileno incluyen etileno ($-CH_2CH_2-$), propileno ($-CH_2CH_2CH_2-$), dimetilpropileno ($-CH_2C(CH_3)_2CH_2-$), y ciclohexilpropileno ($-CH_2CH_2CH(C_6H_{13})$).

[00144] "Alquenileno" se refiere a un grupo divalente insaturado de cadena recta o ramificada que consiste

solamente de átomos de carbono e hidrógeno, que tienen de dos a diez átomos de carbono. Alquenileno es una subserie de alquilo, con referencia a los mismos residuos como alquilo, pero que tienen dos puntos de unión y, específicamente, doble enlace de insaturación. La presente insaturación incluye al menos, un enlace doble.

[00145] "Alquinileno" se refiere a un grupo divalente insaturado de cadena recta o ramificada que consiste solamente de átomos de carbono e hidrógeno que tienen de dos a diez átomos de carbono, por ejemplo, propilid-2-inilo, *n*-butilid-1-inilo, y similares. Alquilidino es una subserie de alquilo, con referencia a los mismos residuos como alquilo, pero que tienen dos puntos de unión y, específicamente, triple enlace de insaturación. La presente insaturación incluye al menos, un enlace triple.

[00146] Cualquiera de los grupos anteriores, "alquileno," "alquenileno" y "alquinileno," cuando se sustituyen opcionalmente, pueden contener sustitución alquilo en la cual la misma contiene insaturación. Por ejemplo, 2-(2-feniletinil-but-3-enil)-naftaleno (nombre IUPAC) contiene un grupo *n*-butilid-3-inilo con un sustituyente vinilo en la posición 2 del grupo.

[00147] "Alcoxi" o "alcoxilo" ambos se refieren al grupo -O-alquilo, en donde el término "alquilo" es como se define en la presente anteriormente. Ejemplos incluyen metoxi, etoxi,

propoxi, isopropoxi, y similares.

[00148] "Arilo" significa un anillo mono o multicíclico de seis a catorce elementos, monovalente, en donde el anillo monocíclico es aromático y al menos uno de los anillos en el anillo multicíclico es aromático. Un anillo multicíclico que contiene solamente un anillo arilo, es propuesto por ser incluido dentro de la definición de arilo. Un arilo puede también ser de seis a diez elementos, o de seis elementos. Ejemplos no limitantes representativos de arilo incluyen, fenilo, naftilo, y similares.

[00149] "Arilalquilo" significa un residuo en el cual una porción arilo, como se define anteriormente, está unida a una estructura precursora vía una del un alquilo (es decir, alquileno, alquenileno, o alquinileno). Ejemplos incluyen bencilo, fenetilo, fenilvinilo, fenilalilo y similares. La porción "alquilo" del grupo puede ser de uno a diez carbono, y en otra modalidad, de uno a seis carbonos; el último puede también ser referido como un arilalquilo C_1-C_6. Cuando un grupo es referido como un "alquilarilo (C_1-C_6)", una porción arilo está unida a una estructura precursora vía un grupo alquileno. Ejemplos incluyen bencilo, fenetilo, y similares.

[00150] En algunos ejemplos, como se aprecia por uno de habilidad ordinaria en la técnica, dos grupos adyacentes en un sistema aromático pueden ser fusionados en conjunto para formar una estructura de anillo. La estructura del anillo

fusionada puede contener heteroátomos y puede ser opcionalmente sustituida con uno o más grupos. Se debe notar adicionalmente, que los carbonos saturados de tales grupos fusionados (es decir, estructura de anillo saturada), pueden contener dos grupos de sustitución.

[00151] "Sistema de anillo fusionado" o "policíclico fusionado", se refiere a un sistema de anillo policíclico que contiene anillos puenteados o fusionados; esto es, en donde dos anillos tienen más de un átomo portado en sus estructuras del anillo. En esta solicitud, sistemas de anillo fusionados y policíclicos fusionados incluyen, sistemas aromáticos y no aromáticos. Típicamente, pero no necesariamente, los policíclicos fusionados portan una serie vecinal de átomos, por ejemplo, naftaleno o 1,2,3,4-tetrahidro-naftaleno. Un sistema de anillo espiro no es un policíclico fusionado por esta definición, pero los sistemas de anillo policíclico fusionados de los compuestos descritos en la presente, pueden los mismos tener anillos espiro unidos a este vía un átomo de anillo único del policíclico fusionado.

[00152] "Halógeno" o "halo" ambos se refieren a fluoro, cloro, bromo o yodo.

[00153] "Haloalquilo" (el cual incluye alquilo opcionalmente sustituido con hasta 8 halógenos) y "haloarilo" se refiere genéricamente a grupos alquilo y arilo que son sustituidos con uno o más halógenos, respectivamente.

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Ejemplos no limitantes de "haloalquilo" incluyen 3,3,3-trifluoro-1-metilpropilo, 2-metil-1-(trifluorometil)propilo, $-CH_2F$, $-CHCl_2$ y $-CF_3$.

[00154] "Heteroátomo" se refiere a O, S, N, o P. En otro ejemplo, el heteroátomo es O u N. En otro ejemplo, el heteroátomo es O. En otro ejemplo, el heteroátomo es N.

[00155] "Heterociclilo" se refiere a un sustituyente de anillo estable de tres a quince elementos que consiste de átomos de carbono y de uno a cinco heteroátomos seleccionados a partir del grupo que consiste de nitrógeno, fósforo, oxígeno y azufre. Para propósitos de esta descripción, el sustituyente heterociclilo puede ser un sistema de anillo monocíclico, bicíclico o tricíclico, el cual puede incluir sistemas de anillo puenteados o fusionados, así como también sistemas espirocíclicos. Los términos "heterocicloalquilo" y "heteroarilo" son grupos que son abarcados por el término más amplio "heterociclilo". Los átomos de nitrógeno, fósforo, carbono o azufre en el grupo heterociclilo, pueden ser opcionalmente oxidados a varios estados de oxidación. En un ejemplo específico, el grupo $-S(O)_{0-2}-$, se refiere a -S- (sulfuro), -S(O)- (sulfóxido), y $-SO_2-$ (sulfona) respectivamente. Por conveniencia, particularmente pero no exclusivamente, aquellos definidos como nitrógenos aromáticos anulares, significan incluir su forma N-óxido correspondiente, aunque no explícitamente definida como tal

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en un ejemplo particular. De este modo, para un compuesto de esta descripción que tiene, por ejemplo, un anillo piridilo; el piridil-N-óxido correspondiente significa estar incluido como otro compuesto de la descripción. Además, los átomos de nitrógeno anulares pueden ser opcionalmente cuaternizados; y el sustituyente del anillo puede ser parcialmente o completamente saturado o aromático. Ejemplos de grupos heterociclilo incluyen, pero no se limitan a, azetidinilo, acridinilo, benzodioxolilo, benzodioxanilo, benzofuranilo, carbazoilo, cinolinilo, dioxolanilo, indolizinilo, naftiridinilo, perhidroazepinilo, fenazinilo, fenotiazinilo, fenoxazinilo, ftalazinilo, pteridinilo, purinilo, quinazolinilo, quinoxalinilo, quinolinilo, isoquinolinilo, tetrazoilo, tetrahidroisoquinolilo, piperidinilo, piperazinilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolidinilo, 2-oxoazepinilo, azepinilo, pirrolilo, 4-piperidonilo, pirrolidinilo, pirazolilo, pirazolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, dihidropiridinilo, tetrahidropiridinilo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, oxazolilo, oxazolinilo, oxazolidinilo, triazolilo, isoxazolilo, isoxazolidinilo, morfolinilo, tiazolilo, tiazolinilo, tiazolidinilo, isotiazolilo, quinuclidinilo, isotiazolidinilo, indolilo, isoindolilo, indolinilo, isoindolinilo, octahidroindolilo, octahidroisoindolilo,

quinolilo, isoquinolilo, decahidroisoquinolilo, bencimidazolilo, tiadiazolilo, benzopiranilo, benzotiazolilo, benzoxazolilo, furilo, tetrahidrofurilo, tetrahidropiranilo, tienilo, benzotienilo, tiamorfolinilo, tiamorfolinilo sulfóxido, tiamorfolinilsulfona, dioxafosfolanilo, oxadiazolilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, y tetrahidroquinolinilo.

[00156] "Heterocicloalquilo" se refiere a un anillo monocíclico o multicíclico estable de 4-12 elementos, en donde al menos uno de los anillos contiene al menos, un heteroátomo y en donde no existen anillos aromáticos. Heterocicloalquilo significa incluir anillos multicíclicos en donde un anillo contiene un heteroátomo y otro anillo no contiene un heteroátomo.

[00157] "Heterocicloalquilalquilo" se refiere a un heterocicloalquilo, como se define en la presente, unido a la porción precursora a través de un "alquilo," como se define en la presente. Un ejemplo no limitante de heterocicloalquilo incluye piperadinilo. Otro ejemplo no limitante de heterocicloalquilo incluye piperazinilo. Otro ejemplo no limitante de heterocicloalquilo incluye furanilo. Otro ejemplo no limitante de heterocicloalquilo incluye pirrolidinilo. Otro ejemplo no limitante de heterocicloalquilo incluye morfolinilo.

[00158] "Amino" se refiere a $-NH_2$.

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[00159] "Alquilamino" se refiere a -NH(alquilo), en donde "alquilo" es como se define anteriormente, y en donde la porción precursora está unida al átomo de nitrógeno. En un ejemplo, alquilamino es (1R)-1,2-dimetilpropilamino. En otro ejemplo, alquilamino es (1S)-1,2-dimetilpropilamino. En otro ejemplo, alquilamino es propilamino. En otro ejemplo, alquilamino es (1R)-1-metilpropil]amino. En otro ejemplo, alquilamino es (1S)-1-metilpropil]amino. En otro ejemplo, alquilamino es (1R)-1,2,2-trimetilpropilamino. En otro ejemplo, alquilamino es (1S)-1,2,2-trimetilpropilamino. En otro ejemplo, alquilamino es 2-metil-1-(1-metiletil)propilamino.

[00160] "Gem-dicicloalquilalq" se refiere a un grupo en donde dos grupos cicloalquilo están unidos al mismo átomo de carbono en un grupo alquilo, y el grupo alquilo está unido a la porción precursora. Un ejemplo no limitante de dicicloalquilo es diciclopropilmetilo que tiene la siguiente estructura:

[00161] "Dialquilamino" se refiere a $-N(alquilo)_2$, en donde "alquilo" es como se define anteriormente, y en donde la porción precursora está unida al átomo de nitrógeno.

[00162] "Dialquilaminoalquilo" se refiere un -

(alquilo)N(alquilo)$_2$, en donde "alquilo" es como se define anteriormente. Uno de tal ejemplo no limitante de "dialquilaminoalquilo" incluyen $-CH_2C(CH_3)_2CH_2N(CH_3)_2$.

[00163] "Aminoalquilo" se refiere a -(alquilo)NH_2, en donde "alquilo" es como se define anteriormente, y en donde la porción precursora está unida al grupo alquilo. El grupo amino puede ser unido en cualquier punto a lo largo del grupo alquilo. Ejemplos no limitantes de aminoalquilo incluyen $-CH(NH_2)CH_3$.

[00164] "Heteroarilo" significa un heterociclilo aromático monocíclico, de 5 a 12 elementos (en donde heterociclilo es como se define en la presente), o un sistema de anillo heterociclilo bicíclico (en donde al menos uno de los anillos en el sistema de anillo bicíclico es aromático), en donde el anillo monocíclico y al menos uno de los anillos en el sistema de anillo bicíclico contiene uno, dos, tres, cuatro o cinco heteroátomo(s) seleccionados a partir de nitrógeno, oxígeno, fósforo y azufre. El anillo que contiene el heteroátomo puede ser aromático o no aromático. Ejemplos representativos incluyen piridinilo, imidazolilo, pirimidinilo, pirazolilo, triazolilo, pirazinilo, tetrazolilo, furilo, tienilo, isoxazolilo, tiazolilo, oxazolilo, isotiazolilo, pirrolilo, quinolinilo, isoquinolinilo, indolilo, bencimidazolilo, benzdioxolilo, benzofuranilo, cinolinilo, indazolilo, indolizinilo,

ftalazinilo, piridazinilo, triazinilo, isoindolilo, pteridinilo, purinilo, oxadiazolilo, triazolilo, tiadiazolilo, tiadiazolilo, furazanilo, benzofurazanilo, benzotiofenilo, benzotiazolilo, benzoxazolilo, quinazolinilo, quinoxalinilo, naftiridinilo, y furopiridinilo. Porciones fusionadas, puenteadas y espiro, también están incluidas dentro del alcance de esta definición.

[00165] "Carbonilo" se refiere al grupo "-C(O)-", el cual es bivalente.

[00166] "Aminocarbonilo" se refiere al grupo "-C(O)-NH_2," en donde la porción precursora está unida al grupo carbonilo.

[00167] "Alcoxicarbonilo" se refiere al grupo "-C(O)alcoxi," en donde alcoxi es como se define anteriormente, y la porción precursora está unida al carbonilo. Un ejemplo no limitante incluye -C(O)-$OC(CH_3)_3$.

[00168] "Hidroxialquinilo" se refiere a un grupo en donde la porción precursora está unida al grupo alquinilo, y un grupo hidroxilo está unido al alquinilo. Un ejemplo no limitante incluye 4-hidroxibut-1-in-1-ilo.

[00169] "Hidroxialquilo" se refiere a un grupo en donde la porción precursora está unida al grupo alquilo, y un grupo hidroxilo unido al alquilo, y en donde la porción alquilo es como se define en la presente.

[00170] "Amino(imino)alquilo" se refiere a un grupo representado por -alquilo-C(=NH)-NH_2, en donde alquilo es

como se define anteriormente. Un ejemplo no limitante incluye amino(imino)metilo.

[00171] "Dihidroxialquilo" se refiere a un grupo en donde la porción precursora está unida al grupo alquilo, y dos grupos hidroxilo están unidos al alquilo, y en donde la porción alquilo es como se define en la presente.

[00172] "Alquilaminoalquilo" se refiere a -(alquilo)NH(alquilo), en donde las porciones "alquilo" son como se definen anteriormente.

[00173] "Alquilaminoalquilamino" se refiere a -N(H)(alquil)NH(alquilo), en donde "alquilo" es como se define anteriormente.

[00174] "Aminoalquilamino" se refiere a -N(H)(alquilo)NH_2, en donde "alquilo" es como se define anteriormente.

[00175] "Arilalquilamino" se refiere a -N(H)(alquil)arilo, en donde "alquilo" y arilo son como se definen anteriormente.

[00176] "Alquilsulfonilheterocicloalquilamino" se refiere a -N(H)-alquilheterocicloalquilo-$S(O)_2$-alquilo, en donde el amino está unido a la porción precursora.

[00177] "Cicloalquilalquilamino" se refiere a -N(H)-alquilcicloalquilo, en donde el amino está unido a la porción precursora.

[00178] "Cicloalcoxi" se refiere a -O-cicloalquilo, en donde cicloalquilo es como se define anteriormente y el

oxígeno está unido a la porción precursora.

[00179] "Dialquilaminoalcoxi" se refiere a -(alcoxi)N(alquilo)$_2$, en donde "alcoxi" y "alquilo" son ambos definidos anteriormente. Uno de tales ejemplos no limitantes de "dialquilaminoalcoxi" incluyen dimetilaminoetiloxi representado por -O-$(CH_2)_2N(CH_3)_2$.

[00180] "Alquilsulfonilalquilamino" se refiere a -NH_2-$S(O)_2$-alquilo, en donde la porción amino de este grupo está unida a la porción precursora, y en donde "alquilo" es como se define anteriormente. Un ejemplo no limitante incluye metilsulfoniletilamino.

[00181] Cuando una porción del término (tal como la porción "alquilo" de "arilalquilo") es referida por ser definida anteriormente o definida en la presente, esto significa que esta porción tiene el mismo significado como la definición de este término dentro de su especificación.

[00182] Las frases "el compuesto en esta descripción", los compuestos en la descripción, los compuestos descritos en la presente, compuestos de esta descripción y frases similares que contienen ambas palabras "compuestos" y "descripción", están significando compuestos de la Fórmula I, II o III, y todas las modalidades para cada uno de estos tres compuestos.

[00183] En el caso en donde existe un punto de unión para un sustituyente monovalente, tal como -CH_3, -NH_2, o -OH, la indicación de en donde está el punto de unión no es

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necesaria. Esto es, $-CH_3$ tiene el mismo significado como CH_3, $-NH_2$ tiene el mismo significado como NH_2, y $-OH$ tiene el mismo significado como OH.

[00184] En las Tablas 1 y II, en donde parece que hay un vacío de valencia para oxígeno o nitrógeno para cualquiera de los compuestos listados en esta tabla, en donde el nombre de estructura requiere que la valencia vacía se llene con hidrógeno, se asume que la valencia perdida se llena con hidrógeno para cada uno de estos casos.

[00185] Cuando un grupo es referido como "heterociclilalquilo $-(C_1-C_6)$", el heterociclilo está unido a una estructura precursora vía un grupo alquilo.

[00186] "Hidroxialquilo" significa -alquilo-OH, en donde alquilo es como se define en la presente anteriormente.

[00187] "Opcional" u "opcionalmente", significa que el evento o circunstancia subsecuentemente descrito puede o no puede ocurrir, y que la descripción incluye casos en donde el evento o circunstancia ocurre y casos en los cuales no ocurre. Uno de habilidad ordinaria en la técnica podrá entender que con respecto a cualquier molécula descrita por contener uno o más sustituyentes opcionales, significa estar incluidos solamente compuestos estéricamente prácticos y/o sintéticamente factibles. "Opcionalmente sustituido", se refiere a todos los modificadores sustituyentes en un término. Así, por ejemplo, en el término "arilalquilo

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opcionalmente sustituido", tanto la porción "alquilo" como la porción "arilo" de la molécula, puede o no puede ser sustituida.

[00188] A menos que se especifique de otro modo, el término "opcionalmente sustituido" aplica a la porción química inmediatamente precedente. Por ejemplo, si un grupo variable (tal como R) es definido como arilo, alquilo opcionalmente sustituido o cicloalquilo, entonces solamente el grupo alquilo es opcionalmente sustituido.

[00189] "Sistema de anillo puenteado saturado", se refiere a un sistema de anillo bicíclico o policíclico que no es aromático. Tal sistema puede contener insaturación conjugada o aislada, pero no anillos aromáticos o heteroaromáticos en su estructura nuclear (pero, pueden tener sustitución aromática en este). Por ejemplo, hexahidro-furo[3,2-b]furano, 2,3,3a,4,7,7a-hexahidro-1H-indeno, 7-aza-biciclo[2.2.1]-heptano, y 1,2,3,4,4a,5,8,8a-octahidro-naftaleno, están todos incluidos en la clase "sistema de anillo puenteado saturado".

[00190] "Anillo espirocíclico" o "espirociclilo", se refiere a un anillo que se origina a partir de un átomo de carbono particular de otro anillo. Por ejemplo, como se representa abajo, un átomo del anillo de un sistema de anillo puenteado (anillos B y B'), pero no un anillo de cabeza puenteada, puede ser un átomo portado entre el sistema de

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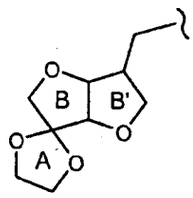
anillo puenteado saturado y un espirociclilo (anillo A) unido a este. Un espirociclilo puede ser carbocíclico o heteroalicíclico.



[00191] Algunos de los compuestos de la descripción pueden tener sustituyentes imino, amino, oxo o hidroxi de sistemas de anillo heterociclilo aromático. Para propósitos de esta descripción, se entiende que tales sustituyentes imino, amino, oxo o hidroxi, pueden existir en su forma tautomérica correspondiente, es decir, amino, imino, hidroxi u oxo, respectivamente.

[00192] "Animal" para los propósitos de esta descripción, incluye humanos (que incluye pacientes que reciben tratamiento) y otros animales, particularmente mamíferos y otros organismos. De este modo, los métodos son aplicables a tanto a aplicaciones de terapia humana como veterinaria. En una modalidad preferida, el paciente es un mamífero, y en una modalidad más preferida, el paciente es humano.

[00193] "Condiciones o enfermedades dependientes de cinasa", se refieren a condiciones patológicas que dependen de la actividad de una o más proteínas cinasas. Las cinasas participan ya sea directamente o indirectamente en las trayectorias de transducción de señal de una variedad de

actividades celulares que incluyen, proliferación, adhesión, migración diferenciación e invasión. Enfermedades asociadas con actividades de cinasa incluyen, crecimiento de tumor, la neovascularización patológica que soporta el crecimiento de tumor sólido, y asociado con otras enfermedades, en donde está involucrada la vascularización local excesiva tal como enfermedad ocular (retinopatía diabética, degeneración macular relacionada con la edad, y similares), e inflamación (psoriasis, artritis reumatoide y similares).

[00194] Mientras no se desee ligar por teoría, las fosfatasas también pueden jugar un papel en las "condiciones o enfermedades dependientes de cinasa", como conatos de cinasa; esto es, las cinasas fosforilan y las fosfatasas desfosforilan, por ejemplo, sustratos de proteína. Por lo tanto, compuestos de esta invención, mientras modulan la actividad de cinasa como se describe en la presente, también pueden modular, ya sea directamente o indirectamente, la actividad de fosfatasa. Esta modulación adicional, si está presente, puede ser sinergística (o no) a la actividad de compuestos de esta descripción hacia una familia cinasa o cinasa independiente de otro modo o relacionada. En cualquier caso, como se declara previamente, los compuestos de esta descripción son útiles para tratar enfermedades caracterizadas en parte, por niveles anormales de proliferación celular (es decir, crecimiento de tumor),

muerte celular programada (apoptosis), migración celular e invasión y angiogénesis asociada con el crecimiento del tumor.

[00195] "Cantidad terapéuticamente efectiva", es una cantidad de un compuesto de esta descripción, que cuando se administra a un paciente, alivia un síntoma de la enfermedad. La cantidad de un compuesto de esta descripción la cual constituye una "cantidad terapéuticamente efectiva", variará dependiendo del compuesto, el estado de enfermedad y su severidad, la edad del paciente a ser tratado y similares. La cantidad terapéuticamente efectiva puede ser determinada de manera rutinaria por uno de habilidad ordinaria en la técnica, habiendo considerado su conocimiento y a esta descripción.

[00196] "Cáncer" como se refiere en la especificación y en las reivindicaciones, se refiere a estados de enfermedad proliferativa celular, que incluyen pero no se limitan a:: Cardiaca: sarcoma (angiosarcoma, fibrosarcoma, rabdomiosarcoma, liposarcoma), mixoma, rabdomioma, fibroma, lipoma y teratoma; Pulmonar: carcinoma broncogénico (célula escamosa, célula pequeña no diferenciada, célula grande no diferenciada, adenocarcinoma), alveolar (bronquiolar), carcinoma, adenoma bronquial, sarcoma, linfoma, hamartoma condromatoso, mesotelioma; Gastrointestinal: esófago (carcinoma de células escamosas, adenocarcinoma,

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leiomiosarcoma, linfoma), estómago (carcinoma, linfoma, leiomiosarcoma), páncreas (adenocarcinoma ductal, insulinoma, glucagonoma, gastrinoma, tumores carcinoides, vipoma), intestino delgado (adenocarcinoma, linfoma, tumores carcinoides, sarcoma Karposi, leiomioma, hemangioma, lipoma, neurofibroma, fibroma), intestino grueso (adenocarcinoma, adenoma tubular, adenoma velloso, hamartoma, leiomioma); Tracto genitourinario: riñón (adenocarcinoma, tumor de Wilm [nefroblastoma], linfoma, leucemia), vejiga y uretra (carcinoma de células escamosas, carcinoma de células transicionales, adenocarcinoma), próstata (adenocarcinoma, sarcoma), testículos (seminoma, teratoma, carcinoma embrional, teratocarcinoma, coriocarcinoma, sarcoma, carcinoma de células intersticiales, fibroma, fibroadenoma, tumores adenomatoides, lipoma); Hepáticas: hepatoma (carcinoma hepatocelular), colangiocarcinoma, hepatoblastoma, angiosarcoma, adenoma hepatocelular, hemangioma; Óseas: sarcoma osteogénico (osteosarcoma), fibrosarcoma, histiocitoma fibroso maligno, condrosarcoma, sarcoma Ewing, linfoma maligno (sarcoma de células reticulares), mieloma múltiple, cordoma de tumor de células gigantes malignas, osteocronfroma (exostosis osteocartilaginosa), condroma benigno, condroblastoma, condromixofibroma, osteoma osteoide y tumores de células gigantes; Sistema nervioso: cráneo (osteoma, hemangioma, granuloma, xanhoma, osteitis

defornians), meninges (meningioma, meningiosarcoma, gliomatosis), cerebro (astrocitoma, meduloblastoma, glioma, ependimoma, germinoma [pinealoma], glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, tumores congénitos), neurofibroma de la médula espinal, meningioma, glioma, sarcoma); Ginecológicas: útero (carcinoma endometrial), cerviz (carcinoma cervical, displasia cervical pre-tumoral), ovarios (carcinoma de ovario [cistadenocarcinoma ceroso, cistadenocarcinoma mucinoso, carcinoma no clasificado], tumores de células tecales y de la granulosa, tumores de células Sertoli-Leydig, dirgerminoma, teratoma maligno), vulva (carcinoma de células escamosas, carcinoma intraepitelial, adenocarcinoma, fibrosarcoma, melanoma), vagina (carcinoma de células claras, carcinoma de células escamosas, sarcoma botrioide (rabdomiosarcoma embrional], trompas de falopio (carcinoma); Hematológicas: sangre (leucemia mieloide [aguda y crónica], leucemia linfoblástica aguda, leucemia linfocítica crónica, enfermedades mieloproliferativas, mieloma múltiple, síndrome mielodisplásico), enfermedad de Hodgkin, linfoma no Hodgkin [linfoma maligno]; Piel: melanoma maligno, carcinoma de células basales, carcinoma de células escamosas, sarcoma Karposi, moles de nevi displásicos, lipoma, angioma, dermatofibroma, queloides, psoriasis; y glándulas adrenales: neuroblastoma. De este modo, el término "célula cancerosa"

como se proporciona en la presente, incluye una célula afligida por cualquiera de las condiciones identificadas anteriormente.

[00197] Una "sal farmacéuticamente aceptable" de un compuesto significa a sal que es farmacéuticamente aceptable y que posee la actividad farmacológica deseada del compuesto precursor. Se entiende que las sales farmacéuticamente aceptables no son tóxicas. Información adicional sobre sales farmacéuticamente aceptables adecuadas se puede encontrar en *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, la cual se incorpora en la presente por referencia o S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19, ambas de las cuales se incorporan en la presente por referencia.

[00198] Ejemplos de sales de adición de ácido farmacéuticamente aceptables incluyen aquellas formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico y similares; así como también sales orgánicas tales como ácido acético, ácido trifluoroacético, ácido propiónico, ácido hexanoico, ácido ciclopentanpropiónico, ácido glicólico, ácido pirúvico, ácido láctico, ácido oxálico, ácido maleico, ácido malónico, ácido succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido cinámico, ácido 3-(4-hidroxibenzoil)benzoico, ácido mandélico, ácido metansulfónico,

ácido etansulfónico, ácido 1,2-etandisulfónico, ácido 2-hidroxietansulfónico, ácido bencensulfónico, ácido 4-clorobencensulfónico, ácido 2-naftalensulfónico, ácido 4-toluensulfónico, ácido canforsulfónico, ácido glucoheptónico, 4,4'-metilenbis-(ácido 3-hidroxi-2-en-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido butilacético terciario, ácido laurilsulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico, ácido mucónico, ácido p-toluensulfónico y ácido salicílico y similares.

[00199] Ejemplos de sales de adición de base farmacéuticamente aceptables incluyen, aquellas formadas cuando un protón acídico presente en el compuesto precursor es reemplazado por un ión metálico, tal como sales de sodio, potasio, litio, amonio, calcio, magnesio, hierro, zinc, cobre, manganeso, aluminio y similares. Sales preferibles son las sales de amonio, potasio, sodio, calcio y magnesio. Sales derivadas de bases no tóxicas orgánicas farmacéuticamente aceptables incluyen, pero no se limitan a, saltes de aminas primarias, secundarias y terciarias, aminas sustituidas que incluyen aminas que se originan naturalmente, aminas cíclicas y resinas de intercambio de ión básico. Ejemplos de bases orgánicas incluyen isopropilamina, trimetilamina, dietilamina, trietilamina, tripropilamina, etanolamina, 2-dimetilaminoetanol, 2-dietilaminoetanol, diciclohexilamina,

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lisina, arginina, histidina, cafeína, procaína, hidrabamina, colina, betaína, etilenediamina, glucosamina, metilglucamina, teobromina, purinas, piperazina, piperidina, N-etilpiperidina, trometamina, *N*-metilglucamina, resinas de poliamina, y similares. Bases orgánicas ejemplares son isopropilamina, dietilamina, etanolamina, trimetilamina, diciclohexilamina, colina, y cafeína.

[00200] "Profármaco", se refiere a compuestos que son transformados (típicamente de manera rápida) *in vivo*, para proporcionar el compuesto precursor de las fórmulas anteriores, por ejemplo, por hidrólisis en sangre. Ejemplos comunes incluyen, pero no se limitan a, formas de éster y amida de un compuesto que tiene una forma activa que porta una porción de ácido carboxílico. Ejemplos de ésteres farmacéuticamente aceptables de los compuestos de esta descripción incluyen, pero no se limitan a, ésteres de alquilo (por ejemplo con entre aproximadamente uno y aproximadamente seis carbonos), el grupo alquilo es una cadena lineal o ramificada. Ésteres aceptables también incluyen ésteres de cicloalquilo y ésteres de arilalquilo, tal como pero no limitado a, bencilo. Ejemplos de amidas farmacéuticamente aceptables de los compuestos de esta descripción incluyen pero no se limitan a, amidas primarias, y amidas secundarias y alquilamidas terciarias (por ejemplo, con entre aproximadamente uno y aproximadamente seis

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carbonos). Amidas y ésteres de los compuestos de esta descripción pueden ser preparados de conformidad con métodos convencionales. Una descripción completa de profármacos se proporciona en T. Higuchi y V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, ambas de las cuales se incorporan en la presente por referencia para todos los propósitos.

[00201] "Metabolito" se refiere al rompimiento o producto final de un compuesto su sal producida por metabolismo o biotransformación en el animal o cuerpo humano; por ejemplo, biotransformación a una molécula más polar tal como por oxidación, reducción o hidrólisis, o a un conjugado (véase Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al., (eds), 1990 para una discusión de biotransformación). Como se usa en la presente, el metabolito de un compuesto de esta descripción o su sal, puede ser la forma biológicamente activa del compuesto en el cuerpo. En un ejemplo, un profármaco puede ser usado de manera que la forma biológicamente activa, un metabolito, es liberado *in vivo*. En otro ejemplo, un metabolito biológicamente activo es descrito espontáneamente, esto es, no se emprende un diseño de profármaco *per se*. Un ensayo para la actividad de un metabolito de un compuesto de esta

descripción, se conoce por uno de habilidad en la técnica en vista de la presente descripción.

[00202] Los compuestos de esta descripción también incluyen derivados de N-óxido y derivados protegidos de compuestos de la Fórmula I, II o III. Por ejemplo, cuando compuestos de la Fórmula I contienen un átomo de nitrógeno oxidable, el átomo de nitrógeno puede ser convertido a un N-óxido por métodos bien conocidos en la técnica. Cuando compuestos de la Fórmula I contienen grupos tales como hidroxi, carboxi, tiol o cualquier grupo que contiene un(os) átomo(s) de nitrógeno, estos grupos pueden ser protegidos con un "grupo protector" o "grupo protectivo" adecuado. Una lista comprensiva de grupos protectores adecuados se puede encontrar en T.W. Greene, *Protective Grupos in Organic Synthesis*, John Wiley & Sons, Inc. 1991, la descripción de la cual se incorpora en la presente por referencia en su totalidad. Los derivados protegidos de compuestos de la Fórmula I pueden ser preparados por métodos bien conocidos en la técnica.

[00203] "Tratar" o "tratamiento" de una enfermedad, trastorno o síndrome, como se usa en la presente incluye, (i) prevenir la enfermedad, trastorno o síndrome de ocurrir en un humano, es decir, provocar que los síntomas clínicos de la enfermedad, trastorno o síndrome, no se desarrollen en un animal que puede ser expuesto a, o predispuesto a la enfermedad, trastorno o síndrome, pero no experimenta o

exhibe aún síntomas de la enfermedad, trastorno o síndrome; (ii) inhibir la enfermedad, trastorno o síndrome, es decir, detener su desarrollo; y (iii) aliviar la enfermedad, trastorno o síndrome, es decir, provocar el regreso de la enfermedad, trastorno o síndrome. Como se conoce en la técnica, ajustes para suministro localizado contra sistémico, edad, peso corporal, salud general, sexo, dieta, tiempo de administración, interacción de fármaco y la severidad de la condición, pueden ser necesarios, y serán valorables en experimentación de rutina por uno de habilidad ordinaria en la técnica.

[00204] Uno de habilidad ordinaria en la técnica podrá entender que ciertos complejos proteína-ligando cristalizados, en particular, complejos de ligando HSP90 y sus coordinados de estructuras de rayos-x correspondientes, pueden ser usados para revelar nueva información estructural útil para el entendimiento de la actividad biológica de cinasas como se describe en la presente. También, las características estructurales clave de las proteínas mencionadas anteriormente, particularmente, la forma del sitio de enlace de ligando, son útiles en métodos para diseñar o identificar moduladores selectivos de cinasas y resolver las estructuras de otras proteínas con características similares. Tales complejos de proteína-ligando que tienen compuestos de esta descripción como su componente ligando, son un aspecto de esta descripción.

[00205] También, uno de habilidad ordinaria en la técnica podrá apreciar que tales cristales de calidad de rayos-X adecuada, pueden ser usados como parte de un método para identificar un agente candidato capaz de enlazarse a y modular la actividad de cinasas. Tales métodos pueden ser caracterizados por los siguientes aspectos: a) introducir en un programa de computadora adecuado, información que define un dominio de enlace de ligando de una cinasa en una conformación (por ejemplo, como se define por coordinados de estructura de rayos-x obtenidos de cristales de rayos-x de calidad adecuada, como se describe anteriormente), en donde el programa de computadora crea un modelo de las estructuras tridimensionales del dominio de enlace de ligando, b) introducir un modelo de la estructura tridimensional de un agente candidato en el programa de computadora, c) sobreponer el modelo del agente candidato en el modelo del dominio de enlace de ligando, y d) valorar si el modelo de agente candidato se ajusta espacialmente en el dominio de enlace de ligando. Los aspectos a-d no son necesariamente llevados a cabo en el orden mencionado anteriormente. Tales métodos pueden además vincular: realizar diseño de grupo racional con el modelo de la estructura tridimensional, y seleccionar un agente candidato potencial en conjunto con el modelo de computadora.

[00206] Adicionalmente, uno de habilidad en la técnica podrá apreciar que tales métodos pueden también vincular:

emplear un agente candidato, así determinado para ajustar espacialmente en el dominio de enlace al ligado, en un ensayo de actividad biológica para modulación de cinasa, y determinar si dicho agente candidato modula la actividad de cinasa en el ensayo. Tales métodos también pueden incluir administrar el agente candidato, determinado para modular la actividad de cinasa, a un mamífero que sufre de una condición tratable por la modulación de cinasa, tal como se describe anteriormente.

[00207] También, un experto en la técnica podrá apreciar que compuestos descritos en la presente, pueden ser usados en un método para evaluar la capacidad de un agente de prueba para asociarse con una molécula o complejo molecular que comprende un dominio de enlace al ligado de una cinasa. Tal método puede ser caracterizado por los siguientes aspectos: a) crear un modelo de computadora de un paquete de enlace a cinasa usando coordinados de estructura obtenidos a partir de cristales de calidad de rayos-x adecuada de cinasa, b) emplear algoritmos computacionales para realizar una operación de ajuste entre el agente de prueba y el modelo de computadora del paquete de enlace, y c) analizar los resultados de la operación de ajusta para cuantificar la asociación entre el agente de prueba y el modelo de computadora del paquete de enlace.

Administración General

[00208] En ciertas otras modalidades preferidas, la administración puede ser preferiblemente por la ruta oral. La administración de los compuestos de esta descripción, o sus sales farmacéuticamente aceptables, en forma pura o en composición farmacéutica apropiada, puede llevarse a cabo vía cualquiera de los modos de administración aceptados o agentes para cumplir utilidades similares. De este modo, la administración puede ser, por ejemplo, oralmente, nasalmente, parenteralmente (intravenosa, intramuscular o subcutánea), tópicamente, transdermalmente, intravaginalmente, intravesicalmente, intracisternalmente, o rectalmente, en la forma de un sólido, semi-sólido, polvo liofilizado o formas de dosificación líquidas, tales como por ejemplo, tabletas, supositorios, píldoras, cápsulas de gelatina dura y elástica blandas, polvos, soluciones, suspensiones o aerosoles o similares, preferiblemente en formas de dosificación unitarias adecuadas para administración simple de dosificaciones precisas.

[00209] Las composiciones incluirán un portador o excipiente farmacéutico convencional y un compuesto de esta descripción como el/un agente activo, y, además, puede incluir portadores y adyuvantes, etc.

[00210] Los adyuvantes incluyen agentes preservativos, humectantes, de suspensión, endulzantes, saborizantes,

perfumantes, emulsificantes y dispersantes. La prevención de la acción de microorganismos puede ser asegurada por varios agentes antibacterianos y antifúngicos, por ejemplo, parabenos, clorobutanol, fenol, ácido sórbico y similares. También puede ser deseable incluir agentes isotónicos, por ejemplo, azúcares, cloruro de sodio y similares. La absorción prolongada de la forma farmacéutica inyectable puede ser llevada aproximadamente por el uso de agentes que retardan la absorción, por ejemplo, monoestearato de aluminio y getina.

[00211] Si se desea, una composición farmacéutica de los compuestos en esta descripción también puede contener cantidades menores de sustancias auxiliares tales como agentes humectantes o emulsificantes, agentes amortiguadores de pH, antioxidantes y similares, tales como por ejemplo, ácido cítrico, monolaurato de sorbitán, oleato de trietanolamina, hidroxitolueno butilado, etc.

[00212] La elección de la formulación depende de varios factores tales como, el modo de administración del fármaco (por ejemplo, para administración oral, formulaciones en forma de tabletas, píldoras o cápsulas, son preferidas), y la biodisponibilidad de la sustancia del fármaco. Recientemente, se han desarrollado formulaciones farmacéuticas especialmente para fármacos que muestran escasa biodisponibilidad, basados en los principios que la biodisponibilidad puede ser incrementada incrementando el área de superficie, es decir,

reduciendo el tamaño de partícula. Por ejemplo, la patente Estadounidense No. 4,107,288 describe una formulación farmacéutica que tiene partículas en el intervalo de tamaño desde 10 hasta 1,000 nm en el cual, el material activo es soportado en una matriz reticulada de macromoléculas. La Patente Estadounidense No. 5,145,684 describe la producción de una formulación farmacéutica en la cual la sustancia de fármaco es pulverizada a nanopartículas (tamaño promedio de partículas de 400 nm), en la presencia de un modificador de superficie y después dispersada en un medio líquido para dar una formulación farmacéutica que exhibe biodisponibilidad remarcablemente alta.

[00213] Las composiciones adecuadas para inyección parenteral pueden comprender soluciones, dispersiones, suspensiones o emulsiones acuosas o no acuosas, estériles, farmacéuticamente aceptables, y polvos estériles para reconstitución en soluciones o dispersiones inyectables estériles. Ejemplos de portadores, diluyentes, solventes o vehículos acuosos y no acuosos incluyen, agua, etanol, polioles (propilenglicol, polietileneglicol, glicerol, y similares), mezclas adecuadas de los mismos, aceites vegetales (tales como aceite de oliva), y ésteres orgánicos inyectables tales como oleato de etilo. Se puede mantener la fluidez apropiada por ejemplo, por el uso de un revestimiento tal como lecitina, por el mantenimiento del tamaño de

partícula requerido en el caso de dispersiones y por el uso de tensoactivos.

[00214] Una ruta preferible de administración es la oral, usando un régimen de dosificación diario conveniente que puede ser ajustado de conformidad con el grado de severidad del estado de enfermedad a ser tratado.

[00215] Las formas de dosificación sólidas para administración oral incluyen, cápsulas, tabletas, píldoras, polvos y gránulos. En tales formas de dosificación sólidas, el compuesto activo es mezclado con al menos, un excipiente habitual inerte (o portador), tal como citrato de sodio o fosfato dicálcico o (a) rellenadores o extendedores, como por ejemplo, almidones, lactosa, sacarosa, glucosa, manitol y ácido silícico, (b) aglutinantes, como por ejemplo, derivados de celulosa, almidón, alginatos, gelatina, polivinilpirrolidona, sacarosa y goma de acacia, (c) humectantes, como por ejemplo, glicerol, (d) agentes desintegrantes, como por ejemplo, agar-agar, carbonato de calcio, almidón de papa o tapioca, ácido algínico, croscarmelosa de sodio, complejos de silicatos y carbonato de sodio, (s) retardadores de solución, como por ejemplo, parafina, (f) aceleradores de absorción, como por ejemplo, compuestos de amonio cuaternario, (g) agentes humectantes, como por ejemplo, alcohol cetílico y monoestearato de glicerol, estearato de magnesio y similares, (h) adsorbentes,

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como por ejemplo, caolín y bentonita, y (i) lubricantes, como por ejemplo, talco, estearato de calcio, estearato de magnesio, polietilenglicoles sólidos, laurilsulfato de sodio, o mezclas de los mismos. En el caso de cápsulas, tabletas y píldoras, las formas de dosificación también pueden comprender agentes amortiguadores.

[00216] Las formas de dosificación sólida, como se describe anteriormente, pueden ser preparadas con recubrimientos y cubiertas, tales como recubrimientos entéricos y otros bien conocidos en la técnica. Pueden contener agentes pacificantes, y también pueden ser de tal composición que liberan el compuesto activo o compuestos en una cierta parte del tracto intestinal en una manera retardada. Ejemplos de composiciones incrustadas que pueden ser usadas son, sustancias polimérica y ceras. Los compuestos activos también puede estar en forma microencapsulada, si es apropiado, con uno o más de los excipientes mencionados anteriormente.

[00217] Las formas de dosificación líquidas para administración oral incluyen, emulsiones, soluciones, suspensiones, jarabes y elixires farmacéuticamente aceptables. Tales formas de dosificación son preparadas, por ejemplo, disolviendo, dispersando, etc., un compuesto(s) de esta descripción, o una sal del mismo farmacéuticamente aceptable, y adyuvantes farmacéuticos opcionales en un portador, tal como por ejemplo, agua, salina, dextrosa

acuosa, glicerol, etanol y similares; agentes solubilizantes y emulsificadores, como por ejemplo, alcohol etílico, alcohol isopropílico, carbonato de etilo, acetato de etilo, alcohol, bencílico, benzoato de bencilo, propilenglicol, 1,3-butilenglicol, dimetilformamida; aceites, en particular, aceite de semilla de algodón, aceite de maní, aceite de germen de maíz, aceite de oliva, aceite de ricino y aceite de sésamo, glicerol, alcohol tetrahidrofurfurilo, polietilenglicoles y ésteres de ácidos grasos de sorbitán; o mezclas de estas sustancias, y similares, para con ello, formar una solución o suspensión.

[00218] Suspensiones, además de los compuestos activos, pueden contener agentes de suspensión, como por ejemplo, alcoholes isoestearilo etoxilados, polioxietilensorbitol y ésteres de sorbitán, celulosa microcristalina, metahidróxido de aluminio, bentonita, agar-agar y tragacanto, o mezclas de estas sustancia, y similares.

[00219] Composiciones para administraciones rectales son, por ejemplo, supositorios que pueden ser preparados mezclando los compuestos de esta descripción con, por ejemplo, excipientes o portadores no irritantes adecuados, tales como manteca de cacao, polietilenglicol o una cera de supositorio, las cuales son sólidas a temperaturas ordinarias, pero líquidas a temperatura corporal y por lo tanto, se derretirán mientras están en una cavidad corporal adecuad y liberarán el

componente activo ahí.

[00220] Las formas de dosificación para administración tópica de un compuesto de esta descripción incluyen, ungüentos, polvos, atomizadores e inhalantes. El componente activo es mezclado bajo condiciones estériles con un portador fisiológicamente aceptable y cualquiera de preservativos, amortiguadores, o propulsores, pueden ser requeridos. Las formulaciones oftálmicas, ungüento para ojos, polvos y soluciones, también están contempladas para los compuestos de esta descripción.

[00221] Los gases comprimidos pueden ser usados para dispersar un compuesto de esta descripción en forma de aerosol. Los gases inertes adecuados para este propósito son nitrógeno, dióxido de carbono, etc.

[00222] En general, dependiendo del modo de administración propuesto, las composiciones farmacéuticamente aceptables contenderán aproximadamente 1% hasta aproximadamente 99% en peso de un compuesto(s) de esta descripción, o una sal del mismo farmacéuticamente aceptable, y 99% hasta 1% en peso de un excipiente farmacéutico adecuado. En un ejemplo, la composición estará entre aproximadamente 5% y aproximadamente 75% en peso de un compuesto(s) de esta descripción, o una sal del mismo farmacéuticamente aceptable, con el resto siendo excipientes farmacéuticos adecuados.

[00223] Métodos actuales para preparar tales formas de

dosificación son conocidos, o serán aparentes, para aquellos expertos en esta técnica; por ejemplo, véase Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). La composición a ser administrada, en cualquier caso, contendrá una cantidad terapéuticamente efectiva de un compuesto de esta descripción, o una sal del mismo farmacéuticamente aceptable, para tratamiento de un estado de enfermedad, de conformidad con las enseñanzas de esta descripción.

[00224] Los compuestos de esta descripción, o su sales farmacéuticamente aceptables, son administrados en una cantidad terapéuticamente efectiva la cual variará dependiendo de una variedad de factores que incluyen, la actividad del compuesto específico empleado, la estabilidad metabólica y longitud de acción del compuesto, la edad, peso corporal, salud general, sexo, dieta, modo y tiempo de administración, velocidad de excreción, combinación de fármaco, la severidad de los estados de enfermedad particular, y la terapia a la que se somete el hospedero. Los compuestos de esta descripción pueden ser administrados a un paciente a niveles de dosificación en el intervalo de aproximadamente 0.1 hasta aproximadamente 1,000 mg por día. Para un adulto humano normal que tiene un peso corporal de aproximadamente 70 kilogramos, una dosis en el intervalo de aproximadamente 0.01 hasta aproximadamente 100 mg por

kilogramos de peso corporal por día, es un ejemplo. La dosificación específica usada, sin embargo, puede variar. Por ejemplo, la dosificación puede depender de un número de factores que incluyen, los requerimientos del paciente, la severidad de la condición siendo tratada, y la actividad farmacológica del compuesto siendo usado. La determinación de las dosificaciones óptimas para un paciente particular es bien conocida para uno de habilidad ordinaria en la técnica.

[00225] Las composiciones incluirán un portador o excipiente farmacéutico convencional, y un compuesto de esta descripción como el/un agente activo, y, además, pueden incluir otros agentes medicinales y agentes farmacéuticos. Las composiciones de los compuestos en esta descripción pueden ser usadas en combinación con agentes anticancerígenos y/o otros, que son en general, administrados a un paciente siendo tratado por cáncer, por ejemplo, cirugía, radiación y/o agente(s) quimioterapéuticos. Los agentes quimioterapéuticos que pueden ser útiles para administración en combinación con compuestos de la Fórmula I en el tratamiento de cáncer incluyen, agentes alquilantes, agentes que contienen platino.

[00226] Si se formula como una dosis fija, tales productos de combinación emplean los compuestos de esta descripción dentro del intervalo de dosificación descrito anteriormente y el(los) otro(s) agente(s) farmacéuticamente activos dentro de

su intervalo de dosificación aprobado. Los compuestos de esta descripción pueden alternativamente, ser usados secuencialmente con agente(s) farmacéuticamente aceptable(s) conocido(s) cuando una formulación de combinación es inapropiada.

[00227] Formulaciones farmacéuticas representativas que contienen los compuestos descritos en la presente, se describen abajo.

Procedimientos Sintéticos

[00228] Los compuestos descritos en la presente, o sus sales farmacéuticamente aceptables, pueden tener átomos de carbono asimétricos, átomos de azufre oxidados o átomos de nitrógeno cuaternizados en su estructura.

[00229] Los compuestos descritos en la presente, y sus sales farmacéuticamente aceptables, pueden existir como estereoisómeros únicos, racematos y como mezclas de enantiómeros y diastereómeros. Los compuestos descritos en la presente, también pueden existir como isómeros geométricos. Todos los estereoisómeros únicos, racematos y mezclas de los mismos, e isómeros geométricos, están propuestos para estar dentro del alcance de los compuestos descritos en la presente.

[00230] Se asume que cuando se consideran descripciones genéricas de los compuestos descritos en la presente, para

propósitos de construir un compuesto, tal construcción resulta en la creación de una estructura estable. Esto es, un de habilidad ordinaria en la técnica podrá reconocer que teóricamente algunos constructos que normalmente no podrán ser considerados como compuestos estables (esto es, estéricamente prácticos y/o sintéticamente factibles, *supra*).

[00231] Los métodos para la preparación y/o separación y aislamiento de estereoisómeros únicos a partir de mezclas racémicas o mezclas no racémicas de estereoisómeros, son bien conocidos en la técnica. Por ejemplo, isómeros (R) y (S) ópticamente activos, pueden ser preparados usando sintonas quirales o reactivos quirales, o resueltos usando técnicas convencionales. Los enantiómeros (isómeros R- y S), pueden ser resueltos por métodos conocidos por uno de habilidad ordinaria en la técnica, por ejemplo mediante: formación de sales o complejos diastereoisoméricos, los cuales pueden ser separados, por ejemplo, mediante cristalización; vía formación de derivados diastereoisoméricos los cuales pueden ser separados, por ejemplo, mediante cristalización, reacción selectiva de un enantiómero con un reactivo específico del enantiómero, por ejemplo, oxidación o reducción enzimática, seguida por separación de los enantiómeros modificados y no modificados; o cromatografía líquida o gas-líquida en un ambiente quiral, por ejemplo, en un soporte quiral, tal como sílice con un ligando quiral unido o en la presencia de un

solvente quiral. Se apreciará que en donde un enantiómero deseado es convertido en otra entidad química por uno de los procedimientos de separación descritos anteriormente, se puede requerir una etapa adicional para liberar la forma enantiomérica deseada. Alternativamente, el enantiómero específico puede ser sintetizado por síntesis asimétrica usando reactivos ópticamente activos, sustratos, catalizadores o solventes, o convirtiendo el enantiómero al otro por transformación asimétrica. Para una mezcla de enantiómeros, enriquecidos en un enantiómero particular, el enantiómero de componente principal puede ser además enriquecido (con pérdida concomitante en rendimiento) por recristalización.

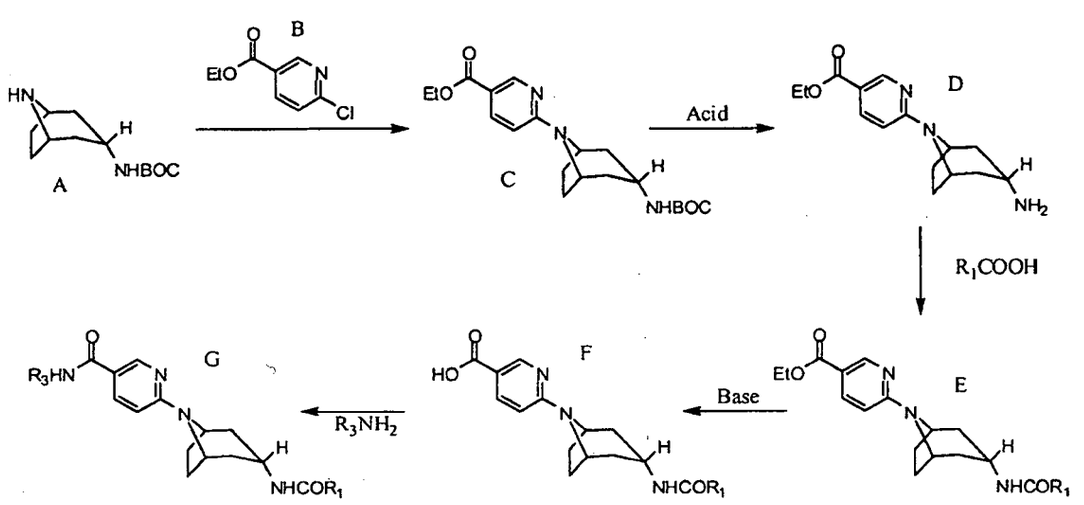
[00232] Además, los compuestos de esta descripción pueden existir en formas no solvatadas así como también solvatadas con solventes farmacéuticamente aceptable tales como agua, etanol y similares. En general, las formas solvatadas son consideradas equivalentes a las formas no solvatadas para los propósitos de los compuestos de esta descripción.

[00233] Además, se pretende que la presente descripción cubra compuestos hechos ya sea usando técnicas sintéticas orgánicas estándares, que incluyen química combinatorial, o por métodos biológicos, tales como digestión bacteriana, metabolismo, conversión enzimática, y similares.

[00234] Los ejemplos y esquemas de reacción siguientes,

representan el procedimiento sintético general para los compuestos descritos en la presente. La síntesis de los compuestos descritos en la presente, no está limitada por estos ejemplos y esquemas de reacción. Un experto en la técnica podrá saber que otros procedimientos pueden ser usados para sintetizar los compuestos descritos en la presente, y que los procedimientos descritos en los ejemplos y esquemas de reacción son solamente uno de tales procedimientos. En las descripciones abajo,, uno de habilidad ordinaria en la técnica podrá reconocer que condiciones de reacción específicas, reactivos agregados, solventes y temperaturas de reacción, pueden ser modificados para la síntesis de compuestos específicos que caen dentro del alcance de esta descripción.

ESQUEMA DE REACCIÓN SINTÉTICA 1:



[00235] El esquema de reacción 1 describe la síntesis de todos los compuestos listados en el Ejemplo 1, en donde R_1 y R_3 son como se definen en la especificación.

[00236] En el esquema de reacción 1, el compuesto (B) es agregado al compuesto (A), bajo condiciones de reacción apropiadas para sufrir una reacción de sustitución nucleofílica aromática para llegar al compuesto (C). El compuesto (C) es entonces desprotegido bajo condiciones acídicas, tal como HCl, para remover el BOC y llegar al compuesto (D). Al compuesto (D), se agrega R_1COOH bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar el enlace amida en el compuesto (E). El carboxilato del compuesto (E) es entonces hidrolizado bajo condiciones básicas para proporcionar el ácido carboxílico del compuesto (F). Entonces se agrega R_3NH_2 al compuesto F bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar el enlace amida en el compuesto (G).

[00237] EJEMPLO 1: 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-({4-[4-(2-metilpropil)piperazin-1-il]fenil}metil)piridin-3-carboxamida.

[00238] ETAPA 1: Se agregan clorhidrato 8-azabiciclo[3.2.1]oct-3-endo-ilcarbamato de 1,1-Dimetiletilo (sintetizado de conformidad con el método del reactivo de la preparación 1) (10.44 g, 40 mmol), 6-cloronicotinato de etilo (7.4 g, 40 mmol) y trietilamina (22.4 mL, 160 mmol) a 1,2-dimetoxietano (40 mL) y la suspensión resultante se calienta a 125 °C por 24 horas en un recipiente de tubo sellado. En enfriamiento a temperatura ambiente, la mezcla se diluye con acetato de etilo (200 mL) después se lava con agua (200 mL). La capa orgánica se lava dos veces con 10% de ácido cítrico acuoso (2x 100 mL), salmuera después se seca sobre sulfato de sodio anhidro. La filtración y concentración proporciona un residuo sólido que después se suspende en éter de etilo. Lo sólido se recolecta por filtración después se lava con éter de etilo adicional para dar 6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (6.78 g, 45% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (s, 1H), 7.90 (d, 1H), 6.90 (br s, 1H), 6.73 (d, 1H), 4.53 (br s, 2H), 4.24 (q, 2H), 3.43 (br s, 1H), 2.14-2.10 (m, 2H), 2.00-1.90 (m, 4H), 1.75 (br d, 2H), 1.39 (s, 9H), 1.28 (tr, 3H).

[00239] ETAPA 2: A una solución de 6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (2.83 g, 7.54 mmol) en etanol (20 mL) se agrega una solución de ácido clorhídrico 4N en dioxano (20 mL), y la mezcla de reacción se somete a reflujo por 2 min. Después del enfriamiento a temperatura ambiente, la mezcla se diluye con acetato de etilo (100 mL), y se agrega carbonato de sodio acuoso saturado hasta que la capa acuosa alcanza pH 10. Las capas se separan, la capa acuosa se extrae adicionalmente con acetato de etilo (2 x 50 mL), las capas orgánicas combinadas se lavan con salmuera (20 mL), se secan sobre sulfato de sodio, y se concentran para dar 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxilato de etilo (1.88 g, 90% de rendimiento). ^{1}H NMR (400 MHz, metanol-d_4): 8.65 (d, 1H), 7.98 (dd, 1H), 6.69 (d, 1H), 5.59 (br s, 2H), 4.30 (q, 2H), 3.00 (m, 1H), 2.30-2.05 (m, 6H), 1.58 (d, 2H), 1.35 (t, 3H); MS (EI) para $C_{15}H_{21}N_3O_2$: 276 (MH^+).

[00240] ETAPA 3: Una solución de 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxilato de etilo (2.63 g, 9.55 mmol), ácido 3-metoxi-2-metilbenzoico (1.59 g, 9.55 mmol), HATU (3.63 g, 9.55 mmol), y diisopropiletilamina (3.70 g, 28.65 mmol) en dimetilformamida (20 mL) se agita a temperatura ambiente por 4 días. La mezcla de reacción se

diluye con acetato de etilo (150 mL), se lava con bicarbonato de sodio saturado (50 mL), 5% de cloruro de litio acuoso (2 x 50 mL), y salmuera (50 mL), se seca sobre sulfato de sodio, y se seca para proporcionar 6-[3-endo-({[2-metil-3-metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo crudo (4.73 g). MS (EI) para $C_{24}H_{29}N_3O_4$: 424 (MH^+).

[00241] ETAPA 4: Una suspensión de 6-[3-endo-({[2-metil-3-metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato etilo crudo (4.72 g, max. 9.55 mmol) e hidróxido de potasio (1.07 g, 19.10 mmol) en metanol (90 mL) y agua (30 mL) se agita a 60 °C por 2 horas. Después del enfriamiento a temperatura ambiente, algo del metanol se evapora, se agrega agua a la mezcla resultante, y el pH se ajusta a 5 con ácido clorhídrico acuoso 1N. Lo precipitado se filtra, se lava con agua, y se seca para proporcionar ácido 6-[3-endo-({[2-metil-3-metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (3.14 g, 83% de rendimiento durante dos etapas). ^{1}H NMR (400 MHz, DMSO-d_6): 12.45 (s, 1H), 6.83 (br s, 1H), 8.64 (d, 1H), 8.24 (d, 1H), 7.91 (dd, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.75 (d, 1H), 4.60 (br s, 2H), 3.86 (m, 1H), 3.80 (s, 3H), 2.21 (m, 2H), 2.14 (s, 3H), 2.07 (m, 2H), 1.97 (m, 2H), 1.87 (d, 2H); MS (EI) para $C_{22}H_{25}N_3O_4$: 396 (MH^+).

[00242] ETAPA 5: Una solución de 4-[4-(aminometil)fenil]piperazin-1-carboxilato de terc-butilo (223 mg, 0.77 mmol), ácido 6-[3-endo-({[2-metil-3-metiloxi)fenil]-carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (324 mg, 0.77 mmol), HATU (291 mg, 0.77 mmol), y diisopropiletilamina (302 mg, 2.34 mmol) en dimetilformamida (5 mL) se agita a temperatura ambiente por 24 horas. La mezcla de reacción se diluye con acetato de etilo (50 mL), se lava con bicarbonato de sodio saturado (25 mL), 5% de cloruro de litio acuoso (2 x 25 mL), y salmuera (25 mL), se seca sobre sulfato de sodio, y se seca para proporcionar 4-(4-{[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino]metil}-fenil)piperazin-1-carboxilato de 1,1-dimetiletilo (498 mg, 97% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 8.58 (d, 1H), 7.90 (dd, 1H), 7.28 (m, 1H), 7.21 (t, 1H), 6.92 (m, 4H), 6.53 (d, 1H), 6.19 (d, 1H), 6.13 (t, 1H), 4.61 (br s, 2H), 4.55 (d, 2H), 4.25 (m, 1H), 3.85 (s, 3H), 3.57 (m, 4H), 3.12 (m, 4H), 2.34 (m, 2H), 2.29 (s, 3H), 2.21 (m, 2H), 2.00 (m, 2H), 1.82 (d, 2H), 1.48 (s, 9H); MS (EI) para $C_{38}H_{48}N_6O_5$: 669 (MH^+).

[00243] ETAPA 6: A una solución de 4-(4-{[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino]metil}-fenil)piperazin-1-carboxilato de 1,1-dimetiletilo (495 mg,

0.74 mmol) en metanol (5 mL) se agrega una solución de ácido clorhídrico 4N en dioxano (5 mL), y la mezcla de reacción se somete a reflujo por 2 min. La concentración y purificación por HPLC preparatoria (0.1% de acetato de amonio acuoso-acetonitrilo) proporcionan sal de acetato 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-piperazin-1-ilfenil)metil]-piridin-3-carboxamida (45 mg, 9% de rendimiento). ^{1}H NMR (400 MHz, metanol-d_4): 8.60 (d, 1H), 7.97 (dd, 1H), 7.27 (d, 2H), 7.23 (t, 1H), 6.99 (m, 3H), 6.90 (d, 1H), 6.75 (d, 1H), 4.60 (br s, 2H), 4.47 (s, 3H), 3.99 (m, 1H), 3.84 (s, 3H), 3.25 (m, 4H), 2.29 (m, 2H), 2.21 (s, 3H), 2.19 (m, 2H), 1.92 (s, 6H), 1.90 (m, 2H); MS (EI) para $C_{33}H_{40}N_6O_3$: 569 (MH^+).

[00244] ETAPA 7: Una mezcla de 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-piperazin-1-ilfenil)metil]piridin-3-carboxamida (276 mg, 0.30 mmol), 1-yodo-2-metilpropano (62 mg, 0.34 mmol), y carbonato de cesio (500 mg, 1.50 mmol) en dimetilformamida (4 mL) se agita a temperatura ambiente por 18 horas. La purificación por HPLC preparatoria (0.1% de acetato de amonio acuoso-acetonitrilo) proporciona sal de acetato 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo-[3.2.1]oct-8-il]-N-({4-[4-(2-metilpropil)piperazin-1-il]fenil}metil)piridin-3-carboxamida (17 mg, 8% de

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rendimiento). ^{1}H NMR (400 MHz, metanol-d_4): 8.60 (d, 1H), 7.97 (dd, 1H), 7.23 (m, 3H), 7.00 (d, 1H), 6.95 (m, 1H), 6.90 (d, 1H), 6.75 (d, 1H), 4.59 (br s, 2H), 4.46 (s, 2H), 3.99 (m, 1H), 3.84 (s, 3H), 3.17 (m, 4H), 2.62 (m, 4H), 2.29 (m, 2H), 2.23 (m, 5H), 2.12 (m, 2H), 1.90 (m, 4H), 0.94 (d, 6H); MS (EI) para $C_{37}H_{48}N_6O_3$: 625 (MH^+).

[00245] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [1(A)-1(FC)]. Se obtienen comercialmente materiales de partida alternativos, a menos que se indique de otra manera.

[00246] 1(B): N-ciclopropil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando ciclopropilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{25}H_{30}N_4O_3$: 435 (MH^+).

[00247] 1(C): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(metiloxi)etil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-metoxietilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{25}H_{32}N_4O_4$: 453 (MH^+).

[00248] 1(D): N-[2-(dimetilamino)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-(dimetilamino)etilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{26}H_{35}N_5O_3$: 466 (MH^+).

[00249] 1(E): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-morfolin-4-iletil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-(morfolin-4il)etilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{28}H_{37}N_5O_4$: 507.99 (MH^+).

[00250] 1(F): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(piridin-3-ilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-aminometilpiridina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{28}H_{31}N_5O_3$: 485.97 (MH^+).

[00251] 1(G): N-ciclopentil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando ciclopentilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{27}H_{34}N_4O_3$: 463.02 (MH^+).

[00252] 1(H): N-[(2-clorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-clorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{31}ClN_4O_3$: 519.99 (MH^+).

[00253] 1(I): N-[(4-clorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-clorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{31}ClN_4O_3$: 519.93 (MH^+).

[00254] 1(J): N-{2-[3,4-bis(metiloxi)fenil]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3,4-dimetoxifenetilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{32}H_{38}N_4O_5$: 558.94 (MH^+).

[00255] 1(K): N-(furan-2-ilmetil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando furfurilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{27}H_{30}N_4O_4$: 474.97 (MH^+).

[00256] 1(L): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-metilpropil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando isobutilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{26}H_{34}N_4O_3$: 451.01 (MH^+).

[00257] 1(M): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(metiloxi)fenil]metil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-metoxibencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{34}N_4O_4$: 514.97 (MH^+).

[00258] 1(N): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(metiloxi)propil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-metoxipropilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{26}H_{34}N_4O_4$: 497.00 (MH^+).

[00259] 1(O): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-metilfenil)metil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-metilbencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{34}N_4O_3$: 498.98 (MH^+).

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[00260] 1(P): N-(1,3-benzodioxol-5-ilmetil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando piperonilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{32}N_4O_5$: 528.94 (MH^+).

[00261] 1(Q): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-prop-2-yn-1-ilpiridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando propargilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{25}H_{28}N_4O_3$: 432.98 (MH^+).

[00262] 1(R): N-{[3,4-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3,4-dimetoxibencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{31}H_{36}N_4O_5$: 544.96 (MH^+).

[00263] 1(S): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(4-metilpiperazin-1-il)propil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-(4-metilpiperazin-1-il)propilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{42}N_6O_3$: 535.03 (MH^+).

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[00264] 1(T): N-[2-(etiltio)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-(etiltio)etilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{26}H_{34}N_4O_3S$: 482.97 (MH^+).

[00265] 1(U): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S,2S)-2-[(fenilmetil)oxi]ciclopentil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (1S,2S)-2-(benciloxi)ciclopentilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{34}H_{40}N_4O_4$: 568.98 (MH^+).

[00266] 1(V): N-[(6-cloropiridin-3-il)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (6-cloropiridin-3-il)metilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{28}H_{30}ClN_5O_3$: 520.92 (MH^+).

[00267] 1(W): N-[(2-cloro-6-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-cloro-6-fluorobencilamina en la etapa 5, después de la omisión de las

etapas 6 y 7. MS (EI) para $C_{29}H_{30}ClFN_4O_3$: 537.90 (MH^+).

[00268] 1(X): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(metiltio)etil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-(metiltio)etilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{25}H_{32}N_5O_3S$: 469.45 (MH^+).

[00269] 1(Y): N-butil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]-carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando butilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{26}H_{34}N_4O_3$: 451.08 (MH^+).

[00270] 1(Z): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(3-morfolin-4-ilpropil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-(morfolin-4-il)propilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{39}N_5O_4$: 522.08 (MH^+).

[00271] 1(AA): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-piridin-4-iletil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-(piridin-4-il)etilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{33}N_5O_3$: 500.45 (MH^+).

[00272] 1(AB): N-{2-[(1-metiletil)oxi]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-[(1-metiletil)oxi]etilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{27}H_{36}N_4O_4$: 481.07 (MH^+).

[00273] 1(AC): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-piridin-3-iletil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-(piridin-3-il)etilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{33}N_5O_3$: 499.99 (MH^+).

[00274] 1(AD): N-[4,4-bis(metiloxi)butil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4,4-bis(metiloxi)butilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{28}H_{38}N_4O_5$: 511.04 (MH^+).

[00275] 1(AE): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(5-metilpirazin-2-il)metil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (5-metilpirazin-2-il)metilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{28}H_{32}N_6O_3$: 501.57 (MH^+).

[00276] 1(AF): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(propiloxi)propil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-(propiloxi)propilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{28}H_{38}N_4O_4$: 495.05 (MH^+).

[00277] 1(AG): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[3,4,5-tris(metiloxi)fenil]metil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3,4,5-tris(metiloxi)bencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{32}H_{38}N_4O_6$: 575.32 (MH^+).

[00278] 1(AH): N-{[3,5-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3,5-bis(metiloxi)bencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{31}H_{36}N_4O_5$: 544.97 (MH^+).

[00279] 1(AI): N-[(1S)-1-(4-{[2-(dietilamino)etil]oxi}fenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 1 usando 2-({4-[(1S)-1-aminoetil]fenil}oxi)-N,N-dietiletanamina (sintetizado

de conformidad con el reactivo de la preparación 4) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, metanol-d_4): 8.59 (d, 1H), 7.97 (dd, 1H), 7.31 (m, 2H), 7.23 (t, 1H), 6.99 (d, 1H), 6.90 (m, 3H), 6.74 (d, 1H), 5.18 (q, 1H), 4.59 (br s, 2H), 4.08 (t, 2H), 3.99 (m, 1H), 3.84 (s, 3H), 2.90 (t, 2H), 2.67 (q, 4H), 2.29 (m, 2H), 2.21 (s, 3H), 2.19 (m, 2H), 2.12 (m, 2H), 1.90 (d, 2H), 1.53 (d, 3H), 1.09 (t, 6H); MS (EI) para $C_{36}H_{47}N_5O_4$: 614 (MH^+).

[00280] 1(AJ): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-({4-[(trifluorometil)oxi]fenil}metil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-trifluorometoxibencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{31}F_3N_4O_4$: 569.59 (MH^+).

[00281] 1(AK): N-(ciclopropilmetil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando ciclopropilmetilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{26}H_{32}N_4O_3$: 499.39 (MH^+).

[00282] 1(AL): N-{[2,4-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2,4-

bis(metiloxi)bencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{31}H_{36}N_4O_5$: 545.66 (MH^+).

[00283] 1(AM): N-[(4-bromofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-bromobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{31}BrN_4O_3$: 564 (MH^+).

[00284] 1(AN): N-[(2,2-dimetil-1,3-dioxolan-4-il)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (2,2-dimetil-1,3-dioxolan-4-il)metilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{28}H_{36}N_4O_5$: 509 (MH^+).

[00285] 1(AO): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3S)-1-(fenilmetil)pirrolidin-3-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (S)-1-bencilpirrolidin-3-amina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{33}H_{39}N_5O_3$: 554 (MH^+).

[00286] 1(AP): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3R)-1-(fenilmetil)pirrolidin-3-il]piridin-3-carboxamida.

Preparada de conformidad con el método del ejemplo 1 usando (R)-1-bencilpirrolidin-3-amina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{33}H_{39}N_5O_3$: 554 (MH^+).

[00287] 1(AQ): N-[3-(dietilamino)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-(dietilamino)propilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{41}N_5O_3$: 508 (MH^+).

[00288] 1(AR): N-{3-[(1-metiletil)oxi]propil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-(1-metiletiloxi)propilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{28}H_{38}N_4O_4$: 495 (MH^+).

[00289] 1(AS): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-propilpiridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando propilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{25}H_{32}N_4O_3$: 437 (MH^+).

[00290] 1(AT): N-[2-(dietilamino)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de

conformidad con el método del ejemplo 1 usando 2-(dietilamino)etilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{28}H_{39}N_5O_3$: 494 (MH^+).

[00291] 1(AU): N-(3-metilbutil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-metilbutilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{27}H_{36}N_4O_3$: 465 (MH^+).

[00292] 1(AV): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3-metilfenil)metil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-metilbencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00293] 1(AW): N-[(3-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-fluorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{31}FN_4O_3$: 503 (MH^+).

[00294] 1(AX): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2-metilfenil)metil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-

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metilbencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00295] 1(AY): N-[(3-clorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-clorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{31}ClN_4O_3$: 520 (MH^+).

[00296] 1(AZ): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(tetrahidrofuran-2-ilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando tetrahidrofurfurilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{27}H_{34}N_4O_4$: 479 (MH^+).

[00297] 1(BA): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(2-oxopirrolidin-1-il)propil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-(2-oxopirrolidin-1-il)propilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{37}N_5O_4$: 520 (MH^+).

[00298] 1(BB): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(1-metilpirrolidin-2-il)etil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando

2-(1-metilpirrolidin-2-il)etilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{39}N_5O_3$: 506 (MH^+).

[00299] 1(BC): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-piperidin-1-iletil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-(piperidin-1-il)etilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{39}N_5O_3$: 506 (MH^+).

[00300] 1(BD): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[2-(metiloxi)fenil]metil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-metoxibencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{34}N_4O_4$: 515 (MH^+).

[00301] 1(BE): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[3-(metiloxi)fenil]metil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-metoxibencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{34}N_4O_4$: 515 (MH^+).

[00302] 1(BF): N-[(2-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-

fluorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{31}FN_4O_3$: 503 (MH^+).

[00303] 1(BG): N-[(4-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-fluorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{31}FN_4O_3$: 503 (MH^+).

[00304] 1(BH): N-[(1R,2R,4S)-biciclo[2.2.1]hept-2-il]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-amino-(1R,2R,4S)-biciclo[2.2.1]heptano en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{36}N_4O_3$: 489 (MH^+).

[00305] 1(BI): N-(3,3-dimetilbutil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3,3-dimetilbutilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{28}H_{38}N_4O_3$: 479 (MH^+).

[00306] 1(BJ): N-{[2,3-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2,3-

dimetoxibencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{31}H_{36}N_4O_5$: 545 (MH^+).

[00307] 1(BK): N-{[2-(etiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-etoxibencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{31}H_{36}N_4O_4$: 529 (MH^+).

[00308] 1(BL): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[1-(fenilmetil)piperidin-4-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 1-bencil-4-aminopipiperidina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{34}H_{41}N_5O_3$: 463 (MH^+).

[00309] 1(BM): 4-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino]pipiperidin-1-carboxilato de etilo. Preparado de conformidad con el método del ejemplo 1 usando 4-aminopipiperidin-1-carboxilato de etilo en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{39}N_5O_5$: 550 (MH^+).

[00310] 1(BN): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-tienilmetil)piridin-3-carboxamida. Preparada de

conformidad con el método del ejemplo 1 usando 2-aminometiltiofeno en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{27}H_{30}N_4O_3S$: 491 (MH^+).

[00311] 1(BO): N-ciclobutil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando ciclobutilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{26}H_{32}N_4O_3$: 449 (MH^+).

[00312] 1(BP): N-[3-(etiloxi)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-(etiloxi)propilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{27}H_{36}N_4O_4$: 481 (MH^+).

[00313] 1(BQ): N-[3-(dimetilamino)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-(dimetilamino)propilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{27}H_{37}N_5O_3$: 480 (MH^+).

[00314] 1(BR): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(trifluorometil)fenil]metil}piridin-3-carboxamida.

Preparada de conformidad con el método del ejemplo 1 usando 4-trifluorometilbencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{31}F_3N_4O_3$: 553 (MH^+).

[00315] 1(BS): N-[(2,4-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2,4-difluorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{30}F_2N_4O_3$: 521 (MH^+).

[00316] 1(BT): N-[(2,5-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2,5-difluorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{30}F_2N_4O_3$: 521 (MH^+).

[00317] 1(BU): N-[(2,6-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2,6-difluorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{30}F_2N_4O_3$: 521 (MH^+).

[00318] 1(BV): N-[(3,4-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de

conformidad con el método del ejemplo 1 usando 3,4-difluorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{29}H_{30}F_2N_4O_3$: 521 (MH^+).

[00319] 1(BW): N-[3-(1H-imidazol-1-il)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-(1H-imidazol-1-il)propilamina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{28}H_{34}N_6O_3$: 503 (MH^+).

[00320] 1(BX): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-metilfenil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-metilanilina en la etapa 5, después de la omisión de las etapas 6 y 7. ^1H NMR (400 MHz, d6-DMSO): 9.61 (s, 1H), 8.75 (s, 1H), 8.25 (s,1H), 8.05 (dd, 1H), 7.32 (d, 1H), 7.21 (m, 3H), 7.02 (d, 1H), 6.86 (d, 1H), 6.81 (d, 1H), 4.58 (s, 2H), 3.87 (s, 1H), 3.81 (s, 3H), 3.32 (s, 1H), 2.23 (s, 3H), 2.21 (m, 1H), 2.14 (s, 3H), 2.10 (m, 1H), 1.99 (m, 2H), 1.86 (d, 2H). MS (EI) para $C_{29}H_{32}N_4O_3$: 485.6 (MH^+).

[00321] 1(BY): N-(3,5-dimetilfenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3,5-dimetilanilina en la etapa 5,

después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.83 (s,1H), 8.72 (s,1H), 8.25 (s, 1H), 8.04 (dd, 1H), 7.38 (s, 1H), 7.24 (t, 1H), 7.02 (d, 1H), 6.87 (d, 1H), 6.80 (d, 1H), 6.72 (s, 1H), 4.59 (s, br, 1H), 3.86 (m, 1H), 3.81 (s, 3H), 2.26 (s, 6H), 2.21 (m, 2H), 2.15 (s, 3H), 2.10 (m, 2H), 1.99 (m, 2H), 1.86 (d, 2H). MS (EI) para $C_{30}H_{34}N_4O_3$: 499.4 (MH^+).

[00322] 1(BZ): N-1,3-benzodioxol-5-il-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando benzo[d][1,3]dioxol-5-amina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.90 (s, 1H), 8.70 (s, 1H), 8.25 (s, 1H), 8.02 (dd, 1H), 7.42 (,s, 1H), 7.24 (t, 1H), 7.14 (dd, 1H), 7.02 (d, 1H), 6.88 (t,2H), 6.80 (d, 1H), 6.00 (s, 2H), 4.59 (s, br, 2H), 3.87 (m, 1H), 3.81 (s, 3H), 2.21 (m, 2H), 2.14 (s, 3H), 2.11 (m, 2H), 1.99 (m, 2H), 1.87 (d, 2H). MS (EI) para $C_{29}H_{30}N_4O_5$: 515.5 (MH^+).

[00323] 1(CA): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(4-metilfenil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-metilanilina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.90 (s, 1H), 8.72 (s, 1h), 8.25 (s, 1H), 8.04 (dd, 1H), 7.63 (m, 2H), 7.23 (t, 1H), 7.13 (d, 2H),

7.02 (d, 1H), 6.86 (d, 1H), 6.80 (d, 1H), 4.58 (s, 2H), 3.87 (m, 1H), 3.81 (s, 3H), 2.27 (m, 5H), 2.12 (m, 5H), 1.99 (m, 2H), 1.87 (d, 2H). MS (EI) para $C_{29}H_{32}N_4O_3$: 485.8 (MH^+).

[00324] 1(CB): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3-metilfenil)metil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-metilanilina en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00325] 1(CC): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(metiloxi)fenil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-metoxianilina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.22 (s,1H), 8.72 (s, 1H), 8.25 (s, 1H), 8.03 (dd, 1H), 7.75 (dd, 1H), 7.23 (t, 1H), 7.15 (t, 1H), 7.08 (d, 1H), 7.02 (d, 1H), 6.95 (t, 1H), 6.87 (d, 1H), 6.80 (d, 1H), 4.57 (s, br, 2H), 3.83 (m, 4H), 3.81 (s, 3H), 2.17 (m, 2H), 2.15 (m, 3H), 2.11 (m, 1H), 1.99 (m, 2H), 1.87 (m, 3H). MS (EI) para $C_{29}H_{32}N_4O_4$: 501 (MH^+).

[00326] 1(CD): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(metiloxi)fenil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-metoxianilina en la etapa 5, después de la omisión de las

etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.93 (s, 1H), 8.70 (s, 1H), 8.23 (s, 1H), 8.03 (dd, 1H), 7.44 (s, 1H), 7.31 (s, 1H), 7.21 (m, 2H), 7.00 (d, 1H), 6.85 (d, 1H), 6.79 (d, 1H), 6.64 (dd, 1H), 4.57 (s, br, 2H), 3.85 (m, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 2.20 (m, 2H), 2.13 (s, 3H), 2.08 (m, 2H), 1.98 (m, 2H), 1.85 (d, 2H). MS (EI) para $C_{29}H_{32}N_4O_4$: 501 (MH^+).

[00327] 1(CE): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[4-(metiloxi)fenil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-metoxianilina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 9.87 (s, 1H), 8.71 (s, 1H), 8.05 (dd, 1H), 7.63 (m, 2H), 7.23 (t, 1H), 7.02 (d, 1H), 6.89 (m, 3H), 6.80 (d, 1H), 4.58 (s, br, 2H), 3.86 (m, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 2.24 (m, 2H), 2.11 (m, 5H), 1.99 (m, 2H), 1.86 (d, 2H). MS (EI) para $C_{29}H_{32}N_4O_4$: 501 (MH^+).

[00328] 1(CF): N-(3-clorofenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-cloroanilina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 10.14 (s, 1H), 8.73 (s, 1H), 8.25 (s, 1H), 8.05 (dd, 1H), 7.95 (s, 1H), 7.67 (d, 1H), 7.37 (t, 1H), 7.24 (t, 1H), 7.13 (d, 1H), 7.02 (1H), 6.85 (m, 2H), 4.60 (s, br, 2H), 3.86 (m, 1H), 3.81 (s, 3H), 2.22 (m, 2H), 2.15 (s, 3H), 2.11

(m, 2H), 1.99 (m, 2H), 1.87 (d, 2H). MS (EI) para $C_{28}H_{29}ClN_4O_3$: 506 (MH^+).

[00329] 1(CG): N-(4-fluorofenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-fluoroanilina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 10.04 (s, 1H), 8.72 (s, 1H), 8.25 (s, 1H), 8.05 (dd, 1H), 7.75 (m, 2H), 7.18 (m, 3H), 7.02 (d, 1H), 6.83 (m, 2H), 4.59 (s, br, 2H), 3.83 (m 1H), 3.80 (s, 3H), 2.21 (m, 2H), 2.14 (m, 5H), 1.99 (m, 2H), 1.87 (d, 2H). MS (EI) para $C_{28}H_{29}FN_4O_3$: 489 (MH^+).

[00330] 1(CH): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[1-(6-piperazin-1-ilpiridin-3-il)etil]piridin-3-carboxamida. ^{1}H NMR (400 MHz, d6-DMSO): 9.76 (br s, 2H), 9.46 (d, 1H), 8.60 (s, 1H), 8.42 (d, 1H), 8.36 (s, 1H), 8.18 (d, 1H), 8.08 (s, 1H), 7.44-7.38 (m, 2H), 7.24 (tr, 1H), 7.03 (d, 1H), 6.88 (d, 1H), 5.20-5.10 (br m, 1H), 4.01 (br, 4H), 3.92 (br, 2H), 3.81 (s, 2H), 3.58 (s, 3H), 3.24 (br, 4H), 2.35-2.28 (br m, 2H), 2.20-2.00 (br m, 6H), 2.15 (s, 3H), 1.52 (d, 3H). Preparado de conformidad con el método del ejemplo 1 usando 4-(5-(1-aminoetil)piridin-2-il)piperazin-1-carboxilato de terc-butilo en la etapa 5 (sintetizado de conformidad con el reactivo de la preparación 7), después de la omisión de la

etapa 6.

[00331] 1(CI): N-[1-(4-bromo-2-fluorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 1-(4-bromo-2-fluorofenil)etanamina (sintetizado de conformidad con el reactivo de la preparación 8) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}HNMR (400MHz, $CDCl_3$): 8.59 (d, 1H), 7.88 (dd, 1H), 7.24-7.19 (m, 4H), 6.92 (dd, 1H), 6.52 (d, 1H), 6.41 (d, 1H), 6.20 (d, 1H), 5.38 (m, 1H), 4.61 (br, 2H), 4.25 (q, 1H), 3.86 (s, 3H), 2.36-2.31 (m, 2H), 2.29 (s, 3H), 2.21, (m, 2H), 2.01 (m, 2H), 1.84 (d, 2H), 1.64 (br, 1H), 1.57 (d, 3H); MS (EI) para $C_{30}H_{32}BrFN_4O_3$: 696 (MH^+).

[00332] 1(CJ): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(1-metilpiperidin-4-il)fenil]metil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-(1-metilpiperidin-4-il)bencilamina (sintetizado de conformidad con el reactivo de la preparación 2) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.81 (dd, 1H), 8.63 (d, 1H), 8.22 (d, 1H), 7.96 (dd, 1H), 7.21 (m, 3H), 7.01 (d, 2H), 6.86 (d, 1H), 6.74 (d, 1H), 4.61 (m, 4H), 4.23 (d, 1H), 3.83 (s, 3H), 3.47 (q, 2H), 3.08 (d, 2H), 2.51 (m, 1H), 2.42 (m, 8H), 2.19 (m, 4H), 1.99 (d, 2H), 1.92-1.80 (br m, 6H), 1.21 (m, 4H). MS

(EI) para $C_{35}H_{43}N_5O_3$: 582 (MH^+).

[00333] 1(CK): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3R)-pirrolidin-3-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (3R)-pirrolidin-3-ilcarbamato e 1,1-dimetiletilo en la etapa 5, después de la omisión de la etapa 7. ^{1}H NMR (400 MHz, d_6-DMSO): 9.48 (s, 1H), 9.36 (s, 1H), 9.09 (s, 1H), 8.60 (s, 1H), 8.33-8.38 (m, 2H), 7.29 (d, 1H), 7.24 (t, 1H), 7.03 (d, 1H), 6.88 (d, 1H), 4.86 (br s, 2H), 4.52-4.57 (m, 2H), 3.91 (s, 1H), 3.81 (s, 3H), 3.34-3.42 (m, 2H), 3.19-3.29 (m, 2H), 2.30 (d, 2H), 2.16-2.23 (m, 2H), 2.15 (s, 3H), 1.98-2.06 (m, 4H). MS (EI) para $C_{26}H_{33}N_5O_3$: 464 (MH^+).

[00334] 1(CL): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-piperidin-3-ilpiridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 1,1-dimetiletil-3-aminopipiperidin-1-carboxilato en la etapa 5, después de la omisión de la etapa 7. ^{1}H NMR (400 MHz, d_6-DMSO): 9.43 (s, 1H), 9.17 (s, 1H), 8.98 (s, 1H), 8.78 (s, 1H), 8.61 (d, 1H), 8.39 (d, 1H), 8.34 (d, 1H), 7.31 (s, 1H), 7.24 (t, 2H), 7.03 (d, 1H), 6.88 (d, 1H), 4.88 (br s, 2H), 4.19-4.27 (m, 1H), 3.88-3.93 (s, 1H), 3.81 (s, 1H), 3.27 (d, 1H), 3.12 (d, 1H), 2.87-2.96 (m, 2H), 2.30 (d, 2H), 2.15 (s, 4H), 1.98-2.06 (m, 3H), 1.87-1.92 (m, 2H), 1.61-1.76 (m, 2H).

MS (EI) para $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00335] 1(CM): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-piperidin-4-ilpiridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 1,1-dimetiletil-4-aminopipiperidin-1-carboxilato en la etapa 5, después de la omisión de la etapa 7. ^{1}H NMR (400 MHz, d_6-DMSO): 9.02 (s, 2H), 8.82 (s, 1H), 8.55 (s, 1H), 8.35 (s, 2H), 7.30 (s, 1H), 7.24 (t, 1H), 7.03 (d, 1H), 6.88 (d, 1H), 4.89 (br s, 1H), 4.04-4.09 (m, 1H), 3.91 (s, 1H), 3.81 (s, 3H), 3.65-3.74 (m, 1H), 3.47-3.52 (m, 1H), 3.31 (d, 2H), 3.00 (s, 2H), 2.30 (d, 2H), 2.15 (s, 4H), 1.94-2.10 (m, 5H), 1.80 (q, 2H). MS (EI) para $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00336] 1(CN): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(pirrolidin-3-ilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 1,1-dimetiletil-3-(aminometil)pirrolidin-1-carboxilato en la etapa 5, después de la omisión de la etapa 7. ^{1}H NMR (400 MHz, d_6-DMSO): 9.31 (t, 2H), 9.14 (t, 1H), 8.77 (br s, 1H), 8.54 (d, 1H), 8.35-8.40 (m, 2H), 7.96 (s, 1H), 7.38 (d, 1H), 7.24 (t, 1H), 7.03 (d, 1H), 6.88 (s, 1H), 3.92 (s, 1H), 3.81 (s, 2H), 3.65-3.74 (m, 2H), 3.45-3.52 (m, 2H), 3.32-3.37 (m, 2H), 3.18-3.28 (m, 2H), 3.07-3.13 (m, 1H), 2.89 (s, 4H), 2.73 (s, 3H), 2.31 (d, 2H), 2.15 (s, 4H), 1.98-2.05 (m, 4H), 1.63-

1.70 (m, 1H). MS (EI) para $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00337] 1(CO): N-ciclohexil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando ciclohexilamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.21 (d, 1H), 7.94 (d, 1H), 7.92 (d, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.73 (d, 1H), 4.54 (s, 2H), 3.80 (s, 4H), 3.73 (s, 1H), 3.34 (s, 3H), 2.19 (d, 2H), 2.14 (s, 2H), 2.06-2.12 (m, 2H), 1.96-1.99 (m, 2H), 1.72-1.85 (m, 5H), 1.60 (d, 1H), 1.29 (t, 3H), 1.01-1.19 (m, 1H). MS (EI) para $C_{28}H_{36}N_4O_3$: 477 (MH^+).

[00338] 1(CP): N-metil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando metilamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.47 (d, 1H), 8.41 (d, 1H), 8.28 (d, 1H), 8.10 (d, 1H), 7.23 (t, 1H), 7.08 (d, 1H), 7.03 (d, 1H), 6.87 (d, 1H), 4.64 (s, 2H), 3.86-3.92 (m, 1H), 3.81 (s, 3H), 2.78 (d, 2H), 2.23-2.28 (m, 2H), 2.11-2.16 (m, 5H), 1.99-2.02 (m, 2H), 1.97 (s, 1H), 1.93 (s, 1H). MS (EI) para $C_{23}H_{28}N_4O_3$: 409 (MH^+).

[00339] 1(CQ): N-etil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el

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método del ejemplo 1 usando etilamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.21 (t, 2H), 7.92 (dd, 1H), 7.23 (t, 1H), 7.01 (d, 1H), 6.86 (d, 1H), 6.74 (d, 1H), 4.54 (s, 2H), 3.82 (s, 1H), 3.80 (s, 3H), 3.34 (s, 3H), 3.22-3.29 (m, 2H), 2.17-2.22 (m, 1H), 2.14 (s, 3H), 2.07-2.12 (m, 2H), 1.96-1.99 (m, 2H), 1.86 (s, 1H), 1.82 (s, 1H), 1.10 (t, 3H). MS (EI) para $C_{24}H_{30}N_4O_3$: 423 (MH^+).

[00340] 1(CR): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1R)-1-feniletil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (1R)-1-feniletanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.72 (d, 1H), 8.57 (d, 1H), 8.27 (d, 1H), 8.14 (d, 1H), 7.31-7.39 (m, 4H), 7.20-7.25 (m, 2H), 7.00-7.04 (m, 2H), 6.87 (d, 1H), 5.12-5.19 (m, 1H), 4.63 (s, 2H), 3.85-3.90 (m, 1H), 3.81 (s, 3H), 2.24 (d, 2H), 2.14 (s, 4H), 2.11 (s, 1H), 2.00-2.03 (m, 2H), 1.94 (s, 1H), 1.91 (s, 1H), 1.47 (d, 3H). MS (EI) para $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00341] 1(CS): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1S)-1-feniletil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (1S)-1-feniletanamina en la etapa 5, después de la omisión de las

etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.55 (d, 1H), 8.28 (d, 1H), 8.16 (d, 1H), 7.31-7.38 (m, 4H), 7.21-7.25 (m, 2H), 7.02-7.05 (m, 2H), 6.87 (d, 1H), 5.12-5.19 (m, 1H), 4.63 (s, 2H), 3.84-3.91 (m, 1H), 3.81 (s, 3H), 2.25 (d, 2H), 2.14 (s, 4H), 2.11 (s, 1H), 2.00-2.03 (m, 2H), 1.96 (s, 1H), 1.92 (s, 1H), 1.47 (d, 3H). MS (EI) para $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00342] 1(CT): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1S)-1-fenilpropil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (1R)-1-fenilpropan-1-amina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.61 (d, 1H), 8.57 (s, 1H), 8.26 (d, 1H), 8.11 (d, 1H), 7.38 (d, 2H), 7.32 (t, 2H), 7.20-7.25 (m, 2H), 7.02 (d, 1H), 6.96 (s, 1H), 6.87 (d, 1H), 4.86-4.92 (m, 1H), 4.61 (s, 2H), 3.86 (s, 1H), 3.81 (s, 3H), 2.24 (d, 2H), 2.14 (s, 4H), 2.10 (s, 1H), 1.97-2.02 (m, 2H), 1.93 (s, 1H), 1.89 (s, 1H), 1.75-1.86 (m, 2H), 0.90 (t, 3H). MS (EI) para $C_{31}H_{36}N_4O_3$: 513 (MH^+).

[00343] 1(CU): N-[(1S)-1-(4-clorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (1R)-1-(4-clorofenil)etanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.71 (d, 1H),

8.57 (d, 1H), 8.25 (d, 1H), 8.10 (d, 1H), 7.39 (s, 4H), 7.23 (t, 1H), 7.02 (d, 1H), 6.97 (d, 1H), 6.87 (d, 1H), 5.09-5.17 (m, 1H), 4.62 (s, 2H), 3.85-3.90 (m, 1H), 3.81 (s, 3H), 2.22-2.27 (m, 2H), 2.14 (s, 2H), 2.08-2.12 (m, 2H), 2.00-2.02 (m, 2H), 1.94 (s, 1H), 1.90 (s, 1H), 1.46 (d, 3H). MS (EI) para $C_{30}H_{33}ClN_4O_3$: 533 (MH^+).

[00344] 1(CV): N-[(1S)-2-amino-1-metil-2-oxoetil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando clorhidrato de L-alaninamida en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.56 (d, 1H), 8.44 (d, 1H), 8.28 (d, 1H), 8.16 (d, 1H), 7.40 (s, 1H), 7.23 (t, 1H), 7.04-7.07 (m, 1H), 7.01 (d, 1H), 6.87 (d, 1H), 4.65 (s, 2H), 4.37-4.44 (m, 1H), 3.87-3.91 (m, 1H), 3.81 (s, 3H), 2.89 (s, 1H), 2.73 (s, 1H), 2.24-2.29 (m, 2H), 2.15 (s, 4H), 2.09-2.13 (m, 1H), 2.01-2.04 (m, 2H), 1.96 (s, 1H), 1.93 (s, 1H), 1.32 (d, 3H). MS (EI) para $C_{25}H_{31}N_5O_4$: 466 (MH^+).

[00345] 1(CW): N-hidroxi-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando clorhidrato de hidroxilamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 10.18 (s, 1H), 8.60 (d, 1H), 8.23 (d, 1H), 7.92 (dd, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H),

6.76 (d, 1H), 4.56 (br s, 2H), 3.85 (s, 1H), 3.80 (s, 3H), 3.34 (s, 6H), 2.20 (d, 1H), 2.14 (s, 1H), 2.07-2.11 (m, 1H), 1.98 (s, 2H), 1.84-1.87 (m, 2H). MS (EI) para $C_{22}H_{26}N_4O_4$: 410 (MH^+).

[00346] 1(CX): N-{8-[5-(hidrazinocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-3-(metiloxi)benzamida. Preparado de conformidad con el método del ejemplo 1 usando clorhidrato de hidrazina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 11.11 (br s, 1H), 8.42 (d, 1H), 8.26 (d, 1H), 7.95 (d, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.96 (d, 1H), 6.87 (d, 1H), 4.60 (s, 2H), 3.87 (s, 1H), 3.81 (s, 3H), 2.21-2.26 (m, 2H), 2.14 (s, 3H), 2.07-2.12 (m, 1H), 1.98-2.00 (m, 2H), 1.93 (s, 1H), 1.89 (s, 1H). MS (EI) para $C_{22}H_{27}N_5O_3$: 411 (MH^+).

[00347] 1(CY): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(1-metilpiperidin-4-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 1-metilpiperidin-4-amina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 10.47 (br s, 1H), 8.71 (d, 1H), 8.54 (d, 1H), 8.32 (d, 1H), 8.25 (d, 1H), 7.20-7.26 (m, 2H), 1.03 (d, 1H), 6.88 (d, 1H), 4.81 (br s, 2H), 3.86-3.94 (m, 1H), 3.81 (s, 3H), 3.43 (d, 2H), 3.30-3.36 (m, 1H), 2.98-3.11 (m, 3H), 2.76 (t, 1H), 2.71-2.74 (m, 3H), 2.28 (d, 2H), 2.15 (s, 4H), 1.84-2.05 (m, 6H). MS (EI) para

$C_{28}H_{37}N_5O_3$: 492 (MH^+).

[00348] 1(CZ): N-(1-metiletil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando propan-2-amina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.22 (d, 1H), 7.95 (t, 1H), 7.93 (d, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.73 (d, 1H), 4.54 (s, 2H), 4.05-4.10 (m, 1H), 3.84 (s, 1H), 3.80 (s, 3H), 3.34 (s, 4H), 2.17-2.22 (m, 2H), 2.14 (s, 2H), 2.06-2.12 (m, 1H), 1.96-1.99 (m, 2H), 1.85 (s, 1H), 1.82 (s, 1H), 1.14 (d, 6H). MS (EI) para $C_{25}H_{32}N_4O_3$: 437 (MH^+).

[00349] 1(DA): 2-[(1-etilpropil)amino]-N4-[8-(5-{[3R]-pirrolidin-3-ilaminocarbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 1 usando ácido 4-(aminocarbonil)-3-[(1-etilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3 y (3R)-3-aminopirrolidin-1-carboxilato de 1,1-dimetiletilo en la etapa 5, después de la omisión de la etapa 7. MS (EI) para $C_{30}H_{41}N_7O_3$: 548.4 (MH^+).

[00350] 1(DB): 2-[(1-etilpropil)amino]-N4-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 1 usando

ácido 4-(aminocarbonil)-3-[(1-etilpropil)amino]benzoico en la etapa 3 (sintetizado de conformidad con el reactivo de la preparación 39) y clorhidrato de (3R)-1-(1-metiletil)pirrolidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{33}H_{47}N_7O_3$: 590.4 (MH^+).

[00351] 1(DC): 2-[(1-etilpropil)amino]-N4-{8-[5-({[(3S)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 1 usando ácido 4-(aminocarbonil)-3-[(1-etilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3 y clorhidrato de (3S)-1-(1-metiletil)pirrolidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{33}H_{47}N_7O_3$: 590.4 (MH^+).

[00352] 1(DD): 2-[(1-etilpropil)amino]-N4-{8-[5-({[(3R)-1-etilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 1 usando ácido 4-(aminocarbonil)-3-[(1-etilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3 y (3R)-1-etilpirrolidin-3-amina

(sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{33}H_{47}N_7O_3$: 590.4 (MH^+).

[00353] 1(DE): 2-[(1-etilpropil)amino]-2-metil-N4-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 1 usando ácido 4-(aminocarbonil)-5-[(1-etilpropil)amino]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 3 y clorhidrato de (3R)-1-(1-metiletil)pirrolidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{34}H_{49}N_7O_3$: 604.4 (MH^+).

[00354] 1(DF): 2-[(1-etilpropil)amino]-N4-{8-(5-{[(3S)-pirrolidin-3-ilamino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 1 usando ácido 4-(aminocarbonil)-5-[(1-etilpropil)amino]-2-metilbenzoico en la etapa 3 (sintetizado de conformidad con el reactivo de la preparación 42) y (3S)-3-aminopipiperidin-1-carboxilato de 1,1-dimetiletilo en la etapa 5, después de la omisión de la etapa 7. MS (EI) para $C_{34}H_{49}N_7O_3$: 562.2 (MH^+).

[00355] 1(DG): 5-[(1-etilpropil)amino]-2-metil-N4-{8-(5-({[(3R)-1-(1-metiletil)piperidin-3-il]amino}carbonil)piridin-

2-il)-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 1 usando ácido 4-(aminocarbonil)-5-[(1-etilpropil)amino]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 3 y (3*R*)-1-(1-metiletil)pipiperidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 5, después de la omisión de las etapas 6 y 7. MS (EI) para $C_{35}H_{51}N_7O_3$: 618.3 (MH^+).

[00356] 1(DH): N-[(4-{[2-(dietilamino)etil]oxi}fenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-{4-(aminometil)fenil]oxi}-N,N-dietiletanamina (sintetizado de conformidad con el reactivo de la preparación 4) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H-NMR(CD_3OD): 8.50 (d, 1H), 8.35(d, 1H), 7.35(s, 1H), 7.35-7.33 (m, 1H), 7.32 (s, 1H), 7.23(t, 1H), 7.02-6.98(m, 3H), 6.89(d, 1H), 4.83(s, 2H), 4.51(s, 2H), 4.33(t, 3H), 4.21-418(m, 1H), 3.85 (s, 3H), 3.61(t, 2H), 3.38-3.36(m, 2H), 3.30-3.29(m, 4H), 2.10(s, 3H), 2.03(s, 2H), 2.00(s, 2H), 1.36(t, 6H). MS (EI) para $C_{35}H_{45}N_5O_4$: 601 (MH^+).

[00357] 1(DI): N-[(3-{[2-(dietilamino)etil]oxi}fenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-

il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2-{3-(aminometil)fenil]oxi}-N,N-dietiletanamina (sintetizado de conformidad con el reactivo de la preparación 4) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H-NMR (CD_3OD): 8.50(s, 1H), 8.49 (s, 1H), 8.21(dd, 1H), 7.32 (t, 1H), 7.26(t, 1H), 7.16 (d, 1H), 7.01-6.94 (m, 3H), 6.93-6.90(m, 2H), 4.68(s, 2H), 4.55(s, 2H), 4.34(t, 2H), 4.06-4.05(m,1H), 3.84(s, 3H), 3.59(t, 2H), 3.37-3.35(m, 2H), 3.35-2.33 (m, 4H), 2.31 (s, 3H), 2.28(s, 2H), 2.21 (s, 2H), 1.38 (t, 6H). MS (EI) para $C_{35}H_{45}N_5O_4$: 601 (MH^+).

[00358] 1(DJ): N-(8-{5-[({[4-(4-metilpiperazin-1-il)fenil]metil}amino)-carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 1 usando monoamida del ácido tereftálico en la etapa 3 y 4-(4-metilpiperazin-1-il)bencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H-NMR (CD_3OD): 8.60(s, 1H), 8.00-7.95(m, 3H), 7.83(d, 2H), 7.25(d, 2H), 6.95(d, 2H), 6.75(s, 1H), 4.62(s, 2H), 4.47(s, 2H), 4.00-4.01(m, 1H), 3.28- 3.21 (m, 4H), 2.87-2.82 (m, 4), 2.51(s, 3H), 2.31-2.16(m, 8H). MS (EI) para $C_{33}H_{39}N_7O_3$: 583(MH^+).

[00359] 1(DK): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[4-(4-metilpiperazin-1-il)fenil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando

4-(4-metilpiperazin-1-il)anilina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H-NMR (DMSO-d_6): 9.79(s, 1H), 8.71(d, 1H), 8.23(d, 1H), 8.03(d, 1H), 7.58(d, 2H), 7.23(t, 1H), 7.02(d, 1H), 6.92-6.90(m, 2H), 6.80(d, 1H), 4.58(s, 2H), 3.82(s, 1H), 3.81(s, 3H), 3.09-2.98(m, 4H), 2.46-2.23 (m, 4H), 2.25(s, 3H), 2.20 (s, 2H), 2.15(s, 3H), 2.11-1.98(m, 4H), 1.86(d, 2H). MS (EI) para $C_{33}H_{40}N_6O_3$: 569 (MH^+).

[00360] 1(DL): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[4-(1-metilpiperidin-4-il)fenil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-(1-metilpiperidin-4-il)anilina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H-NMR (CD_3OD): 8.59(s, 1H), 8.45(d, 1H), 8.35(dd, 1H), 7.64(d, 2H), 7.28-7.23(m, 3H), 7.02(d, 1H), 6.91(d, 1H), 4.73(s, 2H), 3.85-3.82(m, 1H), 3.62(s, 3H), 3.31(s, 1H), 3.30(s, 1H), 3.15(t, 2H), 2.99(s, 1H), 2.92(s, 3H), 2.85(s, 1H), 2.36-2.34(m, 4H), 2.26(s, 3H), 2.15-2.09(m, 2H), 1.96-1.93(m, 2H). MS (EI) para $C_{34}H_{41}N_5O_3$: 569 (MH^+).

[00361] 1(DM): N-(4-{[2-(dimetilamino)etil]oxi}fenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 4-[2-(dietilamino)etoxi]anilina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H-NMR (CD_3OD): 8.57(d, 1H),

8.46(d, 1H), 8.34(d, 1H), 7.64(s, 1H), 7.62(s, 1H), 7.24(t, 2H), 7.07-7.03(m, 3H), 6.91(d, 2H), 4.73(s, 2H), 4.36(t, 2H), 4.04-4.02(m, 1H), 3.85(s, 3H), 3.60(t,2H), 2.99(s, 6H), 2.35-2.33(m, 4H), 2.22(s, 3H), 2.13-2.12(m, 4H). MS (EI) para $C_{32}H_{39}N_5O_4$: 559 (MH^+).

[00362] 1(DN): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1S)-1-metilpropil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (S)-(+)-2-butilamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H-NMR (DMSO-d_6): 8.49(s, 1H), 8.31(d, 1H), 8.27-8.24(m, 1H), 7.22(t, 2H), 7.04(d, 1H), 6.88(d, 1H), 4.72(s, 2H), 3.92-3.91(m, 1H), 3.81(s, 3H), 2.27-2.15(m, 4H), 2.06(s, 3H), 2.01-1.99(m, 4H), 1.52-147(m, 2H), 1.14(d, 2H), 0.88(t, 2H). MS (EI) para $C_{26}H_{34}N_4O_3$: 451 (MH^+).

[00363] 1(DO): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3R)-1-metilpirrolidin-3-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (3R)-1-metilpirrolidin-3-amina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H-NMR (CD_3OD):8.51-8.50(m, 1H), 8.39(d, 1H), 7.39(d, 1H), 7.24(t, 1H), 7.03(d, 1H), 6.91(d, 1H), 4.77(s, 2H), 4.70(s, 1H), 4.11-4.07(m, 1H), 3.92-3.90(m,1H), 3.85(s,3H), 3.81-3.78(m,1H), 3.51-3.49(m, 2H), 3.21-3.19(m, 1H), 3.04(s, 2H), 2.98(s, 3H), 2.42-2.40(m, 1H),

2.37-2.34(m, 4H), 2.22(s, 3H), 2.19-2.15(m, 4H). MS (EI) para $C_{27}H_{35}N_5O_3$: 479 (MH^+).

[00364] 1(DP): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3S)-1-metilpirrolidin-3-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (3S)-1-metilpirrolidin-3-amina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H-NMR (CD_3OD): 8.47(s,1H), 8.38(d, 1H), 7.39(d, 1H), 7.25(t, 1H), 7.03(d, 1H), 6.91(d, 1H), 4.75 (s, 2H), 4.65-4.60(m, 1H), 4.11-4.01(m, 2H), 3.84(s, 3H), 3.81-3.78(m, 1H), 3.45-3.40(m, 1H), 3.22-3.20(m, 1H), 3.11(s, 2H), 2.28(s, 3H), 2.65-2.60(m, 1H), 2.44-2.40(m, 4H), 2.21(s, 3H), 2.18-2.16(m, 4H). MS (EI) para $C_{27}H_{35}N_5O_3$: 479 (MH^+).

[00365] 1(DQ): N-[(2-cloro-3,6-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 1 usando 2-cloro-3,6-difluorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.71 (br s, 1H), 8.51 (s, 1H), 8.25 (d, 1H), 8.04 (d, 1H), 7.50-7.42 (m, 1H), 7.35-7.29 (m, 2H), 7.03-6.85 (m, 3H), 4.62-4.56 (m, 4H), 3.89-3.83 (m, 1H), 3.80 (s, 3H), 2.26-2.20 (m, 2H), 2.15-1.86 (m, 9H). MS (EI) para $C_{29}H_{29}ClF_2N_4O_3$: 556 (MH^+).

[00366] 1(DR): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 1 usando diclorhidrato de (1*S*)-1-[4-(4-metilpiperazin-1-il)fenil]etanamina (sintetizado de conformidad con el reactivo de la preparación 3) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 10.99 (br s, 1H), 9.11 (d, 1H), 8.56 (s, 1H), 8.38-8.33 (m, 2H), 7.38-7.22 (m, 4H), 7.04-6.87 (m, 4H), 5.13-5.05 (m, 1H), 3.94-3.89 (m, 1H), 3.82-3.73 (m, 5H), 3.49-3.43 (m, 2H), 3.16-3.04 (m, 4H), 2.79 (d, 3H), 2.34-1.98 (m, 8H), 1.45 (d, 3H). MS (EI) para $C_{35}H_{44}N_6O_3$: 597 (MH^+).

[00367] 1(DS): N-{[4-fluoro-3-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 1 usando 4-fluoro-3-metoxibencilamina (sintetizado de conformidad con el reactivo de la preparación 6) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.95 (br s, 1H), 8.55 (s, 1H), 8.27 (d, 1H), 8.13 (d, 1H), 7.25-7.11 (m, 3H), 7.08-7.01 (m, 2H), 6.89-6.83 (m, 2H), 4.63 (br s, 2H), 4.44 (d, 2H), 3.91-3.86 (m, 1H), 3.83-3.79 (m, 6H), 2.28-2.22 (m, 2H), 2.17-2.09 (m,

5H), 2.05-1.90 (m, 4H). MS (EI) para $C_{30}H_{33}FN_4O_4$: 533 (MH^+).

[00368] 1(DT): N-{[3-fluoro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 1 usando 3-fluoro-4-metoxibencilamina (sintetizado de conformidad con el reactivo de la preparación 6) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.93 (br s, 1H), 8.55 (s, 1H), 8.27 (d, 1H), 8.11 (d, 1H), 7.26-7.21 (m, 1H), 7.17-7.00 (m, 5H), 6.87 (d, 1H), 4.61 (br s, 2H), 4.40 (d, 2H), 3.91-3.85 (m, 1H), 3.82-3.78 (m, 6H), 2.28-2.20 (m, 2H), 2.17-1.89 (m, 9H). MS (EI) para $C_{30}H_{33}FN_4O_4$: 533 (MH^+).

[00369] 1(DU): N-{[2-cloro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 1 usando 2-cloro-4-metoxibencilamina (sintetizado de conformidad con el reactivo de la preparación 6) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (br s, 1H), 8.56 (s, 1H), 8.27 (d, 1H), 8.14 (d, 1H), 7.30-7.21 (m, 2H), 7.06-7.00 (m, 3H), 6.93-6.85 (m, 2H), 4.63 (br s, 2H), 4.47 (d, 2H), 3.92-3.85 (m, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 2.28-2.25 (m, 2H), 2.17-2.09 (m, 5H), 2.04-1.90 (m, 4H). MS (EI) para $C_{30}H_{33}ClN_4O_4$: 549

(MH$^+$).

[00370] 1(DV): N-{[2,6-difluoro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 1 usando 2,6-Difluoro-4-metoxibencilamina (sintetizado de conformidad con el reactivo de la preparación 6) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.78 (br s, 1H), 8.49 (s, 1H), 8.28 (d, 1H), 8.13 (d, 1H), 7.26-7.21 (m, 1H), 7.10-7.01 (m, 2H), 6.87 (d, 1H), 6.77-6.71 (m, 2H), 4.64 (br s, 2H), 4.42 (d, 2H), 3.92-3.85 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 2.28-2.22 (m, 2H), 2.17-2.08 (m, 5H), 2.04-1.91 (m, 4H). MS (EI) para $C_{30}H_{32}F_2N_4O_4$: 551 (MH$^+$).

[00371] 1(DW): N-{[2-fluoro-6-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 1 usando 2-fluoro-6-metoxibencilamina (sintetizado de conformidad con el reactivo de la preparación 6) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.52 (br s, 1H), 8.47 (s, 1H), 8.27 (d, 1H), 8.15 (d, 1H), 7.36-7.21 (m, 2H), 7.10-7.00 (m, 2H), 6.90-6.78 (m, 3H), 4.64 (br s, 2H), 4.46 (d, 2H), 3.91-3.85 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.28-2.20 (m, 2H), 2.16-

2.08 (m, 5H), 2.04-1.90 (m, 4H). MS (EI) para $C_{30}H_{33}FN_4O_4$: 533 (MH^+).

[00372] 1(DX): N-{[4-fluoro-2-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 1 usando 4-fluoro-2-metoxibencilamina (sintetizado de conformidad con el reactivo de la preparación 6) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.82 (br s, 1H), 8.54 (s, 1H), 8.28 (d, 1H), 8.17 (d, 1H), 7.26-7.17 (m, 2H), 7.11-7.01 (m, 2H), 6.94-6.86 (m, 2H), 6.76-6.70 (m, 1H), 4.65 (br s, 2H), 4.38 (d, 2H), 3.92-3.87 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.28-2.23 (m, 2H), 2.17-2.10 (m, 5H), 2.05-1.92 (m, 4H). MS (EI) para $C_{30}H_{33}FN_4O_4$: 533 (MH^+).

[00373] 1(DY): N-[(2-cloro-6-fluoro-3-metilfenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 1 usando 1-(2-cloro-6-fluoro-3-metilfenil)metanamina (sintetizado de conformidad con el reactivo de la preparación 6) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d_6-DMSO): 8.68 (br s, 1H), 8.49 (d, 1H), 8.27 (d, 1H), 8.11 (d, 1H), 7.40-7.35 (m, 1H), 7.25-7.14 (m, 2H), 7.03-7.00 (m, 2H), 6.86 (d,

1H), 4.62 (br s, 2H), 4.57 (d, 2H), 3.90-3.84 (m, 1H), 3.80 (s, 3H), 2.32 (s, 3H), 2.28-2.21 (m, 2H), 2.15-2.08 (m, 5H), 2.04-1.90 (m, 4H). MS (EI) para $C_{30}H_{32}ClFN_4O_3$: 551 (MH^+).

[00374] 1(DZ): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2,3,6-trifluorofenil)metil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2,3,6-trifluorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.73-8.67 (m,1H), 8.58 (s,1H), 8.22 (s, 1H), 7.95-7.90 (d, 1H), 7.50-7.40 (m, 1H), 7.25-7.19 (m, 1H), 7.17-7.09 (m, 1H), 7.03-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.75-6.71 (d, 1H), 4.57-4.47 (m, 4H), 3.87-3.77 (m, 4H), 2.23-2.16 (d, 2H), 2.14 (s, 3H), 2.11-2.03 (m, 2H), 2.01-1.93 (m, 2H), 1.88-1.79 (d, 2H). MS (EI) para $C_{29}H_{29}F_3N_4O_3$: 539 (MH^+).

[00375] 1(EA): N-{[3-fluoro-4-(4-metilpiperazin-1-il)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-fluoro-4-(4-metilpiperazin-1-il)bencilamina (sintetizado de conformidad con el método del reactivo de la preparación 5) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.79-8.73 (m,1H), 8.64 (s,1H), 8.24-8.20 (m, 1H), 7.99-7.90 (m, 2H), 7.26-7.20 (m, 1H), 7.10-6.98 (m, 3H), 6.88-6.84 (d, 1H),

6.78-6.72 (d, 1H), 4.61-4.50 (m, 2H), 4.40-4.35 (d, 2H), 3.88-3.78 (m, 4H), 3.32-3.30 (m, 4H), 3.11-2.96 (br. s, 4H), 2.59 (s, 3H), 2.24-2.16 (m, 2H), 2.14 (s, 3H), 2.13-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.89-1.79 (d, 2H). MS (EI) para $C_{34}H_{41}FN_6O_3$: 601 (MH^+).

[00376] 1(EB): N-(2,3-dihidroxipropil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 3-aminopropano-1,2-diol en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.61 (s,1H), 8.23-8.18 (m, 2H), 7.97-7.92 (d, 1H), 7.26-7.20 (m, 1H), 7.04-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.76-6.72 (d, 1H), 4.84-4.81 (d, 2H), 4.60-4.50 (m, 4H), 3.88-3.78 (m, 4H), 3.63-3.57 (m, 1H), 3.21-3.11 (m, 2H), 2.24-2.16 (m, 2H), 2.14 (s, 3H), 2.10-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.89-1.79 (d, 2H). MS (EI) para $C_{25}H_{32}N_4O_5$: 469 (MH^+).

[00377] 1(EC): N-[(1S,2S)-2-hidroxiciclopentil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (1S,2S)-2-aminociclopentanol en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.60 (s,1H), 8.24-8.20 (d, 1H), 8.00-7.90 (m, 2H), 7.27-7.19 (m, 1H), 7.04-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.77-6.71 (d, 1H),

4.80-4.76 (d, 2H), 4.60-4.50 (br. s, 2H), 4.01-3.90 (m, 2H), 3.87-3.78 (m, 4H), 2.24-2.16 (m, 2H), 2.14 (s, 3H), 2.10-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.89-1.79 (d, 2H), 1.70-1.60 (m, 4H), 1.51-1.40 (m, 2H). MS (EI) para $C_{27}H_{34}N_4O_4$: 479 (MH^+).

[00378] 1(ED): N-[(1S,2S)-2-hidroxiciclohexil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (1S,2S)-2-aminociclohexanol en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.60 (s,1H), 8.24-8.20 (d, 1H), 7.98-7.93 (d, 1H), 7.88-7.84 (d, 1H), 7.26-7.20 (m, 1H), 7.04-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.77-6.71 (d, 1H), 4.64-4.59 (m, 1H), 4.58-4.50 (br. s, 2H), 3.87-3.78 (m, 4H), 3.66-3.54 (m, 1H), 2.24-2.16 (m, 2H), 2.14 (s, 3H), 2.10-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.90-1.78 (m, 3H), 1.69-1.59 (m, 4H), 1.27-1.16 (m, 4H). MS (EI) para $C_{28}H_{36}N_4O_4$: 493 (MH^+).

[00379] 1(EE): N-azetidin-3-il-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 1,1-dimetiletil-3-aminoazetidin-1-carboxilato en la etapa 5, después de la omisión de la etapa 7. ^{1}H NMR (400 MHz, d_6-DMSO): 9.25 (s, 1H), 8.98 (s, 2H), 8.61 (d, 1H), 8.29 (d, 1H), 8.12 (d, 1H), 7.24 (t, 1H), 7.05 (s, 1H), 7.03 (d, 1H), 6.87 (d, 1H), 4.75-4.84 (m, 2H),

4.70 (s, 2H), 4.07-4.19 (m, 4H), 3.87 (s, 1H), 3.81 (s, 3H), 2.25 (d, 2H), 2.08-2.14 (m, 4H), 2.00-2.03 (m, 2H), 1.95 (s, 1H), 1.92 (s, 1H). MS (EI) para $C_{25}H_{31}N_5O_3$: 450 (MH^+).

[00380] 1(EF): N-[(1S)-2-hidroxi-1-metiletil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (S)-2-aminopropan-1-ol en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.60 (s,1H), 8.25-8.20 (d, 1H), 7.97-7.92 (d, 1H), 7.87-7.81 (d, 1H), 7.26-7.20 (m, 1H), 7.04-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.76-6.72 (d, 1H), 4.75-4.67 (m, 1H), 4.60-4.50 (br. s, 2H), 4.05-3.94 (m, 2H), 3.87-3.78 (m, 4H), 3.48-3.40 (m, 1H), 2.24-2.16 (m, 2H), 2.14 (s, 3H), 2.10-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.89-1.79 (d, 2H), 1.14-1.08 (d, 3H). MS (EI) para $C_{25}H_{32}N_4O_4$: 453 (MH^+).

[00381] 1(EG): N-[(2S)-2-hidroxipropil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (S)-1-aminopropan-2-ol en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, d6-DMSO): 8.60 (s,1H), 8.24-8.16 (m, 2H), 7.97-7.92 (d, 1H), 7.26-7.20 (m, 1H), 7.04-6.99 (d, 1H), 6.88-6.84 (d, 1H), 6.76-6.72 (d, 1H), 4.76-4.73 (d, 1H), 4.57-4.52 (br. s, 2H), 3.87-3.79 (m, 4H), 3.78-3.72 (m, 1H), 3.21-3.13 (m, 2H), 2.24-2.16 (m, 2H), 2.14 (s, 3H),

2.10-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.89-1.79 (d, 2H), 1.07-1.03 (d, 3H). MS (EI) para $C_{25}H_{32}N_4O_4$: 453 (MH^+).

[00382] 1(EH): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[3-(metiloxi)fenil]etil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (S)-1-(3-metoxifenil)etanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.64 (d, 1H), 8.52 (d, 1H), 8.23 (d, 1H), 7.98 (dd, 1H), 7.22 (t, 2H), 7.02 (d, 1H), 6.94 (m, 2H), 6.86 (d, 1H), 6.80 (m, 1H), 6.76 (d, 1H), 5.12 (m, 1H), 4.54 (bs, 2H), 3.85 (m, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 2.20 (m, 2H), 2.15 (s, 3H), 2.08 (m, 2H), 1.98 (m, 2H), 1.84 (m, 2H), 1.44 (d, 3H). MS (EI) para $C_{31}H_{36}N_4O_4$: 529 (MH^+).

[00383] 1(EI): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-morfolin-4-ilfenil)metil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (4-morfolinofenil)metanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.70 (t, 1H), 8.63 (d, 1H), 8.22 (d, 1H), 7.96 (dd, 1H), 7.22 (t, 1H), 7.18 (d, 2H), 7.02 (d, 1H), 6.89 (d, 2H), 6.86 (d, 1H), 6.74 (d, 1H), 4.54 (bs, 2H), 4.32 (d, 2H), 3.83 (m, 1H), 3.80 (s, 3H), 3.72 (m, 4H), 3.02 (m, 4H), 2.20 (m, 2H), 2.15 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H). MS (EI) para

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$C_{33}H_{39}N_5O_4$: 570 (MH^+).

[00384] 1(EJ): N-[(1S)-1,2-dimetilpropil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (S)-3-metilbutan-2-amina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.61 (d, 1H), 8.21 (d, 1H), 7.94 (dd, 1H), 7.84 (d, 1H), 7.22 (t, 1H), 7.02 (d, 1H), 6.86 (d, 2H), 6.74 (d, 1H), 4.52 (bs, 2H), 3.82 (m, 2H), 3.80 (s, 3H), 2.20 (m, 2H), 2.14 (s, 3H), 2.09 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H), 1.74 (m, 1H), 1.08 (d, 3H), 0.88 (d, 3H), 0.86 (d, 3H). MS (EI) para $C_{27}H_{36}N_4O_3$: 465 (MH^+).

[00385] 1(EK): N-[(1R)-1,2-dimetilpropil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (R)-3-metilbutan-2-amina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (d, 1H), 8.21 (d, 1H), 7.94 (dd, 1H), 7.85 (d, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 2H), 6.74 (d, 1H), 4.53 (bs, 2H), 3.82 (m, 2H), 3.80 (s, 3H), 2.20 (m, 2H), 2.15 (s, 3H), 2.10 (m, 2H), 1.97 (m, 2H), 1.84 (d, 2H), 1.74 (m, 1H), 1.08 (d, 3H), 0.88 (d, 3H), 0.86 (d, 3H). MS (EI) para $C_{27}H_{36}N_4O_3$: 465 (MH^+).

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[00386] 1(EL): N-[(1S)-1-metil-2-(metiloxi)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (S)-1-metoxipropan-2-amina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.59 (d, 1H), 8.21 (d, 1H), 7.94 (m, 2H), 7.22 (t, 1H), 7.02 (d, 1H), 6.86 (d, 2H), 6.74 (d, 1H), 4.54 (bs, 2H), 4.17 (m, 1H), 3.84 (m, 1H), 3.80 (s, 3H), 3.39 (d, 0.5H), 3.37 (d, 0.5H), 3.26 (d, 0.5H), 3.26 (s, 3H), 3.24 (d, 0.5H), 2.19 (m, 2H), 2.14 (s, 3H), 2.09 (m, 2H), 1.97 (m, 2H), 1.84 (d, 2H), 1.07 (d, 3H). MS (EI) para $C_{26}H_{34}N_4O_4$: 467 (MH^+).

[00387] 1(EM): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(metiloxi)fenil]etil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (S)-1-(4-metoxifenil)etanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (d, 1H), 8.45 (d, 1H), 8.21 (d, 1H), 7.96 (dd, 1H), 7.29 (d, 2H), 7.23 (t, 1H), 7.02 (d, 1H), 6.87 (m, 3H), 6.74 (d, 1H), 5.10 (m, 1H), 4.52 (bs, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.81 (m, 1H), 2.20 (m, 2H), 2.14 (s, 3H), 2.06 (m, 2H), 1.97 (m, 2H), 1.83 (d, 2H), 1.42 (d, 3H). MS (EI) para $C_{31}H_{36}N_4O_4$: 528 (M).

[00388] 1(EN): 6-[3-endo-({[2-metil-3-

(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1R)-1-[4-(metiloxi)fenil]etil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (R)-1-(4-metoxifenil)etanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (d, 1H), 8.45 (d, 1H), 8.21 (d, 1H), 7.96 (dd, 1H), 7.29 (d, 2H), 7.23 (t, 1H), 7.01 (d, 1H), 6.86 (m, 3H), 6.74 (d, 1H), 5.10 (m, 1H), 4.53 (bs, 2H), 3. 82 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.19 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.97 (m, 2H), 1.83 (d, 2H), 1.43 (d, 3H). MS (EI) para $C_{31}H_{36}N_4O_4$: 529 (MH^+).

[00389] 1(EO): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-((1-feniletil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 1-feniletanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.65 (d, 1H), 8.53 (d, 1H), 8.21 (d, 1H), 7.98 (dd, 1H), 7.38 (m, 2H), 7.32 (m, 2H), 7.22 (m, 2H), 7.02 (d, 1H), 6.86 (d, 1H), 6.75 (d, 1H), 5.12 (m, 1H), 4.54 (bs, 2H), 3. 82 (m, 1H), 3.80 (s, 3H), 2.20 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.97 (m, 2H), 1.84 (d, 2H), 1.45 (d, 3H). MS (EI) para $C_{30}H_{34}N_4O_3$: 499 (MH^+).

[00390] 1(EP): N-[1-(4-clorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de

conformidad con el método del ejemplo 1 usando 1-(4-clorofenil)etanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (d, 1H), 8.55 (d, 1H), 8.21 (d, 1H), 7.96 (dd, 1H), 7.39 (m, 4H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.75 (d, 1H), 5.12 (m, 1H), 4.54 (bs, 2H), 3. 84 (m, 1H), 3.80 (s, 3H), 2.20 (m, 2H), 2.13 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H), 1.44 (d, 3H). MS (EI) para $C_{30}H_{33}ClN_4O_3$: 535 (MH^+).

[00391] 1(EQ): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(1-fenilpiperidin-4-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 1-fenilpiperidin-4-amina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.61 (d, 1H), 8.21 (d, 1H), 8.03 (d, 1H), 7.94 (dd, 1H), 7.21 (m, 3H), 7.02 (d, 1H), 6.96 (m, 2H), 6.86 (d, 1H), 6.74 (m, 2H), 4.54 (bs, 2H), 3.94 (m, 1H), 3. 83 (m, 1H), 3.80 (s, 3H), 3.72 (m, 2H), 2.80 (m, 2H), 2.19 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 4H), 1.64 (m, 2H). MS (EI) para $C_{33}H_{39}N_5O_3$: 554 (MH^+).

[00392] 1(ER): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-pirrolidin-1-ilfenil)metil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (4-(pirrolidin-1-il)fenil)metanamina en la etapa 5, después

de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.62 (m, 2H), 8.21 (d, 1H), 7.95 (dd, 1H), 7.22 (t, 1H), 7.11 (m, 2H), 7.01 (d, 1H), 6.85 (d, 1H), 6.73 (d, 1H), 6.47 (m, 2H), 4.52 (bs, 2H), 4.32 (d, 2H), 3. 83 (m, 1H), 3.79 (s, 3H), 3.17 (m, 4H), 2.19 (m, 2H), 2.13 (s, 3H), 2.08 (m, 2H), 1.92-1.98 (m, 6H), 1.84 (d, 2H). MS (EI) para $C_{33}H_{39}N_5O_3$: 553 (M).

[00393] 1(ES): N-[(1S)-1-(4-{[2-(dietilamino)etil]oxi}-2-fluorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (S)-2-(4-(1-aminoetil)-3-fluorofenoxi)-N,N-dietiletanamina (sintetizado de conformidad con el reactivo de la preparación 4) en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.64 (d, 1H), 8.52 (d, 1H), 8.21 (d, 1H), 7.97 (dd, 1H), 7.34 (t, 1H), 7.23 (t, 1H), 7.01 (d, 1H), 6.86 (d, 1H), 6.73-6.79 (m, 3H), 5.30 (m, 1H), 4.54 (bs, 2H), 4.00 (t, 2H), 3. 83 (m, 1H), 3.80 (s, 3H), 2.74 (t, 2H), 2.52 (dd, 4H), 2.20 (m, 2H), 2.13 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H) 1.41 (d, 3H), 0.96 (t, 6H). MS (EI) para $C_{36}H_{46}FN_5O_3$: 633 (MH^+).

[00394] 1(ET): N-{1-[3,4-bis(metiloxi)fenil]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-

azabiciclo[3.2.1]oct-8-il]-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 1-(3,4-dimetoxifenil)etanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (d, 1H), 8.44 (d, 1H), 8.21 (d, 1H), 7.94 (dd, 1H), 7.23 (t, 1H), 7.02 (d, s, 2H), 6.86 (m, 3H), 6.74 (d, 1H), 5.10 (m, 1H), 4.54 (bs, 2H), 3.83 (m, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 2.19 (m, 2H), 2.13 (s, 3H), 2.08 (m, 2H), 1.97 (m, 2H), 1.84 (d, 2H), 1.43 (d, 3H). MS (EI) para $C_{32}H_{38}N_4O_5$: 559 (MH^+).

[00395] 1(EU): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (4-(4-metilpiperazin-1-il)fenil)metanamina en la etapa 5 después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.68 (t, 1H), 8.63 (d, 1H), 8.21 (d, 1H), 7.96 (dd, 1H), 7.22 (t, 1H), 7.15 (m, 2H), 7.02 (d, 1H), 6.87 (m, 3H), 6.74 (d, 1H), 4.53 (bs, 2H), 4.33 (d, 2H), 3.82 (m, 1H), 3.79 (s, 3H), 3.06 (m, 4H), 2.42 (m, 4H), 2.20 (s, m, 5H), 2.14 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H). MS (EI) para $C_{34}H_{42}N_6O_3$: 583 (MH^+).

[00396] 1(EV): N-{(1S)-1-[2-fluoro-4-(metiloxi)fenil]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 1 usando clorhidrato de (1S)-1-(2-fluoro-4-metoxifenil)etanamina en la etapa 5, y después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, Metanol-d_4): 8.60 (d, 1H), 7.97 (dd, 1H), 7.31 (t, 1H), 7.23 (t, 1H), 6.99 (d, 1H), 6.90 (d, 1H), 6.77-6.64 (m, 3H), 5.43-5.35 (m, 1H), 4.60 (br s, 2H), 4.03-3.96 (m, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 2.35-2.06 (m, 9H), 1.90 (d, 2H), 1.52 (d, 3H); MS (EI) para $C_{31}H_{35}FN_4O_4$: 547 (MH^+).

[00397] 1(EW): N-{[2-fluoro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (2-fluoro-4-metoxifenil)metanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, Metanol-d_4): 8.60 (d, 1H), 7.96 (dd, 1H), 7.29 (t, 1H), 7.22 (t, 1H), 6.99 (d, 1H), 6.90 (d, 1H), 6.77-6.66 (m, 3H), 4.60 (br s, 2H), 4.52 (s, 2H), 4.04-3.95 (m, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 2.35-2.07 (m, 9H), 1.91 (d, 2H); MS (EI) para $C_{30}H_{33}FN_4O_4$: 533 (MH^+).

[00398] 1(EX): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2,4,6-trifluorofenil)metil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando (2,4,6-trifluorofenil)metanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (t, 1H), 8.56 (d, 1H), 8.19 (d, 1H), 7.90 (dd, 1H), 7.23-7.11 (m, 3H), 6.99 (d, 1H), 6.83 (d, 1H), 6.70 (d, 1H), 4.51 (br s, 2H), 4.41 (d, 2H), 3.85-3.74 (m, 4H), 2.23-1.99 (m, 7H), 1.98-1.88 (m, 2H), 1.81 (d, 2H); MS (EI) para $C_{29}H_{29}F_3N_4O_3$: 537 (M-H).

[00399] 1(EY): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[3-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 1 usando 1-[3-(4-metilpiperazin-1-il)fenil]metanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, Metanol-d_4): 8.61 (d, 1H), 7.98 (dd, 1H), 7.26-7.20 (m, 2H), 7.02-6.97 (m, 2H), 6.93-6.85 (m, 3H), 6.76 (d, 1H), 4.60 (br s, 2H), 4.51 (s, 2H), 4.04-3.96 (m, 1H), 3.84 (s, 3H), 3.39-3.22 (m, 4H), 2.89-2.81 (m, 4H), 2.54-2.51 (m, 3H), 2.34-2.25 (m, 2H), 2.23-2.08 (m, 7H), 1.96 (s, 3H), 1.90 (d, 2H); MS (EI) para $C_{34}H_{42}N_6O_3$: 583 (MH^+).

[00400] 1(EZ): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[2-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 1-[2-(4-metilpiperazin-1-il)fenil]metanamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.65-8.58 (m, 2H), 8.16 (d, 1H), 7.92 (dd, 1H), 7.19-7.12 (m, 3H), 7.07-6.93(m, 3H), 6.79 (d, 1H), 6.69 (d, 1H), 4.53-4.41 (m, 4H), 3.82-3.75 (m, 1H), 3.73 (s, 3H), 2.89-2.81 (m, 4H), 2.68-2.56 (m, 4H), 2.31 (br s, 3H), 2.18-1.98 (m, 7H), 1.95-1.86 (m, 2H), 1.78 (d, 2H); MS (EI) para $C_{34}H_{42}N_6O_3$: 583 (MH^+).

[00401] 1(FA): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2,4,5-trifluorofenil)metil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando 2,4,5-trifluorobencilamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, DMSO-d_6): 8.77 (t, 1H), 8.62 (d, 1H), 8.21 (d, 1H), 7.94 (dd, 1H), 7.57-7.48 (m, 1H), 7.44-7.34 (m, 1H), 7.20 (t, 1H), 6.99 (d, 1H), 6.84 (d, 1H), 6.74 (d, 1H), 4.53 (br s, 2H), 4.41 (d, 2H), 3.87-3.74 (m, 4H), 2.25-1.75 (m, 11H); MS (EI) para $C_{29}H_{29}F_3N_4O_3$: 537 (M-H).

[00402] 1(FB): N-(2-hidroxietil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 1 usando etanolamina en la etapa 5, después de la omisión de las etapas 6 y 7. ^{1}H NMR (400 MHz, Metanol-d_4): 8.46 (d, 1H), 8.41 (d, 1H), 8.31 (dd, 1H), 7.32 (d, 1H), 7.24 (t, 1H), 7.01 (d, 1H), 6.91(d, 1H), 4.71 (br s, 2H), 4.13-4.07 (m, 1H), 3.85 (s, 3H), 3.71 (t, 2H), 3.50 (t, 2H), 32.41-2.18 (m, 9H), 2.14 (d, 2H); MS (EI) para $C_{24}H_{30}N_4O_4$: 439 (MH^+).

[00403] 1(FC): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]-carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-piperazin-1-ilfenil)metil]piridin-3-carboxamida. Preparado como la sal de acetato en el Ejemplo 1 etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.60 (d, 1H), 7.97 (dd, 1H), 7.27 (d, 2H), 7.23 (t, 1H), 6.99 (m, 3H), 6.90 (d, 1H), 6.75 (d, 1H), 4.60 (br s, 2H), 4.47 (s, 3H), 3.99 (m, 1H), 3.84 (s, 3H), 3.25 (m, 4H), 2.29 (m, 2H), 2.21 (s, 3H), 2.19 (m, 2H), 1.92 (s, 6H), 1.90 (m, 2H); MS (EI) para $C_{33}H_{40}N_6O_3$: 569 (MH^+).

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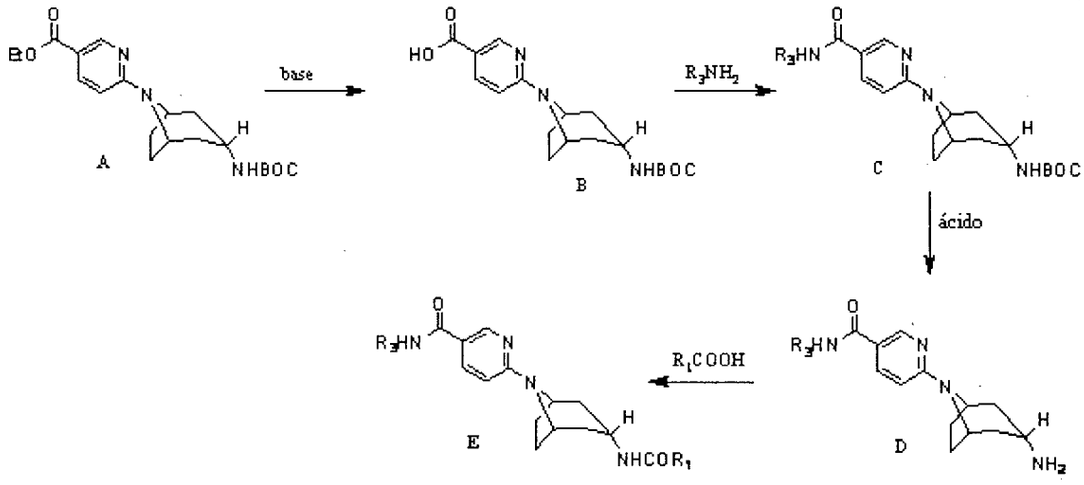
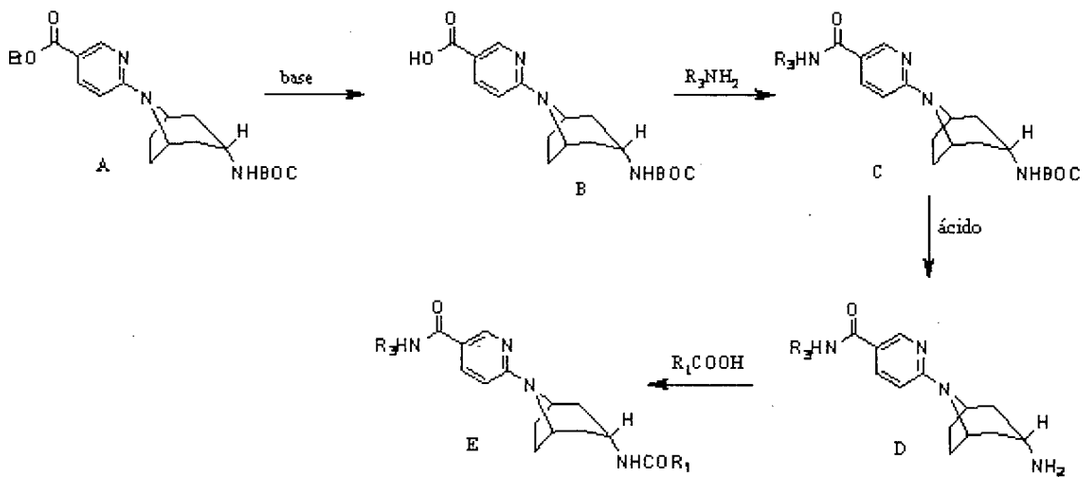
ESQUEMA DE REACCIÓN SINTÉTICA 2:



ESQUEMA DE REACCIÓN SINTÉTICA 2:



[00404] El esquema de reacción 2 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 2, en donde R_1 y R_3 son como se definen en la especificación.

[00405] En el esquema de reacción 2, el carboxilato del compuesto (A) se hidroliza para formar el compuesto (B) bajo condiciones acídicas, tal como con el uso de KOH. Después se agrega R_3NH_2 al compuesto (B) bajo condiciones de reacción

apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (C). Después se desprotege el compuesto (C) bajo condiciones acídicas, tal como con el uso de HCl, para remover BOC y formar el compuesto (D). Al compuesto (D) se agrega R_1COOH bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (E).

[00406] EJEMPLO 2: 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}-amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida.

[00407] ETAPA 1: Una mezcla de 6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}-amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (preparada en el Ejemplo 1) (13.56 g, 36.12 mmol) e hidróxido de potasio (4.05 g, 72.23 mmol) en metanol (120 mL) y agua (40 mL) se agita a 70 °C por 1 h. La mezcla de reacción se concentra y después se acidifica a pH5 con ácido clorhídrico acuoso 1N. Lo precipitado se recolecta por filtración, se lava con agua y se seca para dar ácido 6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (11.69 g, 93% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.46 (br s, 1H), 8.61 (d, 1H), 7.89 (dd, 1H), 6.90 (br s, 1H), 6.71 (d, 1H), 4.52 (br s, 2H), 3.44 (m, 1H), 2.12 (m, 2H), 1.94 (m, 4H), 1.75 (d, 2H),

1.39 (s, 9H); MS (EI) por $C_{18}H_{25}N_3O_4$: 348 (MH^+).

[00408] ETAPA 2: Una mezcla de ácido 6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (643 mg, 1.85 mmol), bencilamina (198 mg, 1.85 mmol), HATU (704 mg, 1.85 mmol), y diisopropiletilamina (598 mg, 4.63 mmol) en DMF (10 mL) se agita a temperatura ambiente por 18 h. La mezcla de reacción se diluye con acetato de etilo (100 mL), se lava con agua (50 mL), 5% de cloruro de litio (2 x 50 mL), y salmuera (50 mL), se seca sobre sulfato de sodio después se filtra y se concentra. Lo sólido resultante se tritura con acetato de etilo (10 mL) después se seca para proporcionar [8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo (612 mg, 76% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.79 (t, 1H), 8.63 (d, 1H), 7.96 (dd, 1H), 7.31 (m, 5H), 7.23 (m, 1H), 6.87 (br s, 1H), 6.72 (d, 1H), 4.49 (br s, 2H), 4.45 (d, 2H), 3.42 (m, 1H), 2.11 (m, 2H), 1.95 (m, 4H), 1.72 (d, 2H), 1.39 (s, 9H); MS (EI) por $C_{25}H_{32}N_4O_3$: 437 (MH^+).

[00409] ETAPA 3: Una solución de [8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo (13.49 g, 30.90 mmol) en metanol (75 mL) y 4M HCl en dioxano

(75 mL) se somete a reflujo por 2 min. La mezcla de reacción se concentra, y se agrega agua (500 mL). La solución acuosa se lava con acetato de etilo (2 x 150 mL), y después se basifica a pH 11 con 50% de hidróxido de sodio. La capa acuosa se extrae con acetato de etilo (3 x 250 mL), y los extractos orgánicos se lavan con salmuera (50 mL). La solución orgánica se seca sobre sulfato de sodio, se filtra y se concentra para dar 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida (9.40 g, 90% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.76 (t, 1H), 8.62 (d, 1H), 7.94 (dd, 1H), 7.30 (m, 5H), 7.23 (m, 1H), 6.63 (d, 1H), 4.49 (br s, 2H), 4.45 (d, 2H), 3.14 (m, 1H), 2.34 (m, 2H), 1.92 (m, 4H), 1.57 (br s, 2H), 1.42 (d, 2H).

[00410] ETAPA 4: Una mezcla de ácido 3-(metiloxi)-2-metilbenzoico (22 mg, 0.13 mmol), 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida (44 mg, 0.13 mmol), HATU (50 mg, 0.13 mmol), y diisopropiletilamina (52 mg, 0.40 mmol) en DMF (2 mL) se agita a temperatura ambiente por 5 h. La mezcla de reacción se diluye con acetato de etilo (50 mL), se lava con bicarbonato de sodio saturado (2 x 30 mL), 5% de cloruro de litio (20 mL), y salmuera (20 mL), se seca sobre sulfato de sodio después se filtra y se concentra. Lo sólido resultante se suspende en acetonitrilo y el producto insoluble se

recolecta por filtración, después se lava con metanol (3x) para proporcionar el compuesto del título (19 mg, 22% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.80 (t, 1H), 8.65 (s, 1H), 8.23 (d, 1H), 7.98 (m, 1H), 7.31 (m, 4H), 7.23 (m, 2H), 7.02 (d, 1H), 6.86 (d, 1H), 6.76 (d, 1H), 4.55 (br s, 2H), 4.46 (d, 2H), 3.84 (m, 1H), 3.80 (s, 3H), 2.26 (m, 2H), 2.14 (s, 3H), 2.09 (m, 2H), 1.97 (m, 2H), 1.85 (d, 2H); MS (EI) por $C_{29}H_{32}N_4O_3$: 485 (MH^+).

[00411] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [2(A)-2(AU)]. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00412] (2B): N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-indol-4-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido indol-4-carboxílico en la etapa 4. ^{1}H-NMR(400 MHz, DMSO-d_6): 11.31(s, 1H), 8.87 (s, 1H), 8.64 (s, 1H), 8.12-8.03 (m, 2H), 7.54(d, 2H), 7.45(t, 1H), 7.35-7.30 (m, 4H), 7.24-7.19 (m,1H), 7.15 (t, 1H), 6.85 (br s, 1H), 6.78 (t, 1H), 4.62 (br s, 2H), 4.47 (d, 2H), 3.94 (br s, 1H), 2.33-2.31 (m, 2H), 2.08-1.96 (m, 6H). MS(EI) para $C_{29}H_{29}N_5O_2$: 478 (M^-).

[00413] (2C): 6-(3-endo-{[(3-hidroxi-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 3-hidroxi-2-metilbenzoico en la etapa 4. ^{1}H-NMR (400 MHz, DMSO-d_6): 9.50 (br s, 1H), 8.95 (br s, 1H), 8.57 (s, 1H), 8.22 (d, 1H), 8.10 (s, 1H), 7.35- 7.26 (m, 2H), 7.25-7.07 (m, 1H), 7.01 (t, 1H), 6.84 (d, 1H), 6.72 (d, 1H), 4.62 (br s, 2H), 4.47 (d, 2H), 3.86 (br s, 1H), 2.26-2.24 (m, 2H), 2.11 (s, 3H), 2.08- 1.99 (m, 2H), 1.94-1.90 (m, 4H). MS(EI) para $C_{28}H_{30}N_4O_3$: 471 (MH^+).

[00414] (2D): 6-(3-endo-{[(3-amino-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 3-amino-2-metilbenzoico en la etapa 4. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.80 (t, 1H), 8.65 (br s, 1H), 8.09 (d, 1H), 7.99-7.96 (m, 1H), 7.33-7.31 (m, 3H), 7.25-7.24 (m, 1H), 6.91 (t, 1H), 6.75 (d, 1H), 6.67 (d, 1H), 6.48 (d, 1H), 4.97 (br s, 2H), 4.55 (s, 1H), 4.46 (d, 2H), 3.82 (s, 1H), 2.21-2.08 (m, 2H), 2.07-1.98 (m, 7H), 1.97-1.84 (m, 2H). MS(EI) para $C_{28}H_{31}N_5O_2$: 468 (M^-).

[00415] (2E): N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando monoamida del ácido tereftálico en la etapa 4. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.80 (t, 1H), 8.66 (s, 1H), 8.32

(d, 1H), 8.10 (s, 1H), 8.00-7.95 (m, 2H), 7.84-7.82 (m, 2H), 7.53 (s, 1H), 7.33-7.31 (m, 2H), 6.78 (d, 1H), 4.58 (s, 2H), 4.46 (d, 2H), 3.86 (s, 1H), 2.23-2.21 (m, 2H), 2.11-1.90 (m, 6H). MS(EI) para $C_{28}H_{29}N_5O_3$: 484 (MH^+).

[00416] (2F): 2-metil-N1-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 4-(aminocarbonil)-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 11) en la etapa 4. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.82 (t, 1H), 8.66 (s, 1H), 8.34 (d, 1H), 8.01-7.98 (m, 2H), 7.75-7.72 (m, 2H), 7.43 (s, 1H), 7.43-7.31 (m, 3H), 7.29-7.14 (m, 2H), 6.77 (d, 1H), 6.59 (s, 1H), 4.56 (s, 2H), 4.46 (d, 2H), 3.87 (s, 1H), 2.37 (s, 3H), 2.22-2.20 (m, 2H), 2.12-2.08 (m, 2H), 1.99-1.87 (m, 4H). MS(EI) para $C_{29}H_{31}N_5O_3$: 496 (M^-).

[00417] (2G): 2-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,3-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 3-(aminocarbonil)-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 10) en la etapa 4. ^{1}H-NMR(400 MHz, DMSO-d_6): 8.87 (t, 1H), 8.62 (d, 1H), 8.35 (d, 1H), 8.03 (dd, 1H), 7.76 (s, 1H), 7.46 (s, 2H), 7.32-7.30 (m, 4H), 7.27 (s, 2H), 7.12 (s, 2H), 6.99 (d, 1H), 4.58 (s,

2H), 4.46 (d, 2H), 3.87 (s, 1H), 2.32 (s, 3H), 2.23-2.20 (m, 2H), 2.11-1.99 (m, 4H), 1.97-1.86 (m, 2H). MS(EI) para $C_{29}H_{31}N_5O_3$: 498 (MH^+).

[00418] (2H): 6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(piridin-3-ilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando 3-(aminometil)piridina en la etapa 2 y ácido 4-(hidroximetil)benzoico en la etapa 4. ^{1}H-NMR (400 MHz, CD_3OD): 8.61(s, 1H), 8.58 (s, 1H), 8.47 (s, 1H), 8.21(d, 1H), 8.02 (d, 1H), 7.99 (d, 1H), 7.93-7.91 (m, 2H), 7.50-7.45 (m, 3H), 6.81 (d, 1H), 4.67 (s, 2H), 4.64 (s, 2H), 4.60 (s, 2H), 4.02 (s, 1H), 2.30-2.18 (m, 6H), 2.00-1.96 (m, 2H). MS(EI) para $C_{27}H_{29}N_5O_3$: 472 (MH^+).

[00419] (2I): N-[8-(5-{[(piridin-3-ilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando 3-(aminometil)piridina en la etapa 2 y monoamida del ácido tereftálico en la etapa 4. ^{1}H-NMR(400 MHz, CD_3OD): 8.53 (d, 1H), 8.46 (s, 1H), 8.35 (d, 1H), 8.27 (d, 1H), 7.91-7.86 (m, 3H), 7.77-7.75 (m, 2H), 7.32 (t, 1H), 6.71 (d, 1H), 4.54 (brs, 2H), 4.49 (s, 2H), 3.92 (br s, 1H), 2.19-2.2.10 (m, 6H), 1.89-1.83 (m, 2H). MS(EI) para $C_{27}H_{28}N_6O_3$: 485 (MH^+).

[00420] (2J): 6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(5-metilpirazin-2-il)metil]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando 2-(aminometil)-5-metilpiperazina en la etapa 2 y ácido 4-(hidroximetil)benzoico en la etapa 4. ^{1}H-NMR (400 MHz, CD_3OD): 8.55 (s, 1H), 8.40- 8. 39 (m, 2H), 7.91 (dd, 1H), 7.68-7.65 (m, 2H), 7.37 (d, 2H), 6.68 (d, 1H), 4.58 (s, 2H), 4.57 (s, 2H), 4.54(s, 2H), 3.92 (br s, 1H), 2.45 (s, 3H), 2.21-2.17 (m, 6H), 189-1.83 (m, 2H). MS (EI) para $C_{27}H_{30}N_6O_3$: 487 (MH^+).

[00421] (2K): N-{8-[5-({[(5-metilpirazin-2-il)metil]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando 2-(aminometil)-5-metilpiperazina en la etapa 2 y monoamida del ácido tereftálico en la etapa 4. ^{1}H-NMR(400 MHz, CD_3OD): 8.51-8.45 (m, 4H), 8.25 (d, 1H), 7.98-7.96 (m, 2H), 7.88-7.85 (m, 2H), 7.18 (d, 1H), 4.72 (s, 2H), 4.68 (s, 2H), 4.10 (br s, 1H), 2.54 (s, 3H), 2.38-2.24 (m, 6H), 2.16-2.12 (m, 2H). MS(EI) para $C_{27}H_{29}N_7O_3$: 500 (MH^+).

[00422] (2L): 6-(3-endo-{[(5-metil-2,3-dihidro-1,4-benzodioxin-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 5-metil-2,3-dihidro-1,4-benzodioxin-6-carboxílico (véase: J. Med.

Chem. 1997, 40, 18-23) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.82-8.77 (m, 1H), 8.65 (s, 1H), 8.08 (d, 1H), 7.98 (dd, 1H), 7.35-7.28 (m, 4H), 7.26-7.21 (m, 1H), 6.81-6.74 (m, 3H), 4.54 (br s, 2H), 4.45 (d, 2H), 4.30-4.22 (m, 4H), 3.84-3.78 (m, 1H), 3.34 (s, 3H), 2.22-1.94 (m, 9H), 1.87-1.80 (m, 2H). MS (EI) para $C_{30}H_{32}N_4O_4$: 513 (MH^+).

[00423] (2M): 6-(3-endo-{[(4-metil-1,3-benzodioxol-5-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 4-metil-1,3-benzodioxol-5-carboxílico (véase: J. Med. Chem. 1997, 40, 18-23. Preparado usando bromoclorometano en lugar de dibromoetano) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.82-8.77 (m, 1H), 8.65 (d, 1H), 8.12 (d, 1H), 7.98 (dd, 1H), 7.35-7.28 (m, 4H), 7.26-7.21 (m, 1H), 6.89 (d, 1H), 6.82 (d, 1H), 6.76 (d, 1H), 6.05 (s, 2H), 4.54 (br s, 2H), 4.45 (d, 2H), 3.84-3.78 (m, 1H), 3.34 (s, 3H), 2.24-2.17 (m, 5H), 2.11-1.95 (m, 4H), 1.88-1.81 (m, 2H). MS (EI) para $C_{29}H_{30}N_4O_4$: 499 (MH^+).

[00424] (2N): 6-(3-endo-{[(5-metil-2,3-dihidro-1,4-benzodioxin-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 2 usando 4-(4-metilpiperazin-1-il)bencilamina en la etapa 2 y ácido 5-metil-2,3-dihidro-1,4-

benzodioxin-6-carboxílico (J. Med. Chem. 1997, 40, pp18-23) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.72-8.66 (m, 1H), 8.63 (d, 1H), 8.09 (d, 1H), 7.96 (dd, 1H), 7.15 (d, 2H), 6.88 (d, 2H), 6.81-6.72 (m, 3H), 4.54 (br s, 2H), 4.37-4.21 (m, 6H), 3.84-3.78 (m, 1H), 3.10-3.06 (m, 4H), 2.45-2.41 (m, 4H), 2.23-2.13 (m, 8H), 2.10-1.94 (m, 4H), 1.90-1.80 (m, 7H). MS (EI) para $C_{35}H_{42}N_6O_4$: 611 (MH^+).

[00425] (2O): 6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 7-metil-1-benzofuran-6-carboxílico (sintetizado de conformidad con el reactivo de la preparación 15) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.82-8.78 (m, 1H), 8.66 (s, 1H), 8.26-8.24 (m, 1H), 8.10 (s, 1H), 8.00-7.97 (m, 1H), 7.56-7.53 (m, 1H), 7.35-7.22 (m, 5H), 7.00 (s, 1H), 6.79-6.75 (m, 1H), 4.57 (br s, 2H), 4.46 (d, 2H), 3.98 (m, 1H), 2.52 (s, 3H), 2.65-2.20 (m, 2H), 2.15-2.07 (m, 2H), 2.03-1.98 (m, 2H), 1.91-1.85 (m, 2H). MS (EI) para $C_{30}H_{30}N_4O_3$: 495 (MH^+).

[00426] (2P): 8-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]quinolin-7-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 8-metilquinolin-7-carboxílico (véase: US2006069144) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.99 (dd, 1H), 8.85-

8.80 (m, 1H), 8.66 (d, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.00 (dd, 1H), 7.88 (d, 1H), 7.61-7.57 (m, 1H), 7.47 (d, 1H), 7.35-7.30 (m, 4H), 7.26-7.21 (m, 1H), 6.82-6.77 (m, 1H), 4.59 (br s, 2H), 4.46 (d, 2H), 3.99-3.93 (m, 1H), 2.76 (s, 3H), 2.28-2.13 (m, 4H), 2.03-1.98 (m, 2H), 1.92-1.86 (m, 2H). MS (EI) para $C_{31}H_{31}N_5O_2$: 506 (MH^+).

[00427] (2Q): 3-metil-4-({[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]amino}carbonil)fenilcarbamato. Sintetizado como la sal de trifluoroacetato, de conformidad con el método del ejemplo 2 usando ácido 4-[(aminocarbonil)oxi]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 12) en la etapa 4. ^{1}H NMR (400 MHz, DMSO): 9.00-8.93 (br s, 1H), 8.59-8.56 (s, 1H), 8.33-8.29 (s, 1H), 8.15-8.10 (d, 1H), 7.37-7.21 (m, 6H), 7.05-6.90 (m, 3H), 4.67-4.59 (br s, 2H), 4.50-4.45 (d, 2H), 4.40-4.00 (br s, 2H), 3.91-3.84 (br s, 2H), 2.36-2.32 (s, 3H), 2.31-2.23 (m, 2H), 2.18-2.08 (m, 2H), 2.05-1.99 (m, 2H), 1.97-1.89 (d, 2H). MS (EI) para $C_{29}H_{31}N_5O_4 \cdot C_2H_1O_2F_3$: 514 ($MH^+$).

[00428] (2R): 2-metil-3-({[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]amino}carbonil)fenilcarbamato. Sintetizado como la sal de trifluoroacetato, de conformidad con el método del ejemplo 2 usando ácido 3-

[(aminocarbonil)oxi]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 12) en la etapa 4. ^{1}H NMR (400 MHz, CD_3OD): 8.51-8.48 (d, 1H), 8.48-8.46 (s, 1H), 8.28-8.23 (d, 1H), 7.38-7.12 (m, 8H), 4.72-4.67 (br s, 2H), 4.58-4.56 (s, 2H), 2.39-2.05 (m, 11H). MS (EI) para $C_{29}H_{31}N_5O_4 \cdot C_2H_1O_2F_3$: 514 ($MH^+$).

[00429] (2S): 6-[3-endo-({[4-(hidroximetil)-2-metilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida. Sintetizado como la sal de trifluoroacetato, de conformidad con el método del ejemplo 2 usando ácido 4-(hidroximetil)-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 13) en la etapa 4. ^{1}H NMR (400 MHz, CD_3OD): 8.37-8.33 (d, 2H), 8.25-8.20 (d, 1H), 7.28-7.13 (m, 8H), 4.64-4.60 (br s, 2H), 4.52.4.50 (s, 2H), 4.49-4.47 (s, 2H), 4.03-3.97 (m, 1H), 2.33-2.30 (s, 3H), 2.29-2.00 (m, 8H). MS (EI) para $C_{29}H_{31}N_5O_4 \cdot C_2H_1O_2F_3$: 485 ($MH^+$).

[00430] (2T): 6-[3-endo-({[4-(hidroximetil)-2-metilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(piridin-3-ilmetil)piridin-3-carboxamida. Sintetizado como la sal de trifluoroacetato, de conformidad con el método del ejemplo 2 usando (piperidin-3-il)metilamina en la etapa 2 y ácido 4-(hidroximetil)-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 13) en la etapa 4. ^{1}H NMR (400 MHz, CD_3OD): 8.86-8.81 (d, 1H), 8.76-8.70 (d, 1H), 8.52-8.47 (m, 2H), 8.29-8.23 (d, 1H), 7.99-7.93 (m, 1H),

7.36-7.30 (d, 2H), 7.27-7.21 (m, 3H), 4.76-4.69 (br s, 4H), 4.62-4.59 (s, 2H), 4.49-4.47 (s, 2H), 4.12-4.04 (m, 1H), 2.83-2.80 (s, 3H), 2.45-2.07 (m, 8H). MS (EI) para $C_{28}H_{31}N_5O_3 \cdot C_2H_1O_2F_3$: 486 ($MH^+$).

[00431] (2U): 6-{3-endo-[({4-[amino(imino)metil]fenil}carbonil)amino]-8-azabiciclo[3.2.1]oct-8-il}-N-(fenilmetil)piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 2 usando clorhidrato del ácido 4-amidinobenzoico en la etapa 4. ^{1}H NMR (400 MHz, metanol-d_4): 8.53 (d, 1H), 8.50 (d, 1H), 8.22 (dd, 1H), 8.00 (d, 2H), 7.90 (d, 2H), 7.33 (m, 5H), 7.26 (m, 1H), 7.13 (d, 1H), 4.71 (br s, 2H), 4.57 (s, 2H), 4.10 (m, 1H), 2.30 (m, 6H), 2.11 (d, 2H); MS (EI) para $C_{28}H_{30}N_6O_2$: 407 (MH^+).

[00432] (2V): 6-[3-endo-({[3-(metiloxi)-2-propilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 2 usando ácido 3-metoxi-2-propilbenzoico (sintetizado de conformidad con el reactivo de la preparación 18) en la etapa 4. ^{1}H NMR (400 MHz, metanol-d_4): 8.47 (d, 1H), 8.39 (d, 1H), 8.25 (dd, 1H), 7.33 (d, 1H), 7.27-7.16 (m, 3H), 7.02 (d, 1H), 6.90 (d, 1H), 4.68 (br s, 2H), 4.57 (s, 2H), 4.06 (m, 1H), 3.83 (s, 3H), 2.67 (m, 2H), 2.33 (m, 4H), 2.20 (m, 2H), 2.06 (d, 2H), 1.57 (m, 2H), 0.92 (t, 3H); MS (EI) para $C_{31}H_{36}N_4O_3$:

886

513 (MH^+).

[00433] (2W): 6-[3-endo-({[3-(metiloxi)-2-prop-2-en-1-ilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 3-(metiloxi)-2-prop-2-en-1-ilbenzoico (sintetizado de conformidad con el reactivo de la preparación 19) en la etapa 4. ^{1}H NMR (400 MHz, metanol-d_4): 8.46 (d, 1H), 8.31 (d, 1H), 8.26 (dd, 1H), 7.37-7.23 (m, 6H), 7.19 (d, 1H), 7.05 (d, 1H), 6.94 (d, 1H), 5.90 (m, 1H), 4.94 (m, 2H), 4.68 (br s, 2H), 4.57 (s, 2H), 4.05 (m, 1H), 3.84 (s, 3H), 3.51 (d, 2H), 2.31 (m, 4H), 2.18 (m, 2H), 2.07 (d, 2H); MS (EI) para $C_{31}H_{34}N_4O_3$: 511 (MH^+).

[00434] (2X): N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[2-(metilsulfonil)etil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando ciclopentilamina en la etapa 2 y ácido 4-(aminocarbonil)-3-{[2-(metilsulfonil)etil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4. ^{1}H NMR (400 MHz, metanol-d_4): 8.57 (d, 1H), 8.14 (d, 1H), 7.95 (dd, 1H), 7.67 (d, 1H), 7.13 (d, 1H), 7.01 (dd, 1H), 6.75 (d, 1H), 4.62 (br s, 2H), 4.30 (m, 1H), 4.00 (m, 1H), 3.81 (t, 2H), 3.47 (t, 2H), 3.01 (s, 3H), 2.24 (m, 6H), 1.97 (m, 4H), 1.78 (m, 2H), 1.60 (m, 4H); MS (EI) para $C_{29}H_{38}N_6O_5S$: 538 (MH^+).

[00435] (2Y): N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-[(4-trans-hidroxiciclohexil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando ciclopentilamina en la etapa 2 y ácido 4-(aminocarbonil)-3-[(trans-4-hidroxiciclohexil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4. ^{1}H NMR (400 MHz, metanol-d_4): 8.57 (d, 1H), 7.96 (dd, 1H), 7.62 (d, 1H), 7.07 (d, 1H), 6.89 (dd, 1H), 6.75 (d, 1H), 4.63 (br s, 2H), 4.30 (m, 1H), 4.00 (m, 1H), 3.63 (m, 1H), 3.41 (m, 1H), 2.20 (m, 8H), 1.99 (m, 6H), 1.78 (m, 2H), 1.60 (m, 4H), 1.38 (m, 4H); MS (EI) para $C_{32}H_{42}N_6O_4$: 575 (MH^+).

[00436] (2Z): N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-indol-6-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 1H-indol-6-carboxílico en la etapa 4. ^{1}H NMR (400 MHz, DMSO-d_6): 11.39 (s, 1H), 8.81 (t, 1H), 8.67 (d, 1H), 8.12 (d, 1H), 7.99 (dd, 1H), 7.88 (s, 1H), 7.59 (d, 1H), 7.50 (dd, 1H), 7.45 (dd, 1H), 7.32 (m, 4.5H), 7.24 (m, 0.5H), 6.78 (d, 1H), 6.49 (m, 1H), 4.60 (bs, 2H), 4.46 (d, 2H), 3. 84 (m, 1H), 2.30 (m, 2H), 2.06 (m, 4H), 1.94 (d, 2H). MS (EI) para $C_{29}H_{29}N_5O_2$: 480 (MH^+).

[00437] (2AA): 1-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-indol-4-carboxamida.

Preparada de conformidad con el método del ejemplo 2 usando ácido 1-metil-1H-indol-4-carboxílico en la etapa 4. ^{1}H NMR (400 MHz, DMSO-d_6): 8.81 (t, 1H), 8.66 (d, 1H), 8.10 (d, 1H), 7.99 (dd, 1H), 7.61 (d, 1H) 7.42 (d, 1H), 7.38 (d, 1H), 7.32 (m, 4H), 7.24 (m, 2H), 6.78 (m, 2H), 4.60 (bs, 2H), 4.46 (d, 2H), 3. 86 (m, 1H), 3.81 (s, 3H), 2.28 (m, 2H), 2.06 (m, 4H), 1.94 (d, 2H). MS (EI) para $C_{30}H_{31}N_5O_2$: 494 (MH^+).

[00438] (2AB): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida. Aislado en forma de sal de trifluoroacetato, de conformidad con el método del ejemplo 2 usando ácido 7-metil-2,3-dihidro-1-benzofuran-6-carboxílico (sintetizado de conformidad con el reactivo de la preparación 16) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 9.02 (m, 1H), 8.55 (d, 1H), 8.18 (m, 2H), 7.32 (m, 4H), 7.25 (m, 1H), 7.10 (m, 2H), 6.81 (d, 1H), 4.65 (amplio s, 2H), 4.53 (t, 2H), 4.47 (d, 2H), 3.87 (m, 1H), 3.20 (t, 2H), 2.27 (m, 2H), 2.14 (s, 3H), 2.11 (m, 2H), 2.02 (m, 2H), 1.97 (d, 2H). MS (EI) para $C_{30}H_{32}N_4O_3$: 497 (MH^+).

[00439] (2AC): 6-(3-endo-{[(8-metil-3,4-dihidro-2H-cromen-7-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 8-metil-3,4-dihidro-2*H*-cromeno-7-carboxílico (Sawada, Y. et al, *Pest Management Science*, 2003, 59(*1*), 36-48.) en la etapa 3. ^{1}H NMR (400 MHz,

d_6-DMSO): 8.79 (t, 1H), 8.63 (d, 1H), 8.10 (d, 1H), 7.91 (dd, 1H), 7.28 (m, 4H), 7.21 (m, 1H), 6.92 (d, 1H), 6.72 (t, 2H), 4.52 (amplio s, 2H), 4.44 (d, 2H), 4.16 (t, 2H), 3.81 (m, 1H), 2.72 (t, 2H), 2.18 (m, 2H), 2.07 (s, 3H), 2.04 (m, 2H), 1.96 (m, 2H), 1.92 (m, 2H), 1.84 (d, 2H). MS (EI) para $C_{31}H_{34}N_4O_3$: 511 (MH^+).

[00440] (2AD): 4-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-bencimidazol-5-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 7-metil-1H-bencimidazol-6-carboxílico (sintetizado de conformidad con el reactivo de la preparación 23) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.81 (m, 1H), 8.66 (dd, 1H), 8.23 (m, 1H), 8.14 (amplio s, 1H), 7.98 (m, 1H), 7.31 (m, 4H), 7.23 (m, 1H), 6.76 (dd, 1H), 4.57 (amplio s, 2H), 4.46 (t, 2H), 3.88 (m, 1H), 2.62 (m, 2H), 2.27 (m, 1H), 2.14 (m, 2H), 2.07 (m, 2H), 1.90 (m, 2H), 1.64 (d, 2H). MS (EI) para $C_{29}H_{30}N_6O_2$: 495 (MH^+).

[00441] (2AE): N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-bencimidazol-5-carboxamida. Aislado como la sal de trifluoroacetato, de conformidad con el método del ejemplo 2 usando ácido 1*H*-bencimidazol-5-carboxílico en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 9.07 (m, 1H), 8.60 (m, 1H), 8.21 (m, 2H), 7.96 (m,

2H), 7.34 (m, 4H), 7.26 (m, 1H), 7.15 (m, 1H), 4.71 (amplio s, 2H), 4.49 (d, 2H), 3.95 (m, 1H), 2.79 (m, 2H), 2.35 (m, 1H), 2.15 (m, 1H), 2.08 (m, 4H). MS (EI) para $C_{28}H_{28}N_6O_2$: 481 (MH^+).

[00442] (2AF): 2-[(ciclopropilmetil)amino]-N4-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando (R)-1-isopropilpirrolidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 2 y ácido 4-(aminocarbonil)-3-[(ciclopropilmeti)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.32-8.24 (m, 2H), 8.17 (d, 1H), 7.96 (dd, 1H), 7.93 (br s, 1H), 7.67 (d, 1H), 7.30 (br s, 1H), 6.98 (d, 1H), 6.89 (dd, 1H), 6.78 (d, 1H), 4.58 (br s, 2H), 4.48-4.35 (m, 1H), 3.85-3.78 (m, 1H), 3.65-2.55 (m, 7H), 3.03 (dd, 2H), 2.25-2.12 (m, 2H), 2.12-1.97 (m, 4H), 1.95-1.86 (m, 2H), 1.29-1.04 (m, 7H), 0.54-0.49 (m, 2H), 0.27-0.22 (m, 2H); MS (EI) para $C_{32}H_{43}F_3N_7O_3$: 574 (MH^+).

[00443] (2AG): 5-[(1-etilpropil)amino]-N-{8-[5-({[(1-etilpirrolidin-2-il)metil]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando 1-(etilpirrolidin-2-il)metanamina en la

etapa 2 y ácido 4-(aminocarbonil)-2-metil-5-[(1-etilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 4. ^{1}H NMR (400 MHz, d_6-DMSO): 8.58 (d, 1H), 8.28 (d, 1H), 8.16 (t, 1H), 8.04 (d, 1H), 7.92 (dd, 1H), 7.84 (br s, 1H), 7.48 (s, 1H), 7.16 (br s, 1H), 6.74 (d, 1H), 6.56 (s, 1H), 4.54 (br s, 2H), 3.82 (br s, 1H), 3.28-3.18 (m, 1H), 3.06-2.96 (m, 2H), 2.88-2.77 (m, 1H), 2.58-2.50 (m, 1H), 2.30-2.20 (m, 3H), 2.18 (s, 3H), 2.16-1.94 (m, 5H), 1.92-1.83 (m, 3H), 1.82-1.72 (m, 1H), 1.68-1.42 (m, 7H), 1.04 (t, 3H), 0.88 (t, 6H); MS (EI) para $C_{34}H_{49}N_7O_3$: 604 (MH^+).

[00444] (2AH): N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando ciclopentilamina en la etapa 2 y ácido 4-(aminocarbonil)-3-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino}benzoico (preparado de conformidad con los métodos en la preparación del reactivo 40) en la etapa 4. ^{1}H NMR (400 MHz, CD_3OD): 8.56 (d, 1H), 7.94 (dd, 1H), 7.72 (d, 1H), 7.43 (d, 1H), 7.05-7.02 (m, 2H), 6.98-6.93 (m, 2H), 6.72 (d, 1H), 4.57 (br s, 2H), 4.36 (m, 3H), 3.93 (m, 1H), 3.86 (s, 3H), 3.42 (m, 2H), 2.89 (s, 6H), 2.21 (m, 2H), 2.09 (br s, 2H), 2.00 (m, 2H), 1.94 (s, 3H), 1.88 (d, 2H), 1.77 (m,

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2H), 1.67-1.52 (m, 4H); MS (EI) para $C_{37}H_{47}N_7O_5$: 670 (MH^+).

[00445] (2AI): 6-[3-endo-({[2-yodo-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 2-yodo-3-metoxibenzoico (sintetizado de conformidad con el reactivo de la preparación 21) en la etapa 4. ^1H NMR (400 MHz, d6-DMSO): 8.95 (br. s,1H), 8.57 (s, 1H), 8.38-8.34 (d, 1H), 8.16-8.09 (d, 1H), 7.42-7.22 (m, 4H), 7.05-6.97 (m, 2H), 6.88-6.84 (d, 2H), 4.66-4.59 (m, 2H), 4.50-4.45 (d, 2H), 3.92-3.83 (m, 4H), 2.36-2.28 (m, 2H), 2.19-2.10 (m, 2H), 2.02-1.89 (m, 4H). MS (EI) para $C_{28}H_{29}IN_4O_3$: 597 (MH^+).

[00446] (2AJ): 2,6-dimetil-N1-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 4-(aminocarbonil)-2,6-dimetilbenzoico en la etapa 4. ^1H NMR (400 MHz, d6-DMSO): 8.83-8.77 (m,1H), 8.66 (s, 1H), 8.41-8.37 (d, 1H), 8.01-7.96 (d, 1H), 7.92 (s, 1H), 7.56 (s, 2H), 7.36-7.21 (m, 6H), 6.78-6.74 (d, 1H), 4.59-4.53 (m, 2H), 4.48-4.44 (d, 2H), 3.96-3.91 (m, 1H), 2.26 (s, 6H), 2.21-2.11 (m, 4H), 2.00-1.91 (m, 2H), 1.83-1.75 (m, 2H). MS (EI) para $C_{30}H_{33}N_5O_3$: 512 (MH^+).

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[00447] (2AK): 2-[(4-trans-hidroxiciclohexil)amino]-N4-{8-[5-({[1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando (3R)-1-(1-metiletil)pirrolidin-3-amina en la etapa 2 (sintetizado de conformidad con el reactivo de la preparación 9) y ácido 4-(aminocarbonil)-3-[(trans-4-hidroxiciclohexil)amino]-benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4. ^{1}H NMR (400 MHz, d6-DMSO): 8.63-8.60 (d,1H), 8.24-8.16 (m, 3H), 8.00-7.87 (m, 2H), 7.68-7.63 (d, 1H), 7.31-7.25 (br. s, 1H), 6.96 (s, 1H), 6.85-6.80 (d, 1H), 6.78-6.73 (d, 1H), 4.64-4.51 (m, 3H), 4.39-4.29 (m, 2H), 3.86-3.80 (m, 1H), 2.84-2.87 (m, 2H), 2.70-2.61 (m, 2H), 2.47-2.40 (m, 2H), 2.38-2.30 (m, 2H), 2.28-2.20 (m, 2H), 2.12-1.92 (m, 4H), 1.79-1.69 (m, 2H), 1.37-1.17 (m, 6H), 1.06-0.99 (m, 6H), 0.97-0.93 (m, 2H). MS (EI) para $C_{34}H_{47}N_7O_4$: 618 (MH^+).

[00448] (2AL): 6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 4-(hidroximetil)benzoico en la etapa 4. ^{1}H NMR (400 MHz, Metanol-d_4): 8.62 (d, 1H), 7.99 (dd, 1H), 7.79-7.74 (m, 2H), 7.48-7.44 (m, 2H), 7.37-7.28 (m, 4H), 7.27-7.20 (m, 1H), 6.77 (d, 1H), 4.67 (s, 2H), 4.62 (br s, 2H), 4.55 (s, 2H), 4.05-

3.97 (m, 1H), 2.35-2.09 (m, 6H), 1.96 (d, 2H); MS (EI) para $C_{28}H_{30}N_4O_3$: 471 (MH^+).

[00449] (2AO): 6-(3-endo-{[(2-amino-6-cloro-9H-purin-9-il)acetil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 2 usando ácido 2-amino-6-cloro-9H-purin-9-acético en la etapa 4. ^{1}H NMR (400 MHz, Metanol-d_4): 8.45 (d, 1H), 8.39 (d, 1H), 8.25 (dd, 1H), 8.07 (s, 1H), 7.18 (d, 1H), 4.67 (br s, 2H), 3.99-3.91 (m, 1H), 3.33-3.28 (s, 2H), 2.38-2.16 (m, 6H), 1.99 (d, 2H); MS (EI) para $C_{27}H_{28}ClN_9O_2$: 456 (MH^+).

[00450] (2AP): 6-[3-endo-({[2-metil-3,4-bis(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 2 usando ácido 3,4-dimetoxi-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 17) en la etapa 4. ^{1}H NMR (400 MHz, Metanol-d_4): 8.42 (d, 1H), 8.36-8.29 (m, 2H), 7.38-7.23 (m, 5H), 6.94 (s, 1H), 6.84 (s, 1H), 4.72 (br s, 2H), 4.57 (s, 2H), 4.12-4.05 (m, 1H), 3.85-3.83 (m, 6H), 2.45-2.20 (m, 9H), 2.14 (d, 2H); MS (EI) para $C_{30}H_{34}N_4O_4$: 515 (MH^+).

[00451] (2AQ): 6-[3-endo-({[2-bromo-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida. Preparada de conformidad

con el método del ejemplo 2 usando ácido 2-bromo-3-metoxibenzoico (sintetizado de conformidad con el reactivo de la preparación 20) en la etapa 4. ^{1}H NMR (400 MHz, DMSO-d_6): 8.80 (t, 1H), 8.65 (d, 1H), 8.38 (d, 1H), 7.98 (dd, 1H), 7.39 (t, 1H), 7.36-7.28 (m, 4H), 7.27-7.20 (m, 1H), 7.14 (dd, 1H), 6.91 (dd, 1H), 6.76 (d, 1H), 4.54 (br s, 2H), 4.46 (d, 2H), 3.90-3.80 (m, 4H), 2.30-2.20 (m, 2H), 2.15-2.04 (m, 2H), 2.00-1.89 (m, 2H), 1.83 (d, 2H); MS (EI) para $C_{28}H_{29}BrN_4O_3$: 547 (M-H).

[00452] (2AR): 4-metil-N-(8-{5-[({[4-(4-metilpiperazin-1-il)fenil]metil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1H-bencimidazol-5-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 2 usando ácido 7-metil-1H-bencimidazol-6-carboxílico (sintetizado de conformidad con el reactivo de la preparación 23) en la etapa 4. ^{1}H NMR (400 MHz, Metanol-d_4): 9.38 (s, 1H), 8.58 (d, 1H), 8.49 (d, 1H), 8.22 (dd, 1H), 7.72 (d, 1H), 7.59 (d, 1H), 7.32-7.28 (m, 2H), 7.16 (d, 1H), 7.02-6.98 (m, 2H), 4.71 (br s, 2H), 4.49 (s, 2H), 4.20-4.09 (m, 1H), 3.87-3.78 (m, 2H), 3.64-3.55 (m, 2H), 3.29-3.20 (m, 2H), 3.07-2.94 (m, 5H), 2.69 (s, 3H), 2.43-2.16 (m, 6H), 2.09 (d, 2H); MS (EI) para $C_{34}H_{40}N_8O_2$: 593 (MH^+).

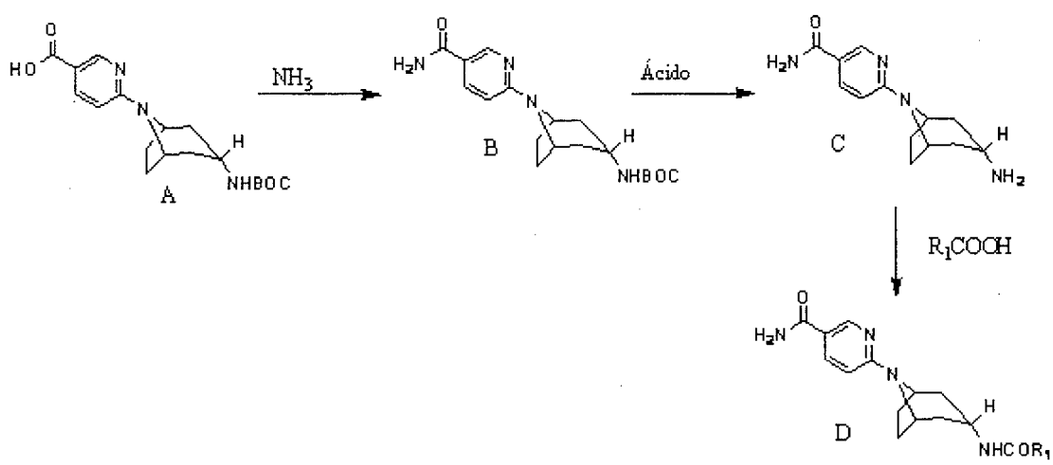
[00453] (2AS): N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 4-aminocarbonil-3-(ciclopropilmetil)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4. ^{1}H NMR (400 MHz, DMSO-d_6): 8.59 (d, 1H), 8.25 (t, 1H), 8.15 (d, 1H), 8.01 (d, 1H), 7.96-7.90 (m, 2H), 7.67 (d, 1H), 7.28 (br s, 1H), 6.98 (s, 1H), 6.88 (dd, 1H), 6.75 (d, 1H), 4.55 (br s, 2H), 4.23-4.16 (m, 1H), 3.85-3.78 (m, 1H), 3.04 (t, 2H), 2.25-1.79 (m, 10H), 1.76-1.43 (m, 6H), 1.17-1.05 (m, 1H), 0.54-0.48 (m, 2H), 0.27-0.22 (m, 2H); MS (EI) para $C_{30}H_{38}N_6O_3$: 531 (MH^+).

[00454] 2(AT): 6-(3-endo-{[(2,3-dimetilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 2 usando ácido 2,3-dimetilbenzoico en la etapa 4. ^{1}H NMR (400 MHz, DMSO-d_6): 8.81-8.79 (m, 1H), 8.65 (d, 1H), 8.23 (d, 1H), 7.97 (dd, 1H), 7.33-7.24 (m, 3H), 7.23-7.07 (m, 3H), 6.76 (d, 1H), 4.55 (br s, 2H), 4.47 (s, 2H), 3.85 (br s, 1H), 2.22 (s, 3H), 2.20 (s, 2H), 2.11 (s, 3H), 2.09-2.08 (m, 2H), 1.98-1.97 (m, 2H), 1.87-1.84 (m, 2H). MS(EI) para $C_{29}H_{32}N_4O_2$: 469 (MH^+).

[00455] 2(AU): 2-[(ciclopropilmetil)amino]-N4-[8-(5-

{[metil(metiloxi)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 2 usando clorhidrato de N,O-dimetilhidroxilamina en la etapa 2 y ácido 4-(aminocarbonil)-3-[(ciclopropilmetil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4. ^{1}H NMR (400 MHz, metanol-d_4): 8.55 (d, 1H), 7.93 (dd, 1H), 7.63 (d, 1H), 7.05 (d, 1H), 6.91 (dd, 1H), 6.75 (d, 1H), 4.63 (br s, 2H), 4.00 (m, 1H), 3.64 (s, 3H), 3.35 (s, 3H), 3.08 (d, 2H), 2.24 (m, 6H), 1.97 (d, 2H), 1.15 (m, 1H), 0.58 (m, 2H), 0.29 (m, 2H); MS (EI) para $C_{27}H_{34}N_6O_4$: 507 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 3:



[00456] El esquema de reacción 3 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 3, en donde R_1 es como se define en la especificación.

[00457] En el esquema de reacción 3, se agrega amoníaco al compuesto (A) bajo condiciones de reacción adecuadas para formar el compuesto (B). El compuesto B después se desprotege bajo condiciones acídicas, tal como con el uso de HCl, para remover BOC y formar el compuesto (C). Al compuesto (C) se agrega R_1COOH bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (D).

[00458] EJEMPLO 3: 6-[3-endo-({[2-fluoro-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida.

[00459] ETAPA 1: A ácido 6-(3-endo-(terc-butoxicarbonilamino)-8-azabiciclo[3.2.1]octan-8-il)nicotínico (preparada en el Ejemplo 2) (4.43 g, 12.8 mmol) en THF (100 ml) se agrega trietilamina (2.69 ml, 19.2 mmol) y cloroformiato de isobutilo (1.67 ml, 13.4 mmol). La mezcla se agita a 0°C por 1 hora, tiempo en el cual se agrega una solución de amoníaco acuoso concentrado al 28% (20 ml). La mezcla de reacción se agita por 3 horas, después el volumen se reduce *in vacuo*. La mezcla resultante se diluye con agua y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio anhidro, se filtra, se concentra *in vacuo* para proporcionar (1.85 g, 42% de rendimiento) de 8-(5-carbamoilpiridin-2-il)-8-azabiciclo[3.2.1]octan-3-endo-

ilcarbamato de terc-butilo, el cual se usa sin purificación adicional. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (s, 1H), 7.94-7.88 (d, 1H), 7.71 (s, 1H), 7.09 (s, 1H), 6.86 (s, 1H), 6.72-6.67 (d, 1H), 4.52-4.40 (m, 2H), 3.45-3.39 (m, 1H), 2.15-2.07 (m, 2H), 2.02-1.87 (m, 2H), 1.86-1.87 (m, 2H), 1.75-1.66 (m, 2H), 1.39 (s, 9H). MS (EI) para $C_{18}H_{26}N_4O_3$: 347 (MH^+).

[00460] ETAPA 2: A 8-(5-carbamoilpiridin-2-il)-8-azabiciclo[3.2.1]octan-3-endo-ilcarbamato de terc-butilo (1.85 g, 5.3 mmol) en metanol (20 ml) se agrega una solución de cloruro de hidrógeno 4N en dioxano (2.65 ml) y la mezcla de reacción se somete a reflujo por cinco minutos. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se concentra y se seca para proporcionar 6-(3-endo-amino-8-azabiciclo[3.2.1]octan-8-il)nicotinamida como la sal de clorhidrato (1.31 g, 100% de rendimiento). MS (EI) para $C_{13}H_{18}N_4O$: 247 (MH^+).

[00461] ETAPA 3: Una mezcla de sal de clorhidrato 8-(5-carbamoilpiridin-2-il)-8-azabiciclo[3.2.1]octan-3-endo-ilcarbamato de terc-butilo (0.050 g, 0.157 mmol), ácido 2-fluoro-3-metoxibenzoico (0.027 g, 0.157 mmol), HOAt (0.314 ml, 0.5 M de solución en dimetilformamida, 0.157 mmol), HATU (0.060 g, 0.157 mmol), y N-metilmorfolina (0.069 ml, 0.628 mmol) en dimetilformamida (0.5 mL) se agita a temperatura

ambiente por 16 h. La mezcla de reacción se vierte en agua (2 ml) y lo precipitado resultante se recolecta por filtración. La torta filtrada se lava con agua (2 x 1 mL), y se seca para dar 6-[3-endo-({[2-fluoro-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida (0.038 g, 61% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.41 (d, 1H), 7.94 (dd, 1H), 7.74 (br s, 1H), 7.36 (t, 1H), 7.20 (dd, 1H), 7.12 (br s, 1H), 6.95 (dd, 1H), 6.73 (d, 1H), 4.54 (br s, 2H), 3.90-3.82 (m, 4H), 2.28-2.18 (m, 2H), 2.14-2.03 (m, 2H), 2.00-1.88 (m, 2H), 1.83 (d, 2H); MS (EI) para $C_{21}H_{23}ClN_4O_3$: 415 (MH^+).

[00462] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [(3B)-(3Q)]. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00463] (3B): 6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 3 usando ácido 2-metil-3-metoxibenzoico en la etapa 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.62 (d, 1H), 8.22 (d, 1H), 7.94 (dd, 1H), 7.74 (br s, 1H), 7.23 (t, 1H), 7.12 (br s, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.73 (d, 1H), 4.54 (br s, 2H), 3.84 (m, 1H), 3.80 (s, 3H), 2.20 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H); MS (EI) para

$C_{22}H_{26}N_4O_3$: 395 (MH^+).

[00464] (3C): 6-[3-endo-({[2-cloro-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 3 usando ácido 2-cloro-3-metoxibenzoico en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.38-8.34 (m, 1H), 7.94 (dd, 1H), 7.74 (br s, 1H), 7.31-7.25 (m, 1H), 7.23-7.16 (m, 1H), 7.12 (br s, 1H), 7.09-7.03 (m, 1H), 6.73 (d, 1H), 4.55 (br s, 2H), 3.87 (s, 3H), 2.28-2.17 (m, 2H), 2.12-1.90 (m, 4H), 1.84 (d, 2H); MS (EI) para $C_{21}H_{23}FN_4O_3$: 399 (MH^+).

[00465] (3D): 6-(3-endo-{[(4-amino-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 3 usando ácido 4-amino-2-metilbenzoico en la etapa 3. ^{1}H NMR (400 MHz, CD_3OD): 8.62 (s, 1H), 8.01-7.96 (d, 1H), 7.18-7.14 (d, 1H), 6.77-6.73 (d, 1H), 6.55-6.50 (m, 2H), 4.64-4.58 (br. s, 2H), 4.00-3.93 (m, 1H), 2.32 (s, 3H), 2.31-2.11 (m, 6H), 1.91 (s, 3H), 1.90-1.88 (m, 2H). MS (EI) para $C_{21}H_{25}N_5O_2$: 380 (MH^+).

[00466] (3E): 6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 3 usando ácido 4-(hidroximetil)benzoico en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.15 (d,

1H), 7.95 (dd, 1H), 7.79-7.70 (m, 3H), 7.41 (d, 2H), 7.12 (br s, 1H), 6.75 (d, 1H), 5.32 (t, 1H), 4.62-4.52 (m, 4H), 3.88-3.82 (m, 1H), 2.26-2.16 (m, 2H), 2.13-1.86 (m, 6H); MS (EI) para $C_{21}H_{24}N_4O_3$: 379 (M-H).

[00467] (3F): N-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 3 usando monoamida del ácido tereftálico en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.54 (br s, 1H), 8.16 (d, 1H), 8.12-8.04 (m, 1H), 7.90 (br s, 1H), 7.47 (d, 2H), 7.41 (d, 2H), 7.38-7.26 (m, 2H), 6.99 (br s, 1H), 4.64 (br s, 2H), 4.53 (s, 2H), 3.92-3.85 (m, 1H), 3.83 (s, 3H), 2.30-2.20 (m, 2H), 2.18-1.92 (m, 6H); MS (EI) para $C_{22}H_{26}N_4O_4$: 409 (M-H).

[00468] (3G): 6-[3-endo-({[4-(hidroximetil)-3-(metiloxi)fenil]carbonil}-amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 3 usando ácido 4-(hidroximetil)-3-metoxibenzoico (sintetizado de conformidad con el reactivo de la preparación 24) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.32 (d, 1H), 8.10 (br s, 1H), 7.98-7.92 (m, 3H), 7.86-7.80 (m, 2H), 7.75 (br s, 1H), 7.53 (br s, 1H), 7.13 (br s, 1H), 6.75 (d, 1H), 4.57 (br s, 2H), 3.91-3.83 (m, 1H), 2.28-2.17 (m, 2H), 2.14-1.96 (m, 4H), 1.91 (d, 2H); MS (EI) para $C_{22}H_{23}N_5O_3$: 392 (M-H).

[00469] (3J): 6-[3-endo-({[2-(4-hidroxibut-1-in-1-il)-3-(metiloxi)fenil]-carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 3 usando ácido 2-(4-hidroxibut-1-inil)-3-metoxibenzoico (sintetizado de conformidad con el reactivo de la preparación 28) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO: 8.61 (d, 1H), 8.21 (d, 1H), 7.95 (dd, 1H), 7.74 (br s, 1H), 7.33 (t, 1H), 7.15-7.06 (m, 2H), 6.94 (d, 1H), 6.73 (d, 1H), 4.83 (br s, 1H), 4.55 (br s, 2H), 3.89-3.84 (m, 1H), 3.82 (s, 3H), 3.58-3.52 (m, 2H), 2.55 (t, 2H), 2.26-2.20 (m, 2H), 2.15-2.05 (m, 2H), 1.97-1.92 (m, 2H), 1.83 (d, 2H); MS (EI) para $C_{25}H_{28}N_4O_4$: 449 (MH+).

[00470] (3K): N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[2-(metiloxi)etil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 3 usando ácido 4-aminocarbonil-3-(2-metoxietilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3. ^{1}H NMR (400 MHz, d_4-MeOH): 8.53 (d, 1H), 7.89 (dd, 1H), 7.54 (d, 1H), 7.80 (d, 1H), 6.84 (dd, 1H), 6.66 (d, 1H), 4.54 (br, 2H), 3.91 (tr, 1H), 2.55 (tr, 2H), 3.30 (tr, 2H), 3.29 (s, 3H), 2.20-2.09 (m, 7H), 1.89 (m, 2H); MS (EI) para $C_{24}H_{30}N_6O_4$: 467 (MH^+).

[00471] (3L): N4-{8-[5-(aminocarbonil)piridin-2-il]-8-

azabiciclo[3.2.1]oct-3-endo-il}-2-[(2-morfolin-4-iletil)oxibencen-1,4-dicarboxilato. Preparado de conformidad con el método del ejemplo 3 usando ácido 4-aminocarbonil-3-(2-morfolinoetoxi)benzoico (sintetizado de conformidad con el reactivo de la preparación 27) en la etapa 3. ^{1}HNMR (400 MHz, d_4-MeOH): 8.50(d, 1H), 8.40(d, 1H), 8.23(dd, 1H), 7.68(d, 1H), 7.62(s, 1H), 7.55(d, 1H), 7.15(d, 1H), 4.72(s, 2H), 4.61(s, 2H), 4.09-3.99(m, 4H), 3.62-3.60(m, 4H), 2.37-2.26(m, 6H), 2.15(d, 2H). MS(EI) para $C_{27}H_{34}N_6O_5$: 523(MH^+).

[00472] (3M): N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(4-hidroxiciclohexil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 3 usando ácido 4-(aminocarbonil)-3-[(trans-4-hidroxiciclohexil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.62 (d, 1H), 8.20 (m, 2H), 7.95 (dd, 1H), 7.91 (br s, 1H), 7.75 (br s, 1H), 7.66 (d, 1H), 7.27 (br s, 1H), 7.12 (br s, 1H), 7.06 (br s, 1H), 6.96 (s, 1H), 6.83 (d, 1H), 6.75 (d, 1H), 4.60 (d, 1H), 4.57 (br s, 2H), 3.83 (m, 1H), 3.48 (m, 1H), 2.24 (m, 2H), 2.10-1.81 (m, 10H), 1.25 (m, 4H); MS (EI) para $C_{27}H_{34}N_6O_4$: 507 (MH^+).

[00473] (3N): 2-(acetilamino)-N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-

90S.

il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 3 usando ácido 3-(acetilamino)-4-(aminocarbonil)benzoico (sintetizado de conformidad con el reactivo de la preparación 29) en la etapa 3. ^{1}H NMR (400 MHz, d_4-MeOH): 8.68 (d, 1H), 8.53 (d, 1H), 7.89 (dd, 1H), 7.73 (d, 1H), 7.42 (dd, 1H) 6.67 (d, 1H),4.54 (br, 2H), 3.93 (tr, 1H), 2.18 (m, 5H), 2.10 (s, 3H), 2.08 (m, 3H), 1.86 (m, 2H);MS (EI) para $C_{23}H_{26}N_6O_4$: 451 (MH^+).

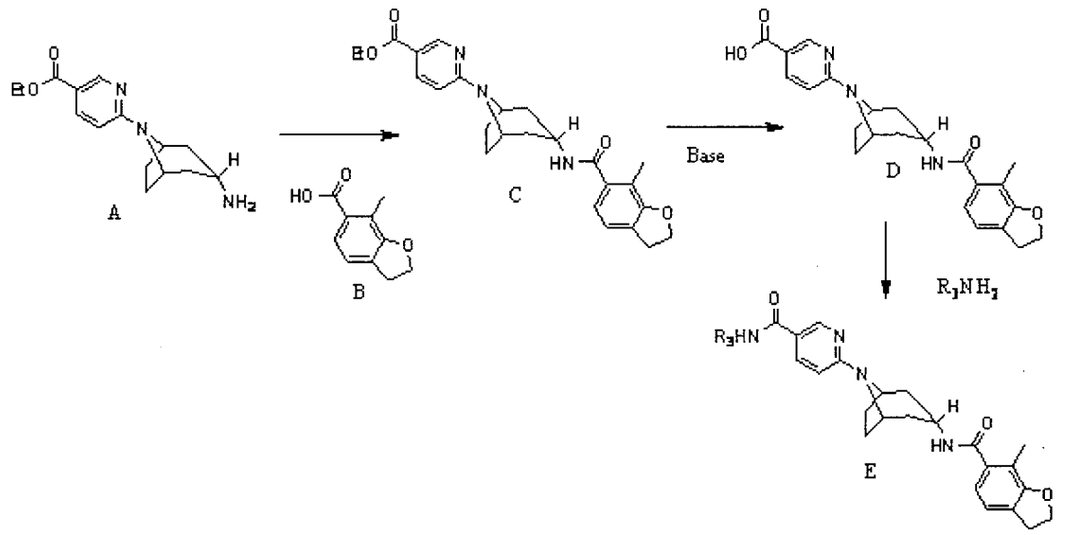
[00474] (3O): N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-1H-indol-4,7-dicarboxamida. Preparada de conformidad con el método del ejemplo 3 usando ácido 7-carbamoil-1H-indol-4-carboxílico (sintetizado de conformidad con el reactivo de la preparación 30) en la etapa 3. ^{1}H NMR (400 MHz, DMSO- d_6): 11.28 (s, 1H), 8.64 (s, 1H), 8.59 (d, 1H), 8.22 (d, 1H), 8.18 (bs, 1H), 8.00 (dd, 1H), 7.74 (d, 1H), 7.52 (bs, 1H), 7.42 (s, 1H), 7.32 (m, 2H), 6.78 (bs, 1H), 6.76 (d, 1H), 4.54 (bs, 2H), 3.84 (m, 1H), 2.28 (m, 2H), 2.08 (m, 4H), 1.96 (m, 2H). MS (EI) para $C_{23}H_{24}N_6O_3$: 432 (MH^+).

[00475] (3P): N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[2-(metilsulfonil)etil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 3 usando ácido 4-(aminocarbonil)-3-{[2-(metilsulfonil)etil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación

39) en la etapa 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.64 (d, 1H), 8.32 (t, 1H), 8.19 (d, 1H), 7.95 (m, 2H), 7.75 (br s, 1H), 7.69 (d, 1H), 7.36 (br s, 1H), 7.12 (br s, 1H), 7.01 (s, 1H), 7.01 (s, 1H), 6.95 (d, 1H), 6.75 (d, 1H), 4.57 (br s, 2H), 3.84 (m, 1H), 3.66 (m, 2H), 3.46 (t, 2H), 3.03 (s, 3H), 2.21 (m, 2H), 2.08 (m, 2H), 2.00 (m, 2H), 1.90 (d, 2H); MS (EI) para $C_{24}H_{30}N_6O_5S$: 515 (MH^+).

[00476] (3Q): N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(ciclobutilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 3 usando ácido 4-(aminocarbonil)-3-[(ciclobutil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO: 8.62 (d, 1H), 8.31 (d, 1H), 8.18 (d, 1H), 7.98-7.92 (m, 2H), 7.74 (br s, 1H), 7.67 (d, 1H), 7.32 (br s, 1H), 7.12 (br s, 1H), 6.89 (d, 1H), 6.85 (s, 1H), 6.75 (d, 1H), 4.57 (br s, 2H), 4.01-3.91 (m, 1H), 3.86-3.79 (m, 1H), 2.44-2.33 (m, 2H), 2.26-2.16 (m, 2H), 2.13-1.70 (m, 10H); MS (EI) para $C_{25}H_{30}N_6O_3$: 463 (MH+).

ESQUEMA DE REACCIÓN SINTÉTICA 4:



[00477] El esquema de reacción 4 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 4, en donde R_3 es como se define en la especificación.

[00478] En el esquema de reacción 4, el compuesto (B) se agrega al compuesto (A) bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (C). El carboxilato del compuesto C se hidroliza con una base, tal como LiOH, para formar el compuesto (D). Al compuesto (D) se agrega R_3NH_2 bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HOBT y EDCI, para condensar y formar la amida unida en el compuesto (E).

[00479] EJEMPLO 4: N-(1-etilazetidin-3-il)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida.

[00480] ETAPA 1: A una solución de ácido 7-metil-2,3-dihidro-1-benzofuran-6-carboxílico (sintetizado en la preparación del reactivo 16) (1.72 g, 9.63 mmol), HATU (3.66 g, 9.63 mmol), y DIEA (6.70 ml, 38.5 mmol) en DMF (25 mL) se agrega 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxilato de etilo (sintetizado en el Ejemplo 1) (2.68 g, 9.63 mmol). La mezcla se agita a 30°C por 22 horas, tiempo en el cual se divide entre acetato de etilo y bicarbonato de sodio saturado. La capa orgánica se separa y se lava con cloruro de litio y después salmuera. La capa orgánica se seca sobre sulfato de sodio anhidro, se filtra después se concentra in vacuo para proporcionar (5.39 g, 129%) de 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxilato de etilo el cual se usa sin purificación adicional. ^{1}H NMR (400 MHz, DMSO-d_6): 8.67-8.64 (s, 1H), 8.18-8.13 (s, 1H), 7.98-7.89 (d, 1H), 7.13-7.07 (d, 1H), 6.83-6.73 (m, 2H), 4.64-4.50 (m, 4H), 4.29-4.21 (m, 2H), 3.88-3.81 (m, 1H), 3.25-3.15 (m, 2H), 2.26-2.18 (d, 2H), 2.16-2.12 (s, 3H), 2.10-1.85 (m, 6H), 1.32-1.26 (m, 3H). MS (EI) para $C_{25}H_{29}N_3O_4$: 436 (MH^+).

[00481] ETAPA 2: A una solución de 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxilato de etilo (4.19 g, 9.63 mmol) en metanol (100 ml) se agrega 2M hidróxido de litio (24.0 ml, 48.0 mmol). La mezcla se agita a 50°C por 24 horas, tiempo en el cual el volumen se reduce in vacuo, el pH se ajusta a 5 con ácido clorhídrico 1 N, y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio anhidro, se filtra, se concentra in vacuo para proporcionar (3.27 g, 83%) de ácido 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxílico, el cual se usa sin purificación adicional. ^{1}H NMR (400 MHz, DMSO-d_6): 12.65-12.34 (br. s, 1H), 8.64-8.61 (s, 1H), 8.16-8.12 (d, 1H), 7.93-7.89 (d, 1H), 7.13-7.07 (d, 1H), 6.82-6.79 (d, 1H), 6.76-6.72 (d, 1H), 4.62-4.50 (m, 4H), 3.88-3.81 (m, 1H), 3.25-3.15 (m, 2H), 2.26-2.18 (d, 2H), 2.15-2.12 (s, 3H), 2.10-1.85 (m, 6H). MS (EI) para $C_{23}H_{25}N_3O_4$: 408 (MH^+).

[00482] ETAPA 3: A una solución de ácido 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxílico (236 mg, 0.580 mmol), HOBT (94 mg, 0.696 mmol), N-metilmorfolina (127 µL, 1.16 mmol) y EDCI (133 mg, 0.696 mmol) en DMF (3 mL) se agrega 3-aminoazetidin-1-carboxilato de terc-butilo (120 mg,

0.696 mmol). La mezcla de reacción se agita a temperatura ambiente por 5 h, tiempo en el cual se concentra in vacuo después se purifica por cromatografía instantánea (5% de metanol en eluyente diclorometano) para proporcionar 3-({[6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il]carbonil}amino)azetidin-1-carboxilato de 1,1-dimetiletilo (270 mg, 83%) como un polvo blanco. MS (EI) para $C_{31}H_{39}N_5O_5$: 560 (M-H).

[00483] ETAPA 4: A una solución de 3-({[6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il]carbonil}amino)azetidin-1-carboxilato de 1,1-dimetiletilo (270 mg, 0.480 mmol) en acetonitrilo (5 mL) se agrega una solución de cloruro de hidrógeno (4.0M en dioxano, 500 µL) a temperatura ambiente y se agita por 15 h. La suspensión blanca se filtra y el producto se lava con éter de dietilo para dar sal de clorhidrato de N-azetidin-3-il-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida (233 mg, 97%). MS (EI) para $C_{26}H_{31}N_5O_3$: 462 (MH^+).

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[00484] ETAPA 5: A una solución de sal de clorhidrato de N-azetidin-3-il-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida (50 mg, 0.100 mmol) en metanol (1 mL) y tetrahidrofurano (1 mL) a 0°C se agrega acetaldehído (11 µL, 0.200 mmol). La mezcla de reacción se agita a 0°C por 20 min, tiempo en el cual se agrega cianoborohidruro de sodio (13 mg, 0.200 mmol) después se agita a temperatura ambiente por 5 h. La mezcla de reacción se apaga con ácido clorhídrico acuoso 1N después se diluye con agua. La solución se purifica por HPLC preparatoria (0.1% de acetato de amonio acuoso-acetonitrilo) para proporcionar el compuesto del título (11.7 mg) como un polvo blanco. ^{1}H NMR (400 MHz, DMSO-d_6): 8.59 (d, 1H), 8.47 (d, 1H), 8.12 (d, 1H), 7.94 (dd, 1H), 7.10 (d, 1H), 6.80 (d, 1H), 6.74 (d, 1H), 4.55-4.51 (m, 4H), 4.45-4.40 (m, 1H), 3.85-3.79 (br m, 1H), 3.51 (t, 2H), 3.20 (t, 2H), 2.87 (t, 2H), 2.42-2.37 (m, 2H), 2.22-2.17 (m, 2H), 2.13 (s, 3H), 2.10-2.04 (m, 2H), 1.99-1.96 (m, 2H), 1.86-1.83 (m, 2H), 0.87 (t, 3H). MS (EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00485] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [(4A)-(4AC)]. Se obtienen comercialmente reactivos de partida alternativos a menos que se indique de otra manera.

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[00486] (4B): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[3-(metiloxi)fenil]etil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (S)-1-(3-metoxifenil)etanamina en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.72 (m, 1H), 8.60 (d, 1H), 8.18 (d, 1H), 8.13 (m, 1H), 7.22 (t, 1H), 7.11 (d, 1H), 6.98 (m, 1H), 6.94 (m, 2H), 6.80 (m, 2H), 5.12 (m, 1H), 4.66 (bs, 2H), 4.52 (m, 2H), 3.86 (m, 1H), 3.74 (s, 3H), 3.20 (m, 2H), 2.24 (m, 2H), 2.16 (s, 3H), 2.09 (m, 2H), 2.02 (m, 2H), 1.94 (m, 2H), 1.46 (d, 3H). MS (EI) para $C_{32}H_{36}N_4O_4$: 541 (MH^+).

[00487] (4C): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (4-(4-metilpiperazin-1-il)fenil)metanamina en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.70 (t, 1H), 8.63 (d, 1H), 8.13 (d, 1H), 7.96 (dd, 1H), 7.15 (d, 2H), 7.11 (d, 1H), 6.88 (m, 2H), 6.80 (d, 1H), 6.74 (d, 1H), 4.58 (m, 4H), 4.34 (d, 2H), 3.82 (m, 1H), 3.20 (m, 2H), 3.08 (m, 4H), 2.43 (m, 4H), 2.21 (s, 3H), 2.20 (m, 2H), 2.13 (s, 3H), 2.07 (m, 2H), 1.97 (m, 2H), 1.84 (d, 2H). MS (EI) para $C_{35}H_{42}N_6O_3$: 595 (MH^+).

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[00488] (4D): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Aislado como sal de clorhidrato. Preparado de conformidad con el método del ejemplo 4 usando amoníaco en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, CD_3OD): 8.44 (d, 1H), 8.36 (d, 1H), 8.32 (dd, 1H), 7.29 (d, 1H), 7.10 (d, 1H), 6.85 (d, 1H), 4.71 (br s, 2H), 4.56 (t, 2H), 4.07 (m, 1H), 3.23 (t, 2H), 2.34 (m, 4H), 2.23 (m, 2H), 2.21 (s, 3H), 2.13 (d, 2H); MS (EI) para $C_{23}H_{26}N_4O_3$: 407 (MH^+).

[00489] (4E): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (S)-1-(4-(4-metilpiperazin-1-il)fenil)etanamina (sintetizado de conformidad con el reactivo de la preparación 3) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, $CDCl_3$ p/10% CD_3OD): 8.59 (d, 1H), 7.88 (dd, 1H), 7.27 (d, 1H), 7.06 (d, 1H), 6.83 (dd, 4H),6.57 (d, 1H), 5.18 (m, 1H), 4.57 (t, 3H), 4.06 (m, 1H), 3.26 (t, 2H), 3.12 (dd, 4H), 2.70 (s, 4H), 2.55 (dd, 4H), 2.35-2.20 (br m, 8H), 2.19-2.04 (br m, 4H), 1.83 (br d, 2H), 1.51 (d, 3H), 1.41 (s, 2H). MS (EI) para $C_{36}H_{44}N_6O_3$: 609 (MH^+).

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[00490] (4F): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{4-(4-metilpiperazin-1-il)fenilmetil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando 4-(1-metilpiperidin-4-il)bencilamina (sintetizado de conformidad con el reactivo de la preparación 2) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, CD_3OD): 8.41 (d, 1H), 8.37 (dd, 1H), 7.38 (d, 1H), 7.31 (dd, 4H), 7.10 (d, 1H), 6.85 (d, 1H), 4.75 (br s, 2H), 4.57 (t, 2H), 4.55 (s, 2H), 4.09 (t, 1H), 3.60 (br d, 2H),3.21 (br m, 6H), 2.91 (s, 4H), 2.88 (s, 2H), 2.40-1.85 (br m, 11H). MS (EI) para $C_{36}H_{43}N_5O_3$: 593 (MH^+).

[00491] (4G): N-[(4-{[2-(dietilamino)etil]oxi}fenil)metil]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando 2-[4-(aminometil)fenoxi]-N,N-dietiletilamina (sintetizado de conformidad con el reactivo de la preparación 4) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR(400 MHz, CD_3OD): 8.40 (d, 1H), 8.39 (dd, 1H), 7.39-7.33 (m, 3H), 7.11 (d, 1H), 7.01- 6.99 (m, 2H), 6.86 (d, 1H), 4.59 (s, 2H), 4.56- 4.36 (m, 4H), 4.34- 4.33 (m, 2H), 4.09 (t, 1H), 3.60 (q, 2H), 3.32-3.31(m, 3H), 3.23 (t, 2H), 2.38-2.33 (m, 4H), 2.32- 2.24 (m, 8H), 1.38(s, 2H), 1.37(s, 2H), 1.35 (s, 2H); MS(EI) para $C_{36}H_{45}N_5O_4$: 612 (MH^+).

[00492] (4H): Clorhidrato de N-(ciclopropilmetil)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando ciclopropilmetanamina en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.70-8.60 (br. s, 1H), 8.52-8.47 (s, 1H), 8.27-8.16 (d, 2H), 7.22-7.09 (m, 2H), 6.84-6.79 (d, 1H), 4.78-4.65 (br. s, 2H), 4.59-4.49 (m, 2H), 3.93-3.88 (m, 1H), 3.25-3.10 (m, 4H), 2.32-2.24 (d, 2H), 2.18-1.97 (m, 9H), 1.07-0.97 (m, 1H), 0.47-0.40 (m, 2H), 0.26-0.19 (m, 2H). MS (EI) para $C_{27}H_{32}N_4O_3$: 461 (MH^+).

[00493] (4I): N-[2-(dietilamino)etil]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Aislado como sal de clorhidrato. Preparado de conformidad con el método del ejemplo 4 usando N,N-dietiletano-1,2-diamina en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 9.08 (br s, 1H), 8.60 (s, 1H), 8.30-8.20 (m, 2H), 7.25-7.10 (m, 2H), 6.81 (d, 1H), 4.77 (br s, 2H), 4.54 (t, 2H), 3.87 (br s, 1H), 3.66-3.61 (m, 2H), 3.25-3.15 (m, 8H), 2.30-1.95 (m, 11H), 1.25-1.21 (t, 6H). MS (EI) para $C_{29}H_{39}N_5O_3$: 506 (MH^+).

[00494] (4J): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-metilpirrolidin-3-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (*R*)-1-metilpirrolidin-3-amina en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR(400 MHz, CD_3OD): 8.50 (s, 1H), 8.40(s, 1H), 7.38 (d, 1H), 7.11 (d, 1H), 6.08 (d, 1H), 4.80(s, 2H), 4.65 (s, 1H), 4.55(t, 2H), 4.08-4.03 (m, 2H), 3.98-3.88(m, 1H), 3.77-3.75(m, 2H), 3.49-3.41(m, 2H), 3.34(t, 4H), 3.05(s, 1H), 2.98(s, 2H), 2.72-2.61 (m, 1H), 2.38-2.19(m, 8H), 2.18 (s, 3H); MS(EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00495] (4K): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-metilpirrolidin-3-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (*S*)-1-metilpirrolidin-3-amina en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, CD_3OD): 8.50(s, 1H), 8.40(s, 1H), 7.38 (d, 1H), 7.10 (d, 1H), 6.85 (d, 1H), 4.76 (s, 2H), 4.66-4.60(m, 1H), 4.57(t, 3H), 4.10-4.08(m, 2H), 3.80-3.77 (m, 2H), 3.46-3.40 (m, 1H), 3.23(t, 3H), 3.18 (s, 2H), 3.05 (s, 2H), 2.70-2.60(m, 1H), 2.38-2.19(m, 8H), 2.26 (s, 3H); MS(EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00496] (4L): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(1-metilpiperidin-4-il)piridin-3-carboxamida. Preparada de

conformidad con el método del ejemplo 4 usando 1-metilpiperidin-4-amina en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.62-8.58 (s, 1H), 8.15-8.11 (d, 1H), 8.05-8.00 (d, 1H), 7.95-7.90 (d, 1H), 7.13-7.09 (d, 1H), 6.82-6.78 (d, 1H), 6.76-6.72 (d, 1H), 4.58-4.48 (m, 4H), 3.87-3.78 (m, 1H), 3.24-3.15 (m, 2H), 3.00-2.91 (m, 1H), 2.39-2.30 (br. s, 4H), 2.25-2.17 (d, 2H), 2.15-2.12 (s, 3H), 2.11-2.03 (m, 2H), 2.01-1.95 (m, 2H), 1.93-1.90 (s, 3H), 1.87-1.77 (m, 4H), 1.68-1.55 (m, 2H). MS (EI) para $C_{27}H_{37}N_5O_3$: 504 (MH^+).

[00497] (4M): N-[(1S)-1-(4-{[2-(dietilamino)etil]oxi}fenil)etil]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (S)-2-[4-(1-aminoetil)fenoxi]-N,N-dietiletilamina (sintetizado de conformidad con el reactivo de la preparación 4) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, CD_3OD): 8.59 (d, 1H), 7.97 (dd, 1H), 7.35 (d, 2H), 7.09 (d, 1H), 6.97 (d, 2H), 6.84 (d, 1H), 6.75 (d, 1H), 5.22-5.14 (m, 1H), 4.64-4.52 (m, 4H), 4.30-4.26 (m, 2H), 4.01-3.94 (m, 1H), 3.51-3.43 (m, 2H), 3.27-3.15 (m, 6H), 2.33-2.09 (m, 9H), 1.89 (d, 2H), 1.53 (d, 3H), 1.31 (t, 6H); MS (EI) para $C_{37}H_{47}N_5O_4$: 626 (MH^+).

[00498] (4N): 7-metil-N-(8-{5-[(4-metilpiperazin-1-il)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2,3-dihidro-1-benzofuran-6-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando 1-metilpiperazina en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.29 (d, 1H), 7.61 (dd, 1H), 7.05 (d, 1H), 6.81 (d, 1H), 6.54 (d, 1H), 6.22 (d, 1H), 4.60 (m, 4H), 4.24 (q, 1H), 3.39 (br s, 3H), 3.24 (t, 2H), 2.45 (br s, 3H), 2.37-2.12 (br m, 7H), 2.05-1.95 (br m, 3H), 1.81 (br d, 2H), 1.25 (s, 3H). MS (EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00499] (4O): N-(1-etilpiperidin-3-il)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando 1-etilpiperidin-3-amina en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.64 (br s, 1H), 7.96 (br s, 1H), 7.05 (d, 1H) 6.87 (d, 1H), 6.54 (d, 1H), 6.23 (d, 1H), 4.58 (m, 2H), 4.36-4.22 (br m, 2H), 3.24 (t, 2H), 2.75-2.15 (br m, 11H), 2.07-1.95 (br m, 2H), 1.80 (br d, 4H), 1.60 (br s, 2H), 1.25 (s, 1H), 1.09 (br s, 2H)). MS (EI) para $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00500] (4P): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-(1-metiletil)pirrolidin-3-il]piridin-3-carboxamida.

Preparada de conformidad con el método del ejemplo 4 usando (R)-1-isopropilpirrolidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.61 (d, 1H), 8.27 (br s, 1H), 8.13 (d, 1H), 7.95 (dd, 1H), 7.11 (d, 1H), 6.80 (d, 1H), 6.76 (d, 1H), 4.56-4.51 (m, 4H), 4.41 (br m, 1H), 3.82 (br m, 1H), 3.20 (t, 2H), 2.23-2.17 (m, 2H), 2.13 (s, 3H), 2.11-2.04 (m, 2H), 2.01-1.96 (m, 2H), 1.87-1.82 (m, 2H), 1.13 (br m, 6H). MS (EI) para $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00501] (4Q): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-metilpiperidin-3-il]piridin-3-carboxamida.

Preparada de conformidad con el método del ejemplo 4 usando (S)-1-metilpiperidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (s, 1H), 8.13 (d, 1H), 7.93 (dd, 1H), 7.11 (d, 1H), 6.80 (d, 1H), 6.76 (d, 1H), 4.56-4.51 (m, 4H), 3.84-3.79 (br m, 2H), 3.20 (t, 4H), 2.22-2.17 (m, 2H), 2.13 (s, 3H), 2.10-2.04 (m, 2H), 2.01-1.96 (m, 2H), 1.87-1.81 (m, 4H). MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00502] (4R): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-(1-metiletil)pirrolidin-3-il]piridin-3-carboxamida.

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Preparada de conformidad con el método del ejemplo 4 usando (S)-1-isopropilpirrolidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.64 (d, 1H), 7.95 (dd, 1H), 7.05 (d, 1H), 6.80 (d, 1H), 6.52 (d, 1H), 6.23 (d, 1H), 4.74 (br s, 1H), 4.60 (br s, 1H), 4.59 (t, 3H), 4.23 (q, 1H), 3.24 (t, 2H), 3.18 (br s, 1H), 2.98 (br d, 1H), 2.73 (dd, 1H), 2.59 m, 1H), 2.47-2.32 (br m, 3H), 2.24 (s, 3H), 2.25-2.19 (br m, 2H), 2.01 (q, 2H), 1.82 (d, 3H), 1.19 (t, 6H). MS (EI) para $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00503] (4S): N-[(3S)-1-etilpirrolidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (S)-1-etilpirrolidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.60 (d, 1H), 7.92 (d, 1H), 7.08 (d, 1H), 6.87 (d, 1H), 6.53 (d, 1H), 6.40 (d, 1H), 6.24 (d, 1H), 4.62 (m, 4H), 4.23 (q, 1H), 3.24 (t, 2H), 2.97 (m, 1H), 2.76 (br m, 1H), 2.55-2.45 (br m, 3H), 2.43-2.26 (br m, 6H), 2.25-2.18 (br m, 2H), 2.02 (m, 3H), 1.82 br d, 2H), 1.72 (m, 1H), 1.12 (t, 3H). MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

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[00504] (4T): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]-amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[1-(1-metiletil)piperidin-4-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando 1-(1-metiletil)piperidin-4-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (d, 1H), 7.91 (d, 1H), 7.05 (d, 1H), 6.87 (d, 1H), 6.53 (d, 1H), 6.21 (d, 1H), 5.77 (d, d, 1H), 4.60 (m, 4H), 4.22 (q, 1H), 3.98(m, 1H), 3.24 (t, 2H), 2.81 (d, 2H), 2.74 (m, 1H), 2.32 (m, 8H), 2.22 (m, 2H), 2.11-1.98 (br m, 4H), 1.82 (br m, 4H), 1.67 (br s, 2H), 1.52 (m, 2H), 1.05 (d, 6H). MS (EI) para $C_{31}H_{41}N_5O_3$: 532 (MH^+).

[00505] (4U): N-[1-etilpiperidin-4-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando 1-etilpiperidin-4-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.56 (d, 1H), 7.91 (d, 1H), 7.04 (d, 1H), 6.86 (d, 1H), 6.53 (d, 1H), 6.22 (d, 1H), 5.86 (d, 1H), 4.60 (m, 4H), 4.22 (q, 1H), 4.01 (m, 1H), 3.24 (t, 2H), 2.93 (br d, 2H), 2.47 (q, 2H), 2.37-2.28 (br m, 5H), 2.27-1.96 (br m, 6H), 1.81 (br d, 2H), 1.61 (m, 2H), 1.11 (t, 3H). MS (EI) para $C_{30}H_{39}N_5O_3$: 518 (MH^+).

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[00506] (4V): N-[(3R)-1-etilpiperidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (R)-1-metilpiperidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (s, 1H), 8.13 (d, 1H), 7.93 (dd, 1H), 7.11 (d, 1H), 6.80 (d, 1H), 6.75 (d, 1H), 4.56-4.51 (m, 4H), 3.82 (br m, 1H), 3.20 (t, 2H), 2.22-2.17 (m, 2H), 2.14 (s, 3H), 2.10-2.04 (m, 2H), 2.00-1.96 (m, 2H), 1.87-1.81 (m, 4H), 1.07 (br m, 3H). MS (EI) para $C_{30}H_{39}N_5O_3$: 516 (M-H).

[00507] (4W): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[1-(1-metiletil)azetidin-3-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando acetona en la etapa 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (d, 1H), 8.50 (br s, 1H), 8.13 (d, 1H), 7.94 (dd, 1H), 7.11 (d, 1H), 6.80 (d, 1H), 6.75 (d, 1H), 4.56-4.51 (m, 4H), 4.40 (br m, 1H), 3.82 (br m, 1H), 3.61 (br s, 1H), 3.22-3.18 (m, 2H), 2.21-2.19 (m, 2H), 2.14 (s, 3H), 2.11-2.04 (m, 2H), 2.00-1.96 (m, 2H), 1.87-1.82 (m, 2H), 0.91 (d, 6H). MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

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[00508] (4X): N-(1-metilazetidin-3-il)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando 1-metilazetidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (d, 1H), 8.48 (d, 1H), 8.13 (d, 1H), 7.94 (dd, 1H), 7.11 (d, 1H), 6.80 (d, 1H), 6.74 (d, 1H), 4.56-4.51 (m, 4H), 4.43-4.38 (m, 1H), 3.82 (br m, 1H), 3.56-3.52 (m, 2H), 3.22-3.18 (m, 4H), 2.94-2.91 (m, 2H), 2.34-2.32 (m, 1H), 2.24 (s, 3H), 2.14 (s, 3H), 2.10-2.05 (m, 2H), 1.99-1.95 (m, 2H). MS (EI) para $C_{27}H_{33}N_5O_3$: 476 (MH^+).

[00509] (4Y): N-[(3R)-1-etilpirrolidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (R)-1-etilpirrolidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00510] (4Z): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-(1-metiletil)piperidin-3-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando

(R)-1-isopropilpiperidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (s, 1H), 7.93 (d, 1H), 7.04 (d, 1H), 6.86 (d, 1H), 6.54 (d, 1H), 6.31 (d, 1H), 4.59 (m, 4H), 4.21 (m, 2H), 3.23 (t, 2H), 2.75 (m, 1H), 2.70-2.50 (br m, 3H), 2.40-1.45 (br m, 8H), 1.01 (dd, 6H). MS (EI) para $C_{31}H_{41}N_5O_3$: 532 (MH^+).

[00511] (4AA): N-[(3S)-1-etilpiperidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (S)-1-etilpiperidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. MS (EI) para $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00512] (4AB): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-(1-metiletil)piperidin-3-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (S)-1-isopropilpiperidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.60 (d, 1H), 7.93 (d, 1H), 7.04 (d, 1H), 6.88 (d, 1H), 6.54 (d, 1H), 6.30 (d, 1H), 4.59 (m, 4H), 4.21 (m, 2H), 3.23 (t, 2H), 2.79-2.42 (br m, 4H), 2.39-2.30 (br m, 6H), 2.28-2.11

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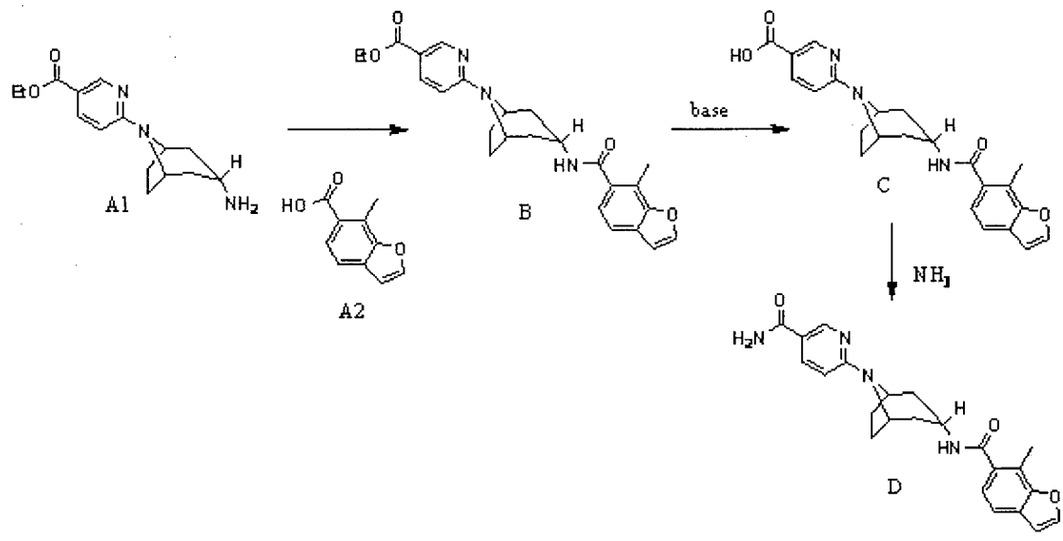
(br m, 2H), 2.03 (m, 2H), 1.92-1.44 (br m, 6H), 1.01 (dd, 6H). MS (EI) para $C_{31}H_{41}N_5O_3$: 532 (MH^+).

[00513] (4AC): 6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]-amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-metilpiperidin-3-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 4 usando (R)-1-metilpiperidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 4, después de la omisión de las etapas 5 y 6. MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 5:



[00514] El esquema de reacción 5 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 5.

[00515] En el esquema de reacción 5, el compuesto (A2) se agrega al compuesto (A1) bajo condiciones de reacción

apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (B). El carboxilato del compuesto B se hidroliza con una base, tal como KOH, para formar el compuesto (C). Al compuesto (C) se agrega NH_3 bajo condiciones de reacción apropiadas para formar el compuesto (D).

[00516] EJEMPLO 5: 6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida.

[00517] ETAPA 1: Una solución de 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxilato de etilo (191 mg, 0.69 mmol, sintetizado en el Ejemplo 1, etapa 2, ácido 7-metil-1-benzofuran-6-carboxílico (sintetizado en la preparación del reactivo 15) (122 mg, 0.69 mmol), HATU (262 mg, 0.69 mmol), y diisopropiletilamina (267 mg, 2.07 mmol) en DMF (5 mL) se agita a temperatura ambiente por 23 h. La mezcla de reacción se diluye con acetato de etilo (100 mL), se lava con bicarbonato de sodio saturado (50 mL), 5% de cloruro de litio acuoso (2 x 20 mL), y salmuera (20 mL), se seca sobre sulfato de sodio, se filtra y se seca para dar 6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxilato de etilo (329 mg). ^{1}H NMR (400 MHz, DMSO-d_6): 8.66 (d, 1H), 8.26 (d, 1H),

8.09 (d, 1H), 7.93 (dd, 1H), 7.54 (d, 1H), 7.25 (d, 1H), 6.99 (d, 1H), 6.78 (d, 1H), 4.61 (br s, 2H), 4.25 (q, 2H), 3.91 (m, 1H), 2.53 (s, 3H), 2.26 (m, 2H), 2.10 (m, 2H), 2.01 (m, 2H), 1.91 (d, 2H), 1.29 (t, 3H); MS (EI) para $C_{25}H_{27}N_3O_4$: 434 (MH^+).

[00518] ETAPA 2: Una suspensión de 6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxilato de etilo (324 mg, 0.75 mmol) e hidróxido de potasio (84 mg, 1.50 mmol) en metanol (9 mL) y agua (3 mL) se agita a 60 °C por 3 h. Después del enfriamiento a temperatura ambiente algo del metanol se evapora, se agrega agua a la mezcla resultante, y el pH se ajusta a 5 con ácido clorhídrico acuoso 1N. Lo precipitado se recolecta por filtración, se lava con agua, y se seca para proporcionar ácido 6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxílico (204 mg, 67% de rendimiento). ^{1}H NMR (400 MHz, DMSO-d_6): 12.47 (br s, 1H), 8.64 (d, 1H), 8.26 (d, 1H), 8.09 (d, 1H), 7.92 (dd, 1H), 7.55 (d, 1H), 7.25 (d, 1H), 7.00 (d, 1H), 6.77 (d, 1H), 4.60 (br s, 2H), 3.91 (m, 1H), 2.25 (m, 2H), 2.10 (m, 2H), 2.01 (m, 2H), 1.90 (d, 2H); MS (EI) para $C_{23}H_{23}N_3O_4$: 406 (MH^+).

[00519] ETAPA 3: Se burbujea amoníaco a través de una solución de ácido 6-(3-endo-{[(7-metil-1-benzofuran-6-il)-

carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxílico (70 mg, 0.17 mmol) y HATU (66 mg, 0.17 mmol) en DMF (3 mL) por 15 min, y la mezcla de reacción se agita por 80 min a temperatura ambiente. La introducción de amoníaco después se repite por otros 15 min, y la agitación a temperatura ambiente se continúa por 22 h. La mezcla se vierte en agua, el producto precipitado se recolecta por filtración, después se purifica adicionalmente por HPLC de fase inversa preparatoria (0.1% eluyente ácido trifluoroacético acuoso-acetonitrilo). Las fracciones puras se concentran y el residuo se liofiliza a partir de ácido clorhídrico acuoso 1N para proporcionar clorhidrato de 6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida (28 mg, 37% de rendimiento). ^{1}H NMR (400 MHz, metanol-d_4): 8.47 (d, 1H), 8.44 (d, 1H), 8.35 (dd, 1H), 7.86 (d, 1H), 7.53 (d, 1H), 7.35 (d, 1H), 7.27 (d, 1H), 6.87 (d, 1H), 4.75 (br s, 2H), 4.15 (m, 1H), 2.59 (s, 3H), 2.38 (m, 4H), 2.26 (m, 2H), 2.19 (d, 2H); MS (EI) para $C_{23}H_{24}N_4O_3$: 405 (MH^+).

[00520] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [(5B)-(5D)]. Se obtienen comercialmente reactivos de partida alternativos a menos que se indique de otra manera.

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[00521] (5B): 6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 5 usando (1S)-1-[4-(4-metilpiperizin-1-il)fenil]etanamina (sintetizado de conformidad con el reactivo de la preparación 3) en la etapa 3. ^{1}H NMR (400 MHz, $CDCl_3$): 8.56 (d, 1H), 7.86 (d, 1H), 7.71 (d, 1H), 7.45 (d,1H), 7.27 (m, 1H), 6.90 (d, 2H), 6.78 (d, 1H), 6.51 (d, 1H), 6.32 (d, 1H), 6.14 (1H), 5.25 (m, 1H), 4.61 (br s, 2H), 4.25 (q, 1H), 3.47 (s, 2H), 3.21 (m, 4H), 2.41-2.29 (br m, 5H), 2.27-2.18 (br m, 2H), 2.09-1.98 (br m, 2H), 1.56 (d, 3H). MS (EI) para $C_{36}H_{42}N_6O_3$: 606 (MH^+).

[00522] (5C): 6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(1-metilpiperidin-4-il)fenil]metil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 5 usando 4-(1-metilpiperidin-4-il)bencilamina (sintetizado de conformidad con el reactivo de la preparación 2) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 10.25 (d, 1H), 8.82 (t, 1H), 8.65 (d, 1H), 8.25 (d, 1H), 8.09 (d, 1H), 7.98 (d, 1H), 7.54 (m, 1H), 7.54 (d, 1H), 7.38-7.17 (br m, 5H), 7.00 (d, 1H), 6.76 (d, 1H), 4.56 (s, 2H), 4.42 (d, 2H), 4.11 (br s, 1H), 3.88 (br s, 1H), 3.47 (d, 2H), 3.17 (s, 3H), 3.04 (br s, 2H), 2.52 (s, 3H), 2.25 (d, 1H), 2.16-1.81 (br m, 6H). MS (EI) para $C_{36}H_{41}N_5O_3$: 592 (MH^+).

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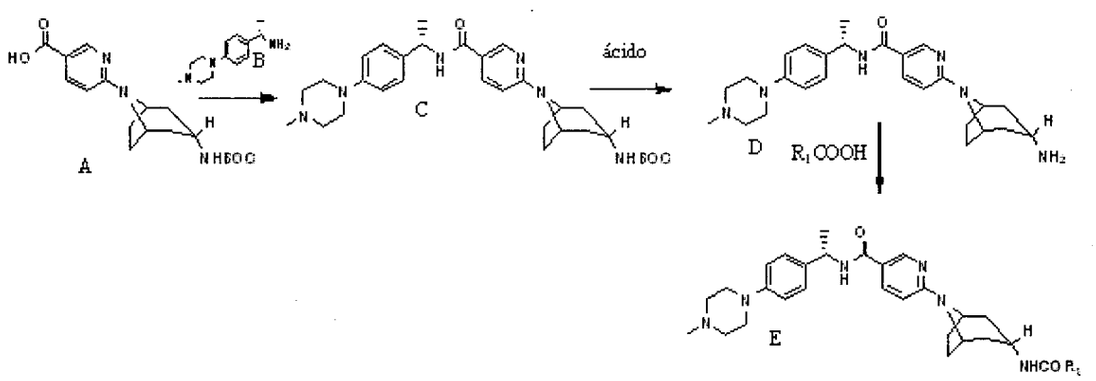
[00523] (5D): 6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 5 usando 4-(4-metilpiperazin-1-il)bencilamina en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 10.95 (br s, 1H), 9.32 (br s, 1H), 8.53 (s, 1H), 8.38-8.32 (m, 2H), 8.10 (s, 1H), 7.55 (d, 2H), 7.36 (d, 1H), 7.27-7.21 (m, 3H), 7.00-6.95 (m, 3H), 4.56 (br s, 2H), 3.96 (br s, 1H), 3.77 (d, 2H), 3.45 (d, 2H), 3.17-3.02 (m, 4H), 2.79 (s, 3H), 2.53 (2, 3H), 2.36-2.32 (m, 2H), 2.24-2.01 (m, 6H). MS (EI) para $C_{35}H_{40}N_6O_3$: 593 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 6:



[00524] El esquema de reacción 6 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 6, en donde R_1 es como se define en la especificación.

[00525] Al compuesto (A) se agrega el compuesto (B) bajo

condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (C). Se desprotege el compuesto (C) para formar el compuesto (D) bajo condiciones acídicas, tal como con el uso de HCl. Al compuesto (D) se agrega R_1COOH bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (E).

[00526] EJEMPLO 6: 6-(3-endo-{[(3-hidroxi-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida.

[00527] ETAPA 1: Una solución de ácido 6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}-amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (preparada en el Ejemplo 2) (164 mg, 0.47 mmol), diclorhidrato de (1*S*)-1-[4-(4-metilpiperazin-1-il)fenil]etanamina (sintetizado de conformidad con el reactivo de la preparación 3) (140 mg, 0.47 mmol), HATU (180 mg, 0.47 mmol) y *N*-metilmorfolina (516 µl, 4.7 mmol) en dimetilformamida (3 mL) se calienta a 40°C por 15 horas. En enfriamiento a temperatura ambiente la solución se diluye con acetato de etilo, después se lava con 5% de cloruro de litio acuoso, 0.5N hidróxido de sodio acuoso, salmuera, y después se seca sobre sulfato de sodio anhidro. La filtración y

concentración proporciona un residuo anaranjado el cual se purifica por cromatografía en columna de gel de sílice eluyendo con 5-10% de metanol en diclorometano. Las fracciones puras se combinan y se concentran para proporcionar 192 mg, 0.35 mmol (74%) de (8-{5-[({(1*S*)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)carbamato de 1,1-dimetiletilo como una espuma amarilla. MS (EI) para $C_{31}H_{44}N_6O_3$: 549 (MH^+).

[00528] ETAPA 2: A una solución de (8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)carbamato de 1,1-dimetiletilo (192 mg, 0.35 mmol) en metanol (5 mL) se agrega una solución de cloruro de hidrógeno 4N en dioxano (2 mL), y la mezcla de reacción se somete a reflujo por 2 min. Después del enfriamiento a temperatura ambiente la mezcla se diluye con acetato de etilo y se basifica usando hidróxido de sodio acuoso 1N hasta que el pH alcanza 10. Las capas se separan, y la capa acuosa se extrae adicionalmente usando acetato de etilo. Las capas orgánicas combinadas se lavan con salmuera después se secan sobre sulfato de sodio anhidro. La filtración y concentración proporciona un residuo incoloro, el cual se purifica por cromatografía en columna de gel de sílice eluyendo con 5-10% de (10% solución de amoníaco acuosa

concentrada en metanol) en cloroformo. Las fracciones puras se combinan y se concentran para dar 6-(3-endo-[amino]-8-azabiciclo[3.2.1]oct-8-il)-*N*-{(1*S*)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida como una espuma blanca. ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (d, 1H), 7.84 (dd, 1H), 7.29 (s, 1H), 6.90 (d, 2H), 6.47 (d, 1H), 6.01 (d, 1H), 5.28-5.21 (m, 1H), 4.51 (br s, 2H), 3.26-3.18 (m, 5H), 2.58-2.55 (m, 4H), 2.35 (s, 3H), 2.33-2.28 (m, 2H), 2.19-2.13 (m, 2H), 2.09-2.04 (m, 2H), 1.56 (d, 3H), 1.48-1.44 (m, 2H). MS (EI) para $C_{26}H_{36}N_6O_1$: 449 (MH^+).

[00529] ETAPA 3: Una solución de 6-(3-endo-[amino]-8-azabiciclo[3.2.1]oct-8-il)-*N*-{(1*S*)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida, ácido 3-hidroxi-2-metilbenzoico (8.5 mg, 0.06 mmol), HATU (22 mg, 0.06 mmol), y *N*-metilmorfolina (18 µl, 0.17 mmol) en dimetilformamida (1 mL) se agita a 40°C por 15 horas. La mezcla de reacción se purifica por HPLC de fase inversa preparativa (eluyente de acetonil acuoso amortiguado con acetato de amonio) para proporcionar 17 mg, 0.03 mmol (50%) de sal de acetato 6-(3-endo-{[(3-hidroxi-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida. ^{1}H NMR (400 MHz, d_6-DMSO): 9.48 (s, 1H), 8.62 (s, 1H), 8.43 (d, 1H), 8.16 (d, 1H), 7.96 (dd 1H), 7.22 (d, 2H), 7.06-7.02 (m, 1H), 6.91-6.83

(m, 3H), 6.75-6.70 (m, 2H), 5.11-5.04 (m, 1H), 4.53 (br s, 2H), 4.53 (d, 2H), 3.81 (br s, 1H), 3.71-3.10 (m, 4H), 2.67-2.56 (m, 2H), 2.37-2.31 (m, 2H), 2.25-2.17 (m, 2H), 2.11-1.82 (m, 12H), 1.42 (d, 3H). MS (EI) para $C_{34}H_{42}N_6O_3$: 583 (MH^+).

[00530] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [(6B-6U)]. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00531] (6B): N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)-carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1,3-benzotiazol-5-carboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 6 usando ácido benzotiazol-5-carboxílico en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 9.51 (s, 1H), 8.64 (d, 1H), 8.52 (d, 1H), 8.44 (d, 1H), 8.41 (d, 1H), 8.28 (d, 1H), 7.99 (dd, 1H), 7.91 (dd, 1H), 7.22 (d, 2H), 6.88 (d, 2H), 6.77 (d, 1H), 5.05-5.12 (m, 1H), 4.59 (br s, 2H), 3.90 (br s, 1H), 3.08 (t, 4H), 2.43 (t, 4H), 2.24-2.29 (m, 2H), 2.21 (s, 3H), 2.10-2.15 (m, 2H), 2.03-2.05 (m, 2H), 1.98 (s, 1H), 1.94 (s, 1H), 1.43 (d, 3H). MS (EI) para $C_{34}H_{39}N_7O_2S$: 610 (MH^+).

[00532] (6C): 6-(3-endo-{[(8-metil-3,4-dihidro-2H-cromen-7-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida.

Preparada como la sal de acetato, de conformidad con el método del ejemplo 6 usando ácido 8-metil-3,4-dihidro-2H-cromen-7-carboxílico (Sawada, Y. et al, *Pest Management Science*, 2003, 59(*1*), 36-48.) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (d, 1H), 8.42 (d, 1H), 8.11 (d, 1H), 7.96 (dd, 1H), 7.20 (d, 2H), 6.94-6.86 (m, 1H), 6.73 (d, 2H), 5.10-5.04 (m, 1H), 4.53 (br s, 2H), 4.20-4.16 (m, 2H), 3.80 (br s, 1H), 3.10-3.06 (m, 4H), 2.76-2.73 (m, 2H), 2.44-2.41 (m, 4H), 2.20-2.02 (m, 10H), 2.00-1.81 (m, 9H), 1.41 (d, 3H). MS (EI) para $C_{37}H_{46}N_6O_3$: 623 (MH^+).

[00533] (6D): 6-[3-endo-({[2-metil-3-(metiltio)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 6 usando ácido 2-metil-3-(metiltio)benzoico (sintetizado de conformidad con el reactivo de la preparación 33) en la etapa 3. ^{1}H NMR (400 MHz, $CDCl_3$): 8.56 (d, 1H), 7.87 (dd, 1H), 7.32-7.27 (m, 3H), 7.22-7.18 (m, 1H), 7.13-7.11 (m, 1H), 6.93 (d, 2H), 6.52 (d, 1H), 6.18 (d, 1H), 6.06 (d, 1H), 5.30-5.22 (m, 1H), 4.60 (br s, 2H), 4.27-4.22 (m, 1H), 3.22-2.96 (m, 4H), 2.66 (s, 3H), 2.60-2.55 (m, 4H), 2.42 (s, 3H), 2.35-2.30 (m, 5H), 2.24-2.18 (m, 2H), 2.02-1.94 (m, 2H), 1.84-1.78 (m, 2H), 1.56 (d, 3H). MS (EI) para $C_{35}H_{44}N_6O_2S$: 613 (MH^+).

[00534] (6E): 2-metil-3-(metiloxi)-N-(8-{5-[({(1S)-1-[4-

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(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 6 usando ácido 4-(aminocarbonil)-2-metil-3-(metiloxi)benzoico (sintetizado de conformidad con el reactivo de la preparación 34) en la etapa 3. ^{1}H NMR (400 MHz, CD_3OD): 8.71 (d, 1H), 8.56-8.48 (m, 2H), 8.17 (d, 1H), 7.69 (d, 1H), 7.33 (d, 2H), 7.19 (d, 1H), 7.08-7.00 (m, 3H), 5.19-5.13 (m, 1H), 4.66 (br s, 2H), 4.10-4.03 (m, 1H), 3.87-3.78 (m, 4H), 3.63-3.55 (m, 2H), 3.04-2.94 (m, 4H), 2.38-2.15 (m, 8H), 2.06-1.99 (m, 2H), 1.54 (d, 3H), 1.34-1.26 (m, 2H). MS (EI) para $C_{36}H_{45}N_7O_4$: 640 (MH^+).

[00535] (6F): 6-{3-endo-[({3-[(4-hidroxiciclohexil)amino]fenil}-carbonil)amino]-8-azabiciclo[3.2.1]oct-8-il}-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 6 usando ácido 3-[(trans-4-hidroxiciclohexil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 37) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (d, 1H), 8.43 (d, 1H), 8.02 (d, 1H), 7.97 (dd, 1H), 7.21 (d, 2H), 7.13 (t, 1H), 6.84-6.89 (m, 4H), 6.75 (d, 1H), 6.67-6.70 (m, 1H), 5.64 (d, 1H), 5.04-5.11 (m, 1H), 4.56 (br s, 2H), 3.81 (br s, 1H), 3.34 (s, 5H), 3.08 (t, 4H), 2.49-2.51 (m, 6H), 2.21 (s, 5H), 1.82-2.02 (m, 6H), 1.62

(s, 1H), 1.42 (d, 3H), 1.12-1.31 (m, 3H). MS (EI) para $C_{39}H_{51}N_7O_3$: 666 (MH^+).

[00536] (6G): N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-(fenilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 6 usando ácido 4-(aminocarbonil)-3-(fenilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3. MS (EI) para $C_{14}H_{12}N_2O_3$: 257 (MH^+); ^{1}HNMR (400MHz, d_4-metanol): 8.49, (d, 1H), 7.85 (dd, 1H), 7.63 (dd, 1H), 7.55 (d, 1H), 7.25-7.15 (m, 6H), 6.97 (m, 2H), 6.86 (d, 2H), 6.61 (d, 1H), 5.06 (q, 1H), 4.47 (br, 2H), 3.85 (tr, 1H), 3.14 (br, 4H), 2.73 (br, 4H), 2.41 (s, 3H), 2.13-1.97 (m, 6H), 1.81 (d, 2H), 1.42 (d, 3H); MS (EI) para $C_{40}H_{46}N_8O_3$: 689 (MH^+).

[00537] (6H): 1,4-dimetil-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-il)-1H-bencimidazol-5-carboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 6 usando ácido 1,4-dimetil-1H-bencimidazol-5-carboxílico (sintetizado de conformidad con el reactivo de la preparación 35) en la etapa 3. ^{1}HNMR (400MHz, d_4-metanol): 8.60 (d, 1H), 8.18 (s, 1H), 7.96 (dd, 1H), 7.45 (d, 1H), 7.35 (d, 1H), 7.29 (d, 2H), 6.95 (d, 2H), 6.74 (d, 1H), 5.17 (q, 1H), 4.61 (br, 2H), 4.04 (tr, 1H), 3.90 (s,

3H), 3.22 (br, 4H), 2.78 (br, 4H), 2.68 (s, 3H), 2.47 (s, 3H), 2.35-2.10 (m, 5H), 1.95 (br, 1H), 1.93 (s, 3H), 1.92 (br, 1H), 1.52 (d, 3H); MS (EI) para $C_{36}H_{44}N_8O_2$: 621 (MH^+).

[00538] (6I): 4-metil-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1H-1,2,3-benzotriazol-5-carboxamida. Preparada de conformidad con el método del ejemplo 6 usando ácido 4-metil-1H-benzotriazol-5-carboxílico (sintetizado de conformidad con el reactivo de la preparación 22) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (d, 1H), 8.43 (d, 1H), 8.26 (d, 1H), 7.97 (dd, 1H), 7.71 (d, 1H), 7.31 (d, 1H), 7.21 (d, 2H), 6.88 (d, 2H), 6.75 (d, 1H), 5.08 (m, 1H), 4.56 (amplio s, 2H), 3.90 (m, 1H), 3.08 (m, 4H), 2.69 (s, 3H), 2.43 (m, 4H), 2.24 (d, 2H), 2.21 (s, 3H), 2.13 (m, 2H), 2.01 (m, 2H), 1.84 (m, 6H), 1.42 (d, 3H). MS (EI) para $C_{34}H_{41}N_9O_2$: 608 (MH^+).

[00539] (6J): 2-(metiloxi)-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 6 usando ácido 4-(aminocarbonil)-3-(metiloxi)benzoico (sintetizado de conformidad con el reactivo de la preparación 26) en la etapa 3. ^{1}H NMR (CD_3OD): 8.60 (s, 1H), 8.46 (d, 1H), 8.03-7.96 (m, 2H), 7.52 (s, 1H), 7.44 (d, 1H), 7.40 (d, 1H), 6.99-6.97 (m, 2H), 6.78 (d, 1H), 5.18-5.16 (m, 1H), 4.04 (s, 2H), 4.03-4.00

(m,4 H), 3.05 (s, 3H), 2.31-2.16 (m, 6H), 1.97-1.93 (m, 2H), 1.53 (d, 3H). MS (EI) para $C_{35}H_{43}N_7O_4$: 626 (MH^+).

[00540] (6K): 2-(ciclobutiloxi)-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 6 usando ácido 4-(aminocarbonil)-3-(ciclobutiloxi)benzoico (sintetizado de conformidad con el reactivo de la preparación 25) en la etapa 3. ^{1}H NMR (CD_3OD): 8.46 (d, 1H), 8.23 (d, 1H), 8.28 (d, 1H), 8.04 (d, 1H), 7.43 (d, 1H), 7.34-7.32 (m, 3H), 7.23 (d, 1H), 7.01-6.99 (m, 1H), 5.18-5.17 (m, 1H), 4.73 (s, 2H), 4.08 (s, 1H), 3.84 (d, 2H), 3.58 (d, 2H), 3.29-3.25 (m, 4H), 3.06-2.98 (m, 4H), 2.58-2.54 (m, 2H), 2.37-2.26 (m, 4H), 2.17 (d, 2H), 1.95-1.93 (m, 1H), 1.92-1.81 (m, 1H), 1.78-1.53 (m, 3H). MS (EI) para $C_{38}H_{47}N_7O_4$: 666(MH^+).

[00541] (6L): 6-[3-endo-({[2-metil-3-(metilamino)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 6 usando ácido 2-metil-3-(metilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 31) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (s, 1H), 8.44-8.40 (d, 1H), 8.10 (s, 1H), 7.99-7.94 (d, 1H), 7.24-7.18 (d, 2H), 7.09-7.04 (m, 1H),

6.91-6.85 (d, 2H), 6.76-6.71 (d, 1H), 6.55-6.49 (m, 2H), 5.19-5.16 (br. s, 1H), 5.11-5.02 (m, 1H), 4.58-4.50 (br. s, 2H), 3.85-3.77 (m, 1H), 3.16 (s, 3H), 3.11-3.05 (m, 4H), 2.75-2.71 (m, 2H), 2.46-2.40 (m, 2H), 2.23-2.16 (m, 5H), 2.12-2.00 (m, 5H), 1.99-1.94 (m, 2H), 1.89-1.81 (m, 5H), 1.44-1.39 (d, 3H). MS (EI) para $C_{35}H_{45}N_7O_2$: 596 (MH^+).

[00542] (6M): 6-[3-endo-({[3-(dimetilamino)-2-metilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 6 usando ácido 3-(dimetilamino)-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 32) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (s, 1H), 8.44-8.40 (d, 1H), 8.21 (s, 1H), 7.99-7.94 (d, 1H), 7.25-7.17 (m, 3H), 7.13-7.09 (d, 1H), 6.95-6.91 (d, 1H), 6.91-6.85 (d, 2H), 6.76-6.71 (d, 1H), 5.11-5.02 (m, 1H), 4.58-4.50 (br. s, 2H), 3.87-3.80 (m, 1H), 3.16 (s, 3H), 3.11-3.05 (m, 4H), 2.63 (s, 6H), 2.46-2.40 (m, 4H), 2.26-2.18 (m, 5H), 2.15-2.05 (m, 2H), 2.02-1.93 (m, 2H), 1.89-1.81 (m, 5H), 1.44-1.39 (d, 3H). MS (EI) para $C_{36}H_{47}N_7O_2$: 610 (MH^+).

[00543] (6N): N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}-amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-(piridin-4-ilamino)bencen-1,4-dicarboxilato. Preparado como la sal de trifluoroacetato, de conformidad con el método del ejemplo 6 usando ácido 4-

aminocarbonil-3-(piridin-4-ilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3. ^{1}H NMR (400 MHz, d_4-metanol): 8.42 (d, 1H), 8.38 (d, 1H), 8.18-8.10 (m, 3H), 7.81-7.71 (m, 3H), 7.26-7.22 (m, 2H), 7.11-7.06 (m, 3H), 6.94-6.88 (m, 2H), 5.11-5.04 (m, 1H), 4.64 (br s, 2H), 4.00 (br s, 2H), 3.77-3.68 (m, 2H), 3.55-3.46 (m, 2H), 3.21-3.12 (m, 2H), 2.99-2.85 (m, 5H), 2.31-1.98 (m, 8H), 1.45 (d, 3H); MS (EI) para $C_{39}H_{45}N_9O_3$: 688 (MH^+).

[00544] (6O): N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}-amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[1-(metilsulfonil)piperidin-4-il]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 6 usando ácido 4-aminocarbonil-3-(1-metilsulfonil)piperidin-4-ilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3. ^{1}H NMR (400 MHz, d_4-metanol): 8.50 (d, 1H), 7.88 (dd, 1H), 7.57 (d, 1H), 7.22-7.17 (m, 2H), 7.02 (br s, 1H), 6.89-6.82 (m, 3H), 6.66 (d, 1H), 5.11-5.04 (m, 1H), 4.53 (br s, 2H), 3.93-3.86 (m, 1H), 3.61-3.47 (m, 2H), 3.16-3.09 (m, 4H), 3.02-2.92 (m, 2H), 2.76 (s, 3H), 2.70-2.63 (m, 4H), 2.36 (s, 3H), 2.25-1.99 (m, 8H), 1.91-1.79 (m, 3H), 1.63-1.46 (m, 2H), 1.43 (d, 3H); MS (EI) para $C_{40}H_{53}N_9O_5S$: 772 (MH^+).

[00545] (6P): 2-(ciclobutilamino)-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-

il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada como la sal de trifluoroacetato, de conformidad con el método del ejemplo 6 usando ácido 4-aminocarbonil-3-(ciclobutilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3. ^{1}H NMR (400 MHz, d_4-metanol): 8.45 (d, 1H), 8.34-8.28 (m, 2H), 7.64 (d, 1H), 7.35-7.31 (m, 2H), 7.28-7.23 (m, 1H), 7.03-6.98 (m, 2H), 6.96-6.93 (m, 1H), 6.92-6.90 (m, 1H), 5.20-5.14 (m, 1H), 4.73 (br s, 2H), 4.11-3.98 (m, 2H), 3.86-3.78 (m, 2H), 3.64-3.54 (m, 2H), 3.29-3.21 (m, 2H), 3.07-2.94 (m, 5H), 2.54-2.11 (m, 8H), 2.00-1.80 (m, 4H), 1.54 (d, 3H); MS (EI) para $C_{38}H_{48}N_8O_3$: 665 (MH^+).

[00546] (6Q): N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[3,4,5-tris(metiloxi)fenil]amino}bencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 6 usando ácido 4-aminocarbonil-3-(3,4,5-trimetoxifenilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3. ^{1}H NMR (400 MHz, d_4-metanol): 8.58 (d, 1H), 7.95 (dd, 2H), 7.72 (d, 1H), 7.54 (d, 2H), 7.31-7.27 (m, 1H), 7.08 (dd, 2H), 6.98-6.93 (m, 2H), 6.72 (d, 1H), 6.55 (s, 2H), 5.19-5.12 (m, 1H), 4.57 (br s, 2H), 3.97-3.90 (m, 1H), 3.81 (s, 6H), 3.74 (s, 3H), 3.27-

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3.21 (m, 4H), 2.89-2.82 (m, 4H), 2.52 (s, 3H), 2.26-2.16 (m, 2H), 2.09 (br s, 4H), 1.96 (s, 3H), 1.89 (d, 2H), 1.52 (d, 3H); MS (EI) para $C_{43}H_{52}N_8O_6$: 777 (MH^+).

[00547] (6R): 3-(etilamino)-2,5-dimetil-N1-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 6 usando ácido 4-(aminocarbonil)-3-(etilamino)-2,5-dimetilbenzoico (sintetizado de conformidad con el reactivo de la preparación 36) en la etapa 3. ^{1}H NMR (400 MHz, CD_3OD): 8.59 (d, 1H), 7.97 (dd, 1H), 7.29 (d, 2H), 6.96 (d, 2H), 6.76 (s, 1H), 6.75 (d, 1H), 5.17 (q, 1H), 4.60 (br, 2H), 3.99 (t, 1H), 3.28-3.19 (m, 4H), 3.11 (q, 2H), 2.79-2.74 (m, 4H), 2.45 (s, 3H), 2.34-2.26 (m, 2H), 2.32 (s, 3H), 2.23-2.09 (m, 4H), 2.22 (s, 3H), 1.93-1.86 (m, 2H), 1.52 (d, 3H), 1.17 (t, 3H); MS (EI) para $C_{38}H_{50}N_8O_3$: 667 (MH^+).

[00548] (6S): 2-[(4-hidroxiciclohexil)amino]-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]-etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 6 usando ácido 4-(aminocarbonil)-3-[(trans-4-hidroxiciclohexil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3. ^{1}H NMR (400 MHz, d_4-metanol): 8.60 (d, 1H), 7.97 (dd, 1H),

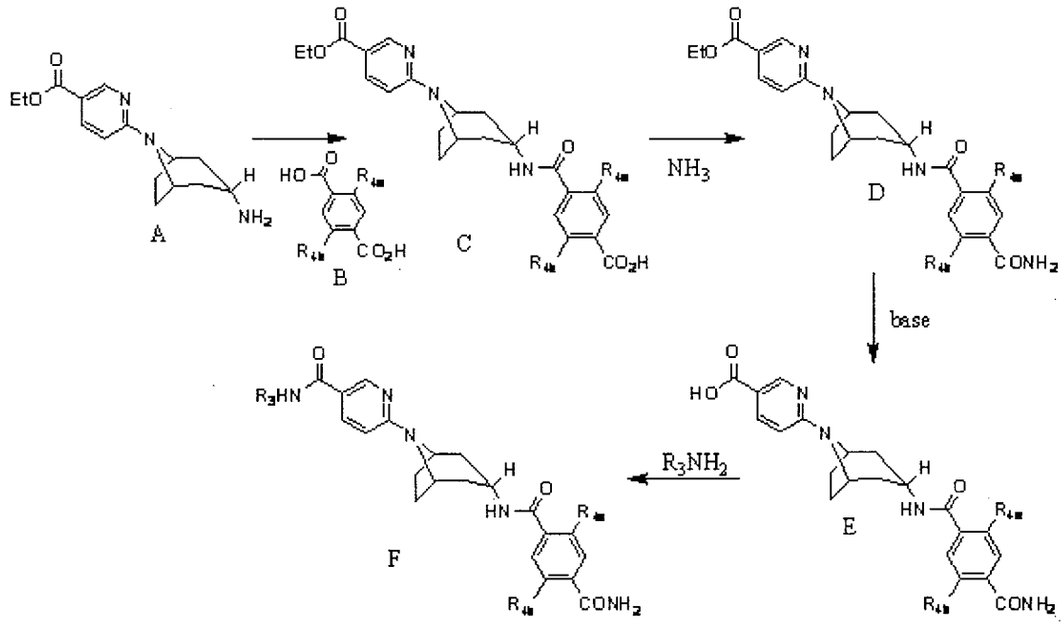
7.62 (d, 1H), 7.31 (d, 2H), 7.07 (s, 1H), 6.98 (d, 2H), 6.89 (dd, 2H), 6.75 (d, 1H), 5.16 (m, 1H), 4.63 (br s, 2H), 3.99 (m, 1H), 3.63 (m, 1H), 3.41 (m, 1H), 3.03 (m, 4H), 2.70 (s, 3H), 2.30-2.12 (m, 8H), 1.98 (m, 4H), 1.53 (d, 3H), 1.50-1.26 (m, 4H); MS (EI) para $C_{40}H_{52}N_8O_4$: 709 (MH^+).

[00549] (6T): N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}-amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[2-(metilsulfonil)etil]amino}bencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 6 usando ácido 4-(aminocarbonil)-3-{[2-(metilsulfonil)etil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (d, 1H), 8.43 (d, 1H), 8.32 (m, 1H), 8.19 (d, 1H), 7.98 (m, 2H), 7.69 (d, 1H), 7.36 (br s, 1H), 7.21 (d, 2H), 7.01 (s, 1H), 6.95 (d, 1H), 6.88 (d, 2H), 6.76 (d, 1H), 5.08 (m, 1H), 4.57 (br s, 2H), 3.83 (br s, 1H), 3.66 (m, 2H), 3.46 (t, 2H), 3.07 (m, 4H), 3.03 (s, 3H), 2.43 (m, 4H), 2.22 (m, 2H), 2.20 (s, 3H), 2.08 (m, 2H), 2.01 (m, 2H), 1.91 (s, 3H), 1.87 (m, 2H), 1.42 (d, 3H); MS (EI) para $C_{37}H_{48}N_8O_5S$: 717 (MH^+).

[00550] (6U): 2-[(ciclopropilmetil)amino]-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida.

Preparada como la sal de acetato, de conformidad con el método del ejemplo 6 usando ácido 4-(aminocarbonil)-3-[(ciclopropilmetil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 3. ^{1}HNMR (400MHz, d_4-metanol): 8.59, (d, 1H), 7.96 (dd, 1H), 7.62 (dd, 1H), 7.29 (d, 2H), 7.05 (br s, 1H), 6.98-6.89 (m, 3H), 6.75 (d, 1H), 5.20-5.14 (m, 1H),4.62 (br s, 2H), 4.01-3.95 (m, 1H), 3.28-3.22 (m, 4H), 3.08 (d, 2H), 2.92-2.87 (m, 4H), 2.56 (s, 3H), 2.30-2.14 (m, 6H), 1.98-1.92 (m, 3H), 1.52 (d, 3H), 1.20-1.11(m, 1H), 0.60-.055 (m, 2H), 0.31-0.26 (m, 2H); MS (EI) para $C_{38}H_{48}N_8O_3$: 665 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 7:



[00551] El esquema de reacción 7 generalmente describe la

síntesis de todos los compuestos listados en el Ejemplo 7, en donde R_3, R_{4a}, y R_{4b} son como se definen en la especificación. Este esquema de reacción es aplicable cuando R_{4a} y R_{4b} son los mismos.

[00552] En el esquema de reacción 7, al compuesto (A) se agrega el compuesto (B) bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (C). Al compuesto (C) se agrega NH_3 bajo condiciones de reacción apropiadas para formar el compuesto (D). El carboxilato del compuesto (D) después se hidroliza con una base, tal como LiOH, para formar el compuesto (E). Al compuesto (E) se agrega R_3NH_2 y un agente de acoplamiento adecuado, tal como HOBT y EDCI, bajo condiciones de reacción apropiadas para formar el compuesto (F).

[00553] EJEMPLO 7: 2,5-dimetil-N-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida

[00554] ETAPA 1: Una solución de ácido 2,5-Dimetilbencen-1,4-dicarboxílico (1.14 g, 5.86 mmol), hexafluorofosfato de 2-(7-aza-1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (2.23 g, 5.86 mmol) y N,N-diisopropiletilamina (4.7 mL, 27 mmol) en N,N-dimetilformamida (20 mL) se agita a temperatura ambiente

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por 30 minutos. Después se agrega clorhidrato 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxilato de etilo (preparado en el Ejemplo 1) (1.66 g, 5.32 mmol) y la solución resultante se agita a 50°C por 12 horas. En enfriamiento a temperatura ambiente, la solución se concentra in vacuo. El residuo se divide en dos porciones y ambas porciones se recuperan en 10 mL N,N-dimetilformamida, y se agregan hexafluorofosfato de 2-(7-aza-1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (1.11 g, 2.93 mmol) y N,N-diisopropiletilamina (2.3 mL, 13 mmol) a cada una. Las soluciones se calientan a 50°C y se burbujea amoníaco (gas) a través de las soluciones por 20 minutos. Las soluciones se combinan, después el solvente se remueve in vacuo. El material crudo se divide entre agua y 10% de metanol en diclorometano. Las capas se separan y la capa acuosa se extrae (2 x 100 mL diclorometano). Las capas orgánicas combinadas se secan (sulfato de magnesio), se filtran y se concentran. Lo sólido crudo se tritura con metanol/hexanos/acetato de etilo y lo sólido se recolecta por filtración para dar 6-[3-endo-({[4-(aminocarbonil)-2,5-dimetilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (1.79 g, 75% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): 8.58 (d, 1H), 8.28 (d, 1H), 8.01 (dd, 1H), 7.70 (br s, 1H), 7.40 (br s, 1H), 7.24 (s, 1H), 7.13 (s, 1H), 6.93 (d, 1H), 4.64 (amplio s,

2H), 4.27 (q, 2H), 3.88 (m, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 2.24 (m, 2H), 2.13 (m, 2H), 2.01 (m, 2H), 1.93 (d, 2H), 1.30 (t, 3H). MS (EI) para $C_{25}H_{38}N_4O_4$: 451 (MH^+).

[00555] ETAPA 2: A una solución de 6-[3-endo-({[4-(aminocarbonil)-2,5-dimetilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (1.00 g, 2.21 mmol) en metanol (6.0 mL) y tetrahidrofurano (6.0 mL) se agrega 3.0 mL de 2.0 M hidróxido de litio (acuoso) y la solución resultante se calienta a 50°C por una hora. Los solventes orgánicos se remueven in vacuo, y la solución acuosa restante se lleva a pH 2 usando ácido clorhídrico acuoso concentrado. Lo sólido así formado se recolecta por filtración y se seca in vacuo para dar 1.18 g (70% de rendimiento) del ácido 6-[3-endo-({[4-(aminocarbonil)-2,5-dimetilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico deseado, el cual se usa sin purificación adicional en la etapa 3.

[00556] ETAPA 3: Una solución de ácido 6-[3-endo-({[4-(aminocarbonil)-2,5-dimetilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (0.050 g, 0.12 mmol), clorhidrato de (3*R*)-1-(1-metiletil)pirrolidin-3-amina (sintetizado en la preparación del reactivo 9) (0.14 mmol), 1-hidroxibenzotriazol (0.019 g, 0.14 mmol),

clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0.027 g, 0.14 mmol), y 4-metilmorfolina (0.05 mL, 0.5 mmol) en N,N-dimetilformamida (2.0 mL) se agita a temperatura ambiente por 12 horas. La solución después se diluye con agua y purifica por HPLC (fase inversa, acetonitrilo/agua con 0.1% de acetato de amonio). La concentración in vacuo y liofilización a partir de agua proporciona 0.034 g (54% de rendimiento) de la 2,5-dimetil-N-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida deseada como la sal de acetato. ^{1}H NMR (400 MHz, d_6-DMSO): 8.61 (d, 1H), 8.22 (dd, 1H), 7.98 (dd, 1H), 7.70 (amplio s, 1H), 7.40 (amplio s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (amplio s, 2H), 4.35 (m, 1H), 3.84 (m, 1H), 2.81 (t, 1H), 2.67 (t, 1H), 2.44 (m, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 2.19 (m, 2H), 2.10 (m, 4H), 1.98 (m, 2H), 1.91 (s, 3H), 1.83 (m, 2H), 1.73 (m, 2H), 1.02 (t, 6H). MS (EI) para $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00557] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [(7B)-(7S)]. Se obtienen comercialmente reactivos de partida alternativos a menos que se indique de otra manera.

[00558] (7B): 2,5-dimetil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-

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azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida. Preparado de conformidad con el método del ejemplo 7 usando 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida (sintetizado en el Ejemplo 2) en la etapa 1 y omitiendo las etapas 2 y 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (s, 1H), 8.71 (s, 1H), 8.31 (d, 1H), 8.07 (d, 1H), 7.76 (s, 1H), 7.46 (s, 1H), 7.41-7.28 (m, 6H), 7.19 (s, 1H), 6.86 (d, 1H), 4.64 (br s, 2H), 4.53 (d, 2H), 3.92 (br s, 1H), 2.41 (s, 3H), 2.36 (s, 3H), 2.30-1.90 (m, 8H). MS (EI) para $C_{30}H_{33}N_5O_3$: 512 (MH^+).

[00559] (7C): 2,5-dicloro-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 7 como una sal de acetato, usando ácido 2,5-dicloroterefálico y 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida (sintetizado en el Ejemplo 2) en la etapa 1 y omitiendo las etapas 2 y 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.83-8.78 (m, 1H), 8.67-8.64 (d, 1H), 8.57-8.54 (d, 1H), 8.03-7.96 (m, 2H), 7.80-7.77 (s, 1H), 7.59 (s, 1H), 7.53 (s, 1H), 7.36-7.29 (m, 4H), 7.26-7.21 (m, 1H), 6.26-6.21 (m, 1H), 4.59-4.53 (br. s, 2H), 4.48-4.44 (d, 2H), 3.92-3.84 (m, 1H), 2.26-2.18 (m, 2H), 2.15-2.07 (m, 2H), 2.01-1.93 (m, 2H), 1.86-1.78 (d, 2H) . MS (EI) para $C_{28}H_{27}Cl_2N_5O_3$: 553 (MH^+).

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[00560] (7D): 2,5-dimetil-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 7 como una sal de acetato, usando 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)-*N*-{(1*S*)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida (sintetizado en el Ejemplo 6) en la etapa 1 y omitiendo las etapas 2 y 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.66-8.61 (s, 1H), 8.47-8.41 (d, 1H), 8.25 (s, 1H), 8.01-7.94 (d, 1H), 7.70 (s, 1H), 7.40 (s, 1H), 7.27-7.21 (m, 3H), 7.12 (s, 1H), 6.95-6.88 (d, 2H), 6.79-6.71 (d, 1H), 5.13-5.03 (m, 1H), 4.59-4.53 (br. s, 2H), 3.86-3.79 (m, 1H), 3.27-3.15 (br. s, 4H), 2.93-2.81 (br. s, 4H), 2.52 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 2.24-2.16-(d, 2H), 2.15-2.07 (m, 2H), 2.02-1.95 (m, 2H), 1.87-1.80 (d, 2H), 1.46-1.39 (d, 3H). MS (EI) para $C_{36}H_{45}N_7O_3$: 624 (MH^+).

[00561] (7E): N-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 7 como una sal de acetato, usando 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida (sintetizado en el Ejemplo 3) en la etapa 1 y omitiendo las etapas 2 y 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.51 (s, 1H), 8.26 (s, 1H), 8.06 (d, 1H), 7.90-7.83 (br. s, 1H), 7.68 (s, 1H), 7.38 (s, 1H), 7.33-7.26 (br. s, 1H), 7.25-7.17 (d, 1H), 7.13-7.04 (d, 1H),

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6.93 (s, 1H), 4.66-4.55 (br. s, 2H), 3.89-3.82 (m, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 2.26-2.19 (m, 2H), 2.15-2.07 (m, 2H), 2.03-1.96 (m, 2H), 1.93-1.86 (d, 2H). MS (EI) para $C_{28}H_{27}N_5O_3$: 422 (MH^+).

[00562] (7F): 2,5-dimetil-N-{8-[5-({[(3S)-1-metilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 7, usando clorhidrato de (3*S*)-1-metilpiperidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.93 (m, 2H), 7.70 (amplio s, 1H), 7.40 (amplio s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (amplio s, 2H), 3.90 (m, 2H), 2.82 (m, 1H), 2.68 (m, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 2.19 (m, 4H), 2.12 (m, 2H), 1.99 (m, 2H), 1.91 (s, 3H), 1.83 (m, 4H), 1.78 (m, 2H), 1.71 (m, 2H), 1.53 (m, 1H), 1.27 (m, 2H). MS (EI) para $C_{30}H_{40}N_6O_3$: 519 (MH^+).

[00563] (7G): N-{8-[5-({[(3R)-1-etilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 7 usando clorhidrato de (3*R*)-1-etilpiperidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.60 (d, 1H), 8.23 (d, 1H), 7.92 (m, 2H), 7.70 (amplio s, 1H), 7.40 (amplio

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s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (amplio s, 2H), 3.88 (m, 3H), 2.88 (m, 1H), 2.76 (m, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.19 (m, 2H), 2.10 (m, 2H), 1.99 (m, 1H), 1.91 (s, 3H), 1.80 (m, 4H), 1.68 (m, 2H), 1.49 (m, 2H), 1.32 (m, 2H), 1.01 (t, 3H). MS (EI) para $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00564] (7H): 2,5-dimetil-N-{8-[5-({[(3R)-1-metilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 7 usando clorhidrato de (3*R*)-1-metilpiperidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.93 (m, 2H), 7.70 (amplio s, 1H), 7.40 (amplio s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (amplio s, 2H), 3.89 (m, 3H), 2.79 (m, 1H), 2.64 (m, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.18 (m, 2H), 2.10 (m, 2H), 1.99 (m, 2H), 1.91 (s, 3H), 1.80 (m, 4H), 1.68 (m, 2H), 1.50 (m, 2H), 1.27 (m, 2H). MS (EI) para $C_{29}H_{38}N_6O_3$: 519 (MH^+).

[00565] (7I): 2,5-dimetil-N-{8-[5-({[(3R)-1-metilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 7 usando (3*R*)-1-metilpirrolidin-3-amina en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.60 (d, 1H), 8.23 (dd,

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1H), 7.96 (d, 1H), 7.70 (amplio s, 1H), 7.40 (amplio s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.73 (d, 1H), 4.54 (amplio s, 2H), 4.37 (m, 1H), 3.83 (m, 1H), 2.68 (m, 1H), 2.57 (m, 1H), 2.39 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.25 (s, 3H), 2.21 (m, 2H), 2.12 (m, 4H), 1.98 (m, 2H), 1.91 (s, 3H), 1.83 (m, 2H), 1.72 (m, 1H). MS (EI) para $C_{28}H_{36}N_6O_3$: 505 (MH^+).

[00566] (7J): 2,5-dimetil-N-[8-(5-{[(1-metilpiperidin-4-il)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 7 usando 1-metilpiperidin-4-amina en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.94 (m, 2H), 7.69 (amplio s, 1H), 7.39 (amplio s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (amplio s, 2H), 3.85 (m, 1H), 3.70 (m, 1H), 2.76 (m, 2H), 2.35 (s, 3H), 2.29 (s, 3H), 2.19 (m, 2H), 2.10 (m, 2H), 2.00 (m, 2H), 1.92 (m, 4H), 1.91 (s, 3H), 1.72 (m, 2H), 1.54 (m, 2H). MS (EI) para $C_{29}H_{38}N_6O_3$: 519 (MH^+).

[00567] (7K): N-[8-(5-{[(1-etilpiperidin-4-il)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2,5-dimetilbencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 7 usando 1-etilpiperidin-4-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.94 (m, 2H), 7.70 (amplio s, 1H), 7.40 (amplio s, 1H), 7.24 (s, 1H), 7.12

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(s, 1H), 6.74 (d, 1H), 4.55 (amplio s, 2H), 3.83 (m, 1H), 3.71 (m, 1H), 2.86 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.19 (m, 2H), 2.10 (m, 2H), 1.99 (m, 2H), 1.91 (s, 3H), 1.90 (m, 4H), 1.75 (m, 2H), 1.52 (m, 2H), 1.00 (t, 3H). MS (EI) para $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00568] (7L): 2,5-dimetil-N-{8-[5-({[1-(1-metiletil)piperidin-4-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 7 usando clorhidrato de 1-(1-metiletil)piperidin-4-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.93 (m, 2H), 7.70 (amplio s, 1H), 7.40 (amplio s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.54 (amplio s, 2H), 3.84 (m, 1H), 3.67 (m, 1H), 2.79 (m, 2H), 2.69 (m, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 2.13 (m, 6H), 2.00 (m, 2H), 1.91 (s, 3H), 1.82 (m, 2H), 1.49 (m, 2H), 0.96 (d, 6H). MS (EI) para $C_{31}H_{42}N_6O_3$: 547 (MH^+).

[00569] (7M): N-{8-[5-({[(3S)-1-etilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 7 as sal de clorhidrato usando clorhidrato de (3S)-1-etilpirrolidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 3. ^{1}H NMR (400 MHz, $CDCl_3$ p/10% CD_3OD): 8.68

(d, 1H), 8.00 (dd, 1H), 7.28 (s, 1H), 7.16 (s, 1H), 6.58 (d, 1H), 4.84 (br s, 1H), 4.61 (br s, 1H), 3.66 (br s, 1H), 3.51 d, 1H), 3.12-2.94 (m, 3H), 2.85 (q, 1H), 2.53-2.42 (m, 1H), 2.43 (s, 3H), 2.43 (s, 3H), 2.35-2.24 (m, 2H), 2.22-2.07 (m, 4H), 1.91 (br d, 2H), 1.33 (t, 3H). MS (EI) para $C_{29}H_{38}N_6O_4$: 519 (MH^+).

[00570] (7N): 2,5-dimetil-N-{8-[5-({[(3R)-1-(1-metiletil)piperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 7 como una sal de acetato usando (3R)-1-(1-metiletil)piperidin-3-amina clorhidrato (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.94 (dd, 1H), 7.89 (d, 1H), 7.70 (s, 1H), 7.40 (s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (br s, 2H), 3.84 (br s, 2H), 2.81 (dd, 1H), 2.65-2.75 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.17-2.22 (m, 2H), 1.97-2.13 (m, 7H), 1.76-1.82 (m, 2H), 1.66-1.69 (m, 1H), 1.41-1.51 (m, 1H), 1.24-1.34 (m, 1H), 0.96 (d, 6H). MS (EI) para $C_{31}H_{42}N_6O_3$: 547 (MH^+).

[00571] (7O): N-{8-[5-({[(3S)-1-etilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 7 como una sal de acetato usando clorhidrato de (3S)-1-etilpipiperidin-3-amina

(sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.90-7.95 (m, 2H), 7.70 (s, 1H), 7.40 (s, 1H), 7.24 (s, 1H), 7.12 (S, 1H), 6.74 (d, 1H), 4.55 (br s, 2H), 3.83-3.92 (m, 2H), 2.87 (dd, 1H), 2.75 (dd, 1H), 2.35 (s, 4H), 2.32 (d, 1H), 2.30 (s, 4H), 2.17-2.22 (m, 2H), 2.08-2.13 (m, 2H), 1.98-2.00 (m, 2H), 1.76-1.82 (m, 5H), 1.66-1.70 (m, 1H), 1.44-1.53 (m, 1H), 1.25-1.35 (m, 1H), 0.99 (t, 3H). MS (EI) para $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00572] (7P): 2,5-dimetil-N-{8-[5-({[(3S)-1-(1-metiletil)piperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 7 como una sal de acetato usando clorhidrato de (3S)-1-(1-metiletil)piperidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 8.24 (d, 1H), 7.94 (dd, 1H), 7.89 (d, 1H), 7.70 (s, 1H), 7.40 (s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.74 (d, 1H), 4.55 (br s, 2H), 3.84 (br s, 2H), 2.81 (d, 1H), 2.65-2.75 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.17-2.22 (m, 2H), 2.07-2.13 (m, 3H), 1.97-2.04 (m, 3H), 1.76-1.82 (m, 2H), 1.66-1.70 (m, 1H), 1.41-1.50 (m, 1H), 1.24-1.34 (m, 1H), 0.96 (d, 6H). MS (EI) para $C_{31}H_{42}N_6O_3$: 547 (MH^+).

[00573] (7Q): 2,5-dimetil-N-{8-[5-({[(3S)-1-(1-

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metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 7 como una sal de clorhidrato usando (S)-1-isopropilpirrolidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 3. ^{1}H NMR (400 MHz, $CDCl_3$ p/ 10% CD_3OD): 8.64 (d, 1H), 7.97 (d, 1H), 7.29 (s, 1H), 7.17 (s, 1H), 6.61 (d, 1H), 4.69-6.60 (br m, 3H), 4.13 (m, 1H), 3.13 (d, 1H), 3.15 (m, 2H), 2.92 (d, 1H), 2.68 (t, 2H), 2.58-2.03 (br m, 10H), 1.92 (d, 2H), 1.09 (dd, 6H). MS (EI) para $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00574] (7R): 2,5-dimetil-N-{8-[5-({[(3S)-1-metilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 7 como una sal de clorhidrato usando (3S)-1-metilpirrolidin-3-amina en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (s, 1H), 7.95 (dd, 1H), 7.46 (d, 1H), 9.29 (s, 1H), 7.17 (s, 1H), 6.60 (d, 1H), 4.75 (m, 1H), 3.36 (m, 3H), 3.15 (q, 1H), 2.85 (br d, 1H), 2.66 (m, 1H), 2.49-2.27 (br m, 12H), 2.25-2.05 (br m, 3H), 1.93-1.75 (br m, 3H), 1.72 (m,1H), 1.11 (t, 1H). MS (EI) para $C_{28}H_{36}N_6O_3$: 505 (MH^+).

[00575] (7S): N-{8-[5-({[(3R)-1-etilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida. Preparada de

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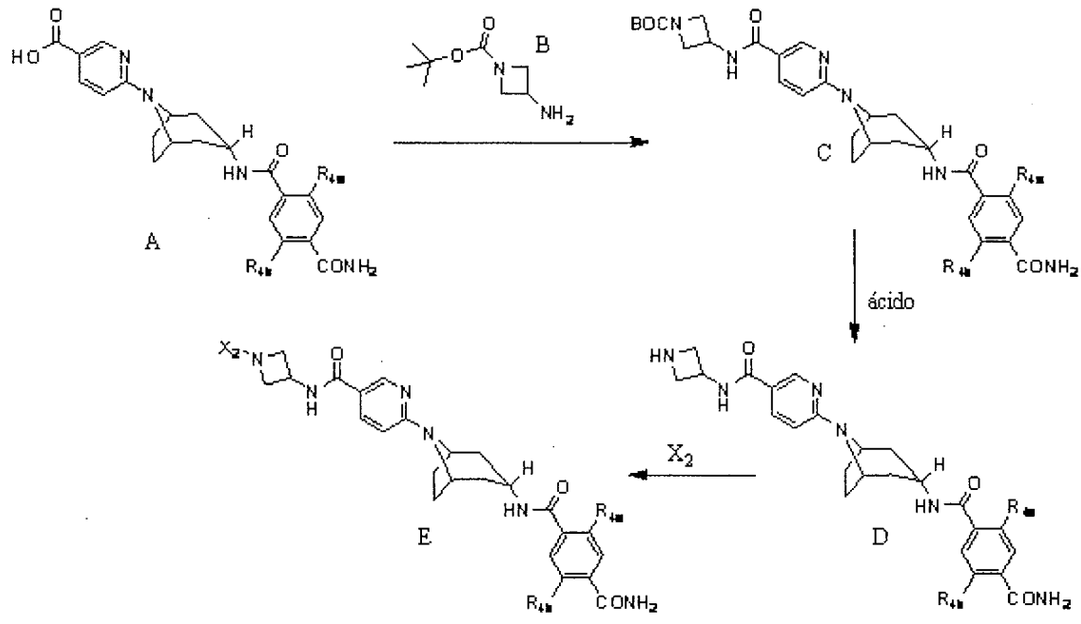
conformidad con el método del ejemplo 7 como una sal de clorhidrato usando clorhidrato de (3R)-1-etilpirrolidin-3-amina (sintetizado de conformidad con el reactivo de la preparación 9) en la etapa 3. ^{1}H NMR (400 MHz, d_6-DMSO): 11.60 (br d, 1H), 8.63 (dd, 1H), 8.32 (d, 1H), 7.70 (s, 1H), 7.40 (s, 1H), 7.25 (s, 1H), 7.13 (s, 1H), 4.78 (br s, 1H), 4.65 (br s, 1H), 3.95-3.05 (br m, 9H), 2.45-1.90 (br m, 14H), 1.25 (dt, 3H). MS (EI) para $C_{29}H_{38}N_6O_3$: 519 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 9:



[00576] El esquema de reacción 9 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 9, en donde X_2 , R_{4a}, y R_{4b} son como se definen en la especificación.

[00577] En el esquema de reacción 9, el compuesto (B) se

agrega al compuesto (A) bajo condiciones de reacción apropiadas y solventes adecuados para condensar y formar la amida unida en el compuesto (C). El compuesto (C) después se desprotege con un ácido, tal como HCl, para remover BOC y formar el compuesto (D). El compuesto (D) después se convierte a (E) por tratamiento con X_2 bajo condiciones de alquilación reductivas, en donde X_2 es ya sea un aldehído o reactivo de cetona que permite reaccionar con (D) en la presencia de un agente de reducción adecuado tal como cianoborohidruro de sodio, y en donde X_2 llega a ser ya sea un grupo metilo, o de otra forma es un grupo alquilo unido al grupo azetidinilo por medio de un enlazador de metileno.

EJEMPLO 10: N-{(1S)-2-amino-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida.

[00578] ETAPA 1: Una solución de sal trifluoroacetato de 2-amino-2-(4-metoxifenil)acetato (S)-metilo (sintetizado de conformidad con el reactivo de la preparación 38) (0.30 g, 1.00 mmol), ácido 6-[3-endo-({[2-metil-3-metiloxi)fenil]-carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (preparada en el Ejemplo 1, ETAPA 4) (0.43 g, 1.00 mmol), HOBt (0.16 g, 1.20 mmol), EDCI (0.23 g, 1.20 mmol) y 4-metilmorfolina (0.88 mL, 8.00 mmol) en

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dimetilformamida (5 mL) se agita a temperatura ambiente por 18 horas. La mezcla de reacción se divide entre acetato de etilo (100 mL) y salmuera (50 mL). La capa orgánica se separa y se lava con salmuera (50 mL), se seca sobre sulfato de sodio, se filtra y el solvente se concentra. El residuo se somete a cromatografía en columna (hexano:acetato de etilo 4:1 hasta 3:2) para dar (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoato de metilo, (0.51 g, 89% de rendimiento). MS (EI) para $C_{32}H_{36}N_4O_6$: 573 (MH^+).

[00579] ETAPA 2: Una solución de (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoato de metilo (0.48 g, 0.84 mmol) y una solución acuosa de 4M hidróxido de potasio (0.42 mL, 1.68 mmol) en metanol (10 mL), tetrahidrofurano (5 mL) y agua (5 mL) se agita a 50 °C por 30 minutos. Después del enfriamiento a temperatura ambiente, el solvente se evapora y el pH se ajusta a 2 con ácido clorhídrico acuoso concentrado. Lo precipitado se recolecta por filtración, se lava con agua, y se seca para proporcionar ácido (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoico

(0.42 g, 89%). MS (EI) para $C_{31}H_{34}N_4O_6$: 557 (M-H).

[00580] ETAPA 3: Una solución de ácido (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoico (0.10 g, 0.18 mmol), una solución 2M de amoníaco en metanol (0.18 mL, 0.36 mmol), HOBt (0.027 g, 0.20 mmol), EDCI (0.042 g, 0.22 mmol) y 4-metilmorfolina (0.10 mL, 0.90 mmol) en dimetilformamida (3 mL) se agita a temperatura ambiente por 18 horas. El solvente se concentra in vacuo y el residuo se purifica por HPLC de fase inversa preparatoria (0.1% de acetato de amonio en fase móvil de acetonitrilo acuoso) para dar N-{(1S)-2-amino-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida (17 mg, 11% de rendimiento). MS (EI) para $C_{31}H_{35}N_5O_5$: 558 (MH^+).

[00581] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [(9B)-(9E)]. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00582] (9B): (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}-amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]-etanoato

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de metilo. Preparado en el Ejemplo 10 etapa 1. MS (EI) para $C_{32}H_{36}N_4O_6$: 573 (MH^+).

[00583] (9C): Ácido (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}-amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]-etanoico. Preparado en el Ejemplo 10 etapa 2. MS (EI) para $C_{31}H_{34}N_4O_6$: 557 (M-H).

[00584] (9D): N-{(1S)-2-(metilamino)-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 10 usando metilamina en la etapa 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.65 (d, 1H), 8.51 (d, 1H), 8.22 (d, 1H), 8.11 (m, 1H), 8.01 (dd, 1H), 7.38 (m, 2H), 7.22 (t, 1H), 7.01 (d, 1H), 6.90 (m, 2H), 6.86 (d, 1H), 6.73 (d, 1H), 5.54 (d, 1H), 4.54 (bs, 2H), 3.82 (m, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 2.60 (d, 3H), 2.20 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H). MS (EI) para $C_{32}H_{37}N_5O_5$: 572 (MH^+).

[00585] (9E): N-{(1S)-2-(etilamino)-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 10 usando etilamina en la etapa 3. MS (EI) para $C_{33}H_{39}N_5O_5$: 586 (MH^+).

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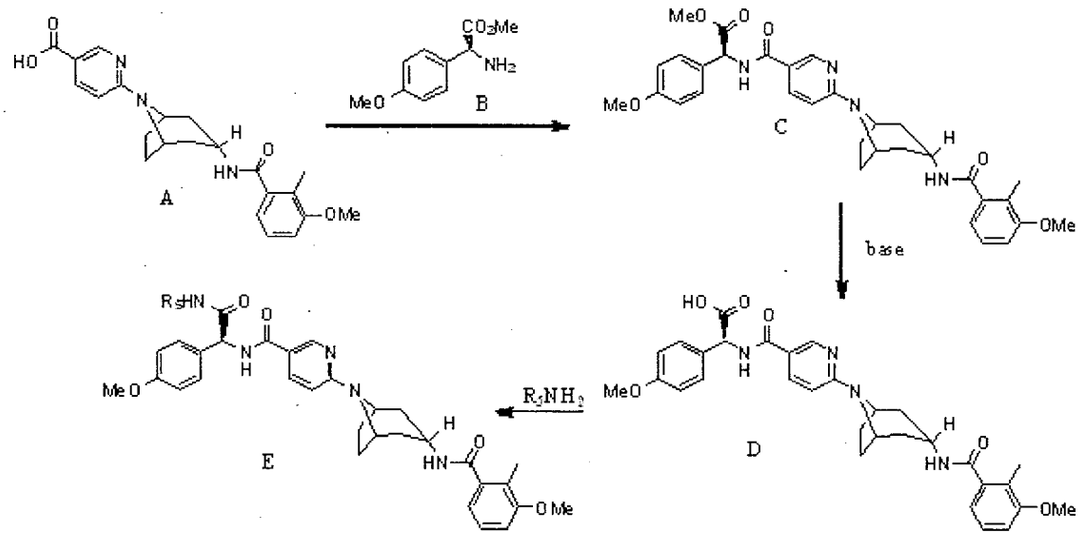
ESQUEMA DE REACCIÓN SINTÉTICA 10:



[00586] El esquema de reacción 10 generalmente describe la síntesis de de todos los compuestos listados en el Ejemplo 10, en donde R_5 es como se define en la especificación.

[00587] En el esquema de reacción 10, el compuesto (B) se agrega al compuesto (A) bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como EDCI y HOBT, para condensar y formar la amida unida en el compuesto (C). El éster en el compuesto (C) después se hidroliza con una base, tal como KOH, para formar el compuesto (D). Al compuesto (D) se agrega R_5NH_2 bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como EDCI y HOBT, para condensar y formar la amida unida en el compuesto (E).

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[00588] EJEMPLO 10: N-{(1S)-2-amino-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida.

[00589] ETAPA 1: Una solución de sal trifluoroacetato de 2-amino-2-(4-metoxifenil)acetato (S)-metilo (sintetizado de conformidad con el reactivo de la preparación 38) (0.30 g, 1.00 mmol), ácido 6-[3-endo-({[2-metil-3-metiloxi)fenil]-carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (preparada en el Ejemplo 1, ETAPA 4) (0.43 g, 1.00 mmol), HOBt (0.16 g, 1.20 mmol), EDCI (0.23 g, 1.20 mmol) y 4-metilmorfolina (0.88 mL, 8.00 mmol) en dimetilformamida (5 mL) se agita a temperatura ambiente por 18 horas. La mezcla de reacción se divide entre acetato de etilo (100 mL) y salmuera (50 mL). La capa orgánica se separa y se lava con salmuera (50 mL), se seca sobre sulfato de sodio, se filtra y el solvente se concentra. El residuo se somete a cromatografía en columna (hexano:acetato de etilo 4:1 hasta 3:2) para dar (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoato de metilo, (0.51 g, 89% de rendimiento). MS (EI) para $C_{32}H_{36}N_4O_6$: 573 (MH^+).

[00590] ETAPA 2: Una solución de (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoato de metilo (0.48 g, 0.84 mmol) y una solución acuosa de 4M hidróxido de potasio (0.42 mL, 1.68 mmol) en metanol (10 mL), tetrahidrofurano (5 mL) y agua (5 mL) se agita a 50 °C por 30 minutos. Después del enfriamiento a temperatura ambiente, el solvente se evapora y el pH se ajusta a 2 con ácido clorhídrico acuoso concentrado. Lo precipitado se recolecta por filtración, se lava con agua, y se seca para proporcionar ácido (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoico (0.42 g, 89%). MS (EI) para $C_{31}H_{34}N_4O_6$: 557 (M-H).

[00591] ETAPA 3: Una solución de ácido (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoico (0.10 g, 0.18 mmol), una solución 2M de amoníaco en metanol (0.18 mL, 0.36 mmol), HOBt (0.027 g, 0.20 mmol), EDCI (0.042 g, 0.22 mmol) y 4-metilmorfolina (0.10 mL, 0.90 mmol) en dimetilformamida (3 mL) se agita a temperatura ambiente por 18 horas. El solvente se concentra in vacuo y el residuo se purifica por HPLC de fase inversa preparatoria (0.1% de acetato de amonio en fase móvil de

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acetonitrilo acuoso) para dar N-{(1S)-2-amino-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida (17 mg, 11% de rendimiento). MS (EI) para $C_{31}H_{35}N_5O_5$: 558 (MH^+).

[00592] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos los siguientes compuestos [(10B)-(10E)] se preparan. Materiales de partida alternativos se obtienen comercialmente a menos que se indique de otra manera.

[00593] (10B): (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoato de metilo. Preparada en el Ejemplo 10 etapa 1. MS (EI) para $C_{32}H_{36}N_4O_6$: 573 (MH^+).

[00594] (10C): Ácido (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoico. Preparada en el Ejemplo 10 etapa 2. MS (EI) para $C_{31}H_{34}N_4O_6$: 557 (M-H).

[00595] (10D): N-{(1S)-2-(metilamino)-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 10 usando metilamina en la etapa 3. ^1H NMR

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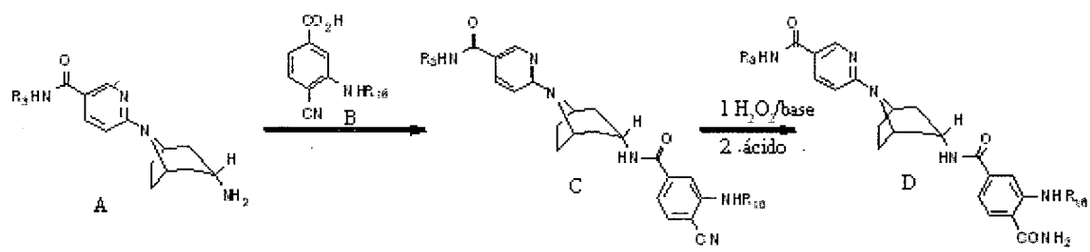
(400 MHz, DMSO-d_6): 8.65 (d, 1H), 8.51 (d, 1H), 8.22 (d, 1H), 8.11 (m, 1H), 8.01 (dd, 1H), 7.38 (m, 2H), 7.22 (t, 1H), 7.01 (d, 1H), 6.90 (m, 2H), 6.86 (d, 1H), 6.73 (d, 1H), 5.54 (d, 1H), 4.54 (bs, 2H), 3.82 (m, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 2.60 (d, 3H), 2.20 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.84 (d, 2H). MS (EI) para $C_{32}H_{37}N_5O_5$: 572 (MH^+).

[00596] (10E): N-{(1S)-2-(etilamino)-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 10 usando etilamina en la etapa 3. MS (EI) para $C_{33}H_{39}N_5O_5$: 586 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 11:



[00597] El esquema de reacción 11 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 11, en donde R_3 y R_{16} son como se definen en la especificación.

[00598] En el esquema de reacción 11, el compuesto (B) se agrega al compuesto (A) bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal

como HOBT, para condensar y formar la amida unida en el compuesto (C). El compuesto (C) después se convierte al compuesto (D) por hidrólisis del nitrilo aromático por tratamiento con una base, tal como carbonato de potasio, en la presencia de un oxidante adecuado, tal como peróxido de hidrógeno, para llegar a la carboxamida aromática (D).

EJEMPLO 11: N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(trans-4-aminociclohexil)amino]bencen-1,4-dicarboxamida

[00599] ETAPA 1: A una solución de 3-bromo-4-cianobenzoato de metilo (200 mg, 0.83 mmol) en diclorometano (1.5 mL) y metanol (1.5) se agrega 1.0 N hidróxido de sodio acuoso (1.7 mL, 1.7 mmol). La mezcla se agita vigorosamente por 2 h a temperatura ambiente. Los solventes volátiles después se remueven in vacuo. El residuo acuoso se acidifica con ácido clorhídrico acuoso 1 N y después se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de magnesio, se filtra, y se concentra para proporcionar ácido 3-bromo-4-cianobenzoico (190 mg, 0.83 mmol, rendimiento cuantitativo). ^{1}H NMR (400 MHz, $CDCl_3$): 8.42 (d, 1H), 8.15 (dd, 1H), 7.80 (d, 1H).

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[00600] ETAPA 2: A una solución de ácido 3-bromo-4-cianobenzoico (1.51 g, 6.69 mmol) en acetona (30 mL) se agrega carbonato de cesio (4.4 g, 13.4 mmol) y bromuro de bencilo (790 uL, 6.69 mmol). La mezcla se agita a reflujo por 15 horas punto en el cual se agrega bromuro de bencilo adicional (200 uL, 1.68 mmol). La mezcla se agita a reflujo por 2 h adicionales y después se enfría a temperatura ambiente. Se agregan agua y acetato de etilo y las capas se separan. La fase acuosa después se satura con cloruro de litio y se extrae con acetato de etilo. Los extractos orgánicos se combinan, se secan sobre sulfato de magnesio, se filtran, y se concentran. El residuo se purifica por cromatografía en columna (4:1 hexanos:acetato de etilo) para proporcionar 3-bromo-4-cianobenzoato de fenilmetilo (957 mg, 3.03 mmol, 45% de rendimiento) como un aceite anaranjado amarillento que lentamente se solidifica. ^{1}H NMR (400 MHz, $CDCl_3$): 8.35 (d, 1H), 8.09 (dd, 1H), 7.73 (d, 1H), 7.46-7.35 (m, 5H), 5.35 (s, 2H).

[00601] ETAPA 3: Un recipiente de presión que contiene una barra agitadora magnética se carga con 3-bromo-4-cianobenzoato de fenilmetilo (100 mg, 0.32 mmol), (*trans*-4-aminociclohexil)carbamato de 1,1-dimetiletilo (69 mg, 0.32 mmol), carbonato de cesio (125 mg, 0.38 mmol), XANTPHOS (19 mg, 0.032 mmol), tris(dibencilidenacetona)dipaladio(0) (15

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mg, 0.016 mmol) y dioxano (1.5 mL). El recipiente después se sella y calienta a 95°C. La suspensión se agita por aproximadamente 24 h a esta temperatura y después se deja enfría a temperatura ambiente. La suspensión se vierte en agua, y la mezcla acuosa resultante se extrae dos veces con acetato de etilo. Los extractos orgánicos se combinan, se secan sobre sulfato de magnesio, se filtran, y se concentran in vacuo. El residuo después se purifica por cromatografía en columna (4:1 hexanos:acetato de etilo) para proporcionar 4-ciano-3-{[*trans*-4-({[(1,1-dimetiletil)oxi]carbonil}-amino)ciclohexil]amino}benzoato de fenilmetilo impuro (71.8 mg, 0.16 mmol) como un polvo amarillo. Este material se lleva en la subsecuente etapa sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$): 7.45-7.28 (m, 8H), 5.37 (s, 2H), 4.47 (m, 1H), 3.40 (m, 1H), 2.12 (m, 4H), 1.46 (s, 9H), 1.31 (m, 4H).

[00602] ETAPA 4: Se agrega paladio en carbono 10% en peso tipo Degussa (50 mg) a una solución de 4-ciano-3-{[*trans*-4-({[(1,1-dimetiletil)oxi]carbonil}amino)ciclohexil]amino}benzoato de fenilmetilo (71.8 mg, 0.16 mmol) en acetato de etilo (3 mL) y metanol (400 uL). La mezcla se somete a 1 atm de hidrógeno por 70 min. Después se remueve el catalizador por filtración a través de celite. Lo filtrado resultante se concentra para proporcionar ácido 4-ciano-3-{[*trans*-4-({[(1,1-

dimetiletil)oxi]carbonil}amino)ciclohexil]amino}benzoico (55.8 mg, 0.16 mmol) el cual se lleva en la subsecuente etapa sin purificación adicional. ^{1}H NMR (400 MHz, CD_3OD): 7.47 (d, 1H), 7.37 (s, 1H), 7.24 (d, 1H), 3.47-3.21 (m, 2H), 2.09 (m, 2H), 1.98 (m, 2H), 1.88 (m, 2H), 1.43 (s, 9H), 1.24 (m, 2H); MS (EI) para $C_{19}H_{25}N_3O_4$: 304 (MH^+-*terc-butilo*).

[00603] ETAPA 5: A una solución de ácido 4-ciano-3-{[*trans*-4-({[(1,1-dimetiletil)oxi]carbonil}amino)ciclohexil]amino}benzoico (55.8 mg, 0.16 mmol) se agrega HATU (59 mg, 0.16 mmol). La mezcla resultante se agita a temperatura ambiente por 2.5 h. Después se agrega más HATU (60 mg, 0.16 mmol), y la mezcla se agita por 40 min adicionales a temperatura ambiente. En este punto se agrega 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida (sintetizada en el Ejemplo 3) (45 mg, 0.16 mmol) seguido por diisopropiletilamina (167 uL, 0.96 mmol). La solución se agita 45 min a temperatura ambiente después de lo cual se agrega agua. La mezcla acuosa después se extrae dos veces con acetato de etilo. Los extractos orgánicos se combinan, se lavan con 10% solución cloruro de litio acuoso, se secan sobre sulfato de magnesio, se filtran, y se concentran. El residuo se somete a cromatografía en columna (5% de metanol en diclorometano) para proporcionar [*trans*-4-({5-[({8-[5-(aminocarbonil)piridin-2-il]-8-

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azabiciclo[3.2.1]oct-3-endo-il}amino)carbonil]-2-cianofenil}amino)ciclohexil]carbamato de 1,1-dimetiletilo (50.8 mg, 0.061 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): 8.62 (d, 1H), 7.94 (dd, 1H), 7.44 (d, 1H), 7.15 (s, 1H), 6.80 (d, 1H), 6.62 (d, 1H), 6.56 (d, 1H), 4.65 (br s, 2H), 4.53 (d, 1H), 4.47 (br d, 1H), 4.22 (m, 1H), 3.55-3.36 (m, 2H), 2.39-2.25 (m, 4H), 2.18-2.02 (m, 6H), 1.86 (d, 2H), 1.45 (s, 9H), 1.37-1.22 (m, 4H); MS (EI) para $C_{32}H_{41}N_7O_4$: 588 (MH^+).

[00604] ETAPA 6: A una solución de [*trans*-4-({5-[({8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}amino)carbonil]-2-cianofenil}amino)ciclohexil]carbamato de 1,1-dimetiletilo (40.7 mg, 0.069 mmol) en DMSO (1 mL) se agrega carbonato de potasio (19 mg, 0.138 mmol) seguido por peróxido de hidrógeno acuoso (30%, 2 gotas). La mezcla se agita a temperatura ambiente por 1 h. Después se agrega peróxido de hidrógeno adicional (4 gotas), y la mezcla se agita 35 min adicionales a 45°C. Después del enfriamiento a temperatura ambiente, la solución se diluye a 2 mL de volumen total con acetonitrilo:agua (2.5:1), y la mezcla se purifica por HPLC de fase inversa preparativa para proporcionar [*trans*-4-({2-(aminocarbonil)-5-[({8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}amino)carbonil]fenil}amino)ciclohexil]carbamato de 1,1-dimetiletilo (17.6 mg, 0.029 mmol, 42% de rendimiento). ^{1}H

NMR (400 MHz, CD_3OD): 8.64 (d, 1H), 7.99 (dd, 1H), 7.63 (d, 1H), 7.06 (s, 1H), 6.88 (dd, 1H), 6.76 (d, 1H), 4.64 (br s, 2H), 4.00 (m, 1H), 3.37 (m, 2H), 2.30-2.12 (m, 8H), 2.02-1.93 (m, 4H), 1.43 (s, 9H), 1.35 (m, 4H).

[00605] ETAPA 7: A un matraz que contiene [*trans*-4-({2-(aminocarbonil)-5-[({8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}amino)carbonil]fenil}amino)ciclohexil]carbamato de 1,1-dimetiletilo (17.6 mg, 0.029 mmol) se agrega 2.0 M ácido clorhídrico acuoso (2 mL, 4 mmol). La mezcla se agita por 1 h a temperatura ambiente después la solución resultante después se liofiliza para dar N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(*trans*-4-aminociclohexil)amino]bencen-1,4-dicarboxamida como la sal de clorhidrato. ^{1}H NMR (400 MHz, CD_3OD): 8.45 (d, 1H), 8.38 (dd, 1H), 8.13 (d, 1H), 8.03 (d, 1H), 7.96 (dd, 1H), 7.40 (d, 1H), 4.82 (br s, 2H), 4.15 (br s, 1H), 3.77 (m, 1H), 3.20 (m, 1H), 2.49 (m, 2H), 2.43-2.24 (m, 6H), 2.17 (m, 4H), 1.71 (m, 2H), 1.56 (m, 2H); MS (EI) para $C_{27}H_{35}N_7O_3$: 506 (MH^+).

[00606] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [(11B)-(11C)]. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00607] (11B): N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 11 usando 3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)anilina (Gaster et al. *J. Med Chem.* 1998, *41*, 1218-1235) en la etapa 3 después de la omisión de la etapa 7. ^{1}H NMR (400 MHz, CD_3OD): 8.42 (d, 1H), 8.37 (dd, 1H), 7.74 (d, 1H), 7.48 (d, 1H), 7.36 (d, 1H), 7.08-6.99 (m, 3H), 6.95 (d, 1H), 4.75 (br s, 2H), 4.34 (m, 2H), 4.06 (m, 1H), 3.88 (s, 3H), 3.58 (m, 2H), 3.02 (s, 6H), 2.33-2.15 (m, 8H); MS (EI) para $C_{32}H_{39}N_7O_5$: 602 (MH^+).

[00608] (11C): N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-[(2-morfolin-4-iletil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 11 procediendo directamente a la etapa 5 usando 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida (sintetizado en el Ejemplo 6) y ácido 3-bromo-4-cianobenzoico (sintetizado en la etapa 1 anterior) después conduciendo a la etapa 3 usando 2-morfolin-4-iletanamina y etapa 6. ^{1}H NMR (400 MHz, CD_3OD): 8.60 (d, 1H), 7.97 (dd, 1H), 7.63 (d, 1H), 7.29 (d, 2H), 7.08 (s, 1H), 6.96 (d, 2H), 6.93 (d, 1H), 6.75 (d, 1H), 5.17 (q,

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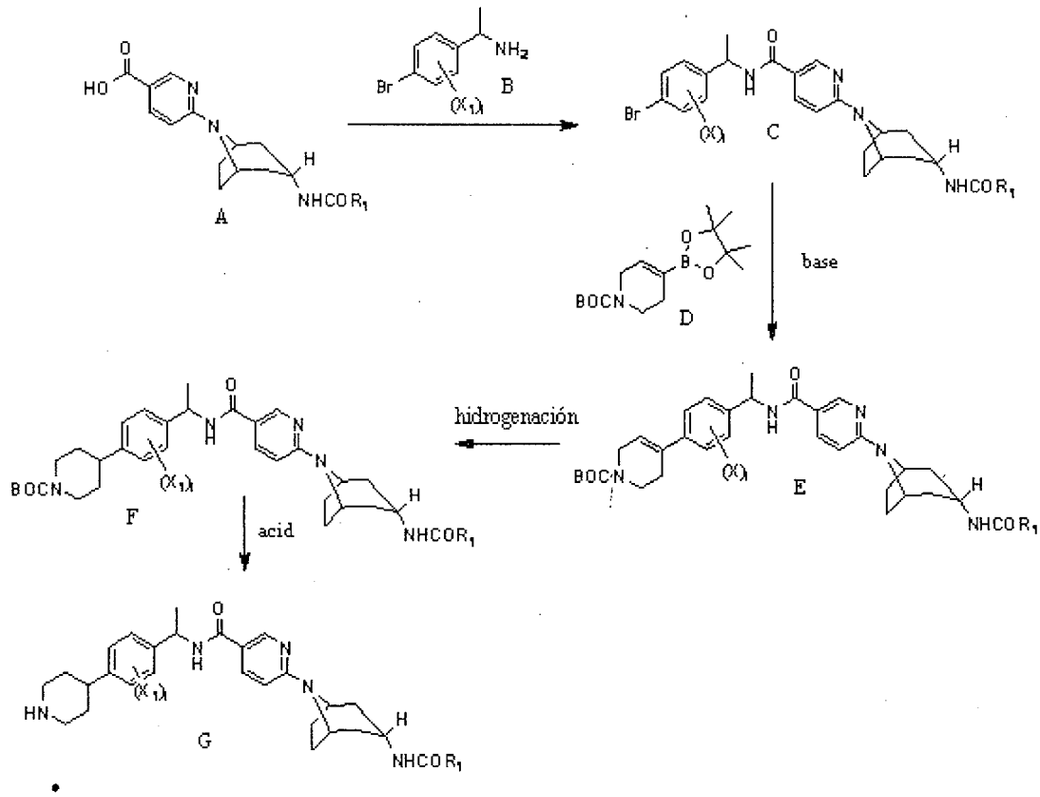
1H), 4.62 (br s, 2H), 3.98 (m, 1H), 3.73 (m, 4H), 3.35 (t, 2H), 3.24 (m, 4H), 2.84 (m, 4H), 2.68 (t, 2H), 2.54 (m, 4H), 2.51 (s, 3H), 2.30-2.12 (m, 6H), 1.97 (m, 2H), 1.94 (s, 6H), 1.52 (d, 3H); (EI) para $C_{40}H_{53}N_9O_4$: 724.6 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 12:



[00609] El esquema de reacción 12 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 12, en donde X_1, R_1 y (i) son como se definen en la especificación.

[00610] En el esquema de reacción 12, el compuesto (B) se agrega al compuesto (A) bajo condiciones de reacción

apropiadas y con un reactivo de acoplamiento adecuado, tal como EDCI y HOBT, para condensar y formar la amida unida en el compuesto (C). Después se trata Bromuro de arilo (C) con un éster de boroato (D) bajo condiciones de reacción adecuadas en la presencia de un catalizador de paladio apropiado para llegar a un compuesto (E). El compuesto (E) se reduce con un agente de reducción, tal como 10% de paladio en carbón vegetal, para llegar a un compuesto (F). El compuesto (F) después se desprotege en la presencia de un ácido, tal como HCl, para remover BOC y llegar al compuesto (G).

[00611] EJEMPLO 12: N-[1-(2,6-difluoro-4-piperidin-4-ilfenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida.

[00612] ETAPA 1: A una mezcla de 1-(4-bromo-2,6-difluorofenil)etanona (450 mg, 0.91 mmol), isopropóxido de titanio (1.14 mL, 4.61 mmol) en etanol (10 mL) se agrega una solución de amoníaco a 2M en etanol (4.8 mL, 9.6 mmol), y la mezcla resultante se agita a temperatura ambiente. Después de 18 horas, (115 mg, 3.48 mmol) se agrega borohidruro de sodio y la agitación se continúa a temperatura ambiente por tres horas. La mezcla de reacción se vierte en una solución de hidróxido de amoníaco acuoso 2M (100 mL) después se filtra.

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Lo filtrado se extrae con acetato de etilo (3 x 50 mL), y el extracto combinado se lava con agua (100 mL), después salmuera (100 mL), se seca sobre sulfato de sodio, se filtra y se concentra para dar 1-(4-bromo-2,6-difluorofenil)etanamina (236 mg, 62% de rendimiento), MS (EI) para $C_8H_8BrF_2N$: 237 (MH^+).

[00613] ETAPA 2: Una mezcla de ácido 6-[3-endo-({[2-metil-3-(metiloxi)fenil]-carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (sintetizado en el Ejemplo 1)(276 mg, 0.70 mmol), EDCI (95 mg, 0.70 mmol), 1-hidroxibenzotriazol (95 mg, 0.70 mmol), y N,N-diisopropiletilamina (0.37 mL, 2.1 mmol) en N,N-dimetilformamida (3 mL) se agita a temperatura ambiente por 15 minutos. A esta mezcla se agrega una solución de 1-(4-bromo-2,6-difluorofenil)etanamina (165 mg, 0.70 mmol) en N,N-dimetilformamida (0.5 mL) y la agitación se continúa por 18 horas. La mezcla de reacción se diluye con acetato de etilo (30 mL), se lava con 5% solución acuosa de cloruro de litio (2x10 mL), solución saturada de bicarbonato de sodio (10 mL), se seca sobre sulfato de sodio, se filtra y se concentra. El producto crudo se purifica por cromatografía instantánea (65-95% de acetato de etilo-hexanos) para dar el N-[1-(4-bromo-2,6-difluorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-

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il]piridin-3-carboxamida (348 mg, 81% de rendimiento). ^{1}HNMR (400MHz, $CDCl_3$): 8.58 (d, 1H), 7.86 (dd, 1H), 7.20-7.17 (dd, 1H), 7.08 (s, 1H), 7.06 (s, 1H), 6.95 (dd, 2H), 6.70 (br, 1H), 6.36-6.35(br, 1H), 6.69-6.67 (m, 1H), 4.50 (br, 2H), 4.22-4.20 (m, 1H), 3.86 (s, 3H), 2.29-2.27 (m, 2H), 2.28 (s, 3H), 2.20-2.17 (m, 2H), 2.00 (d, 2H), 1.85-1.81 (d, 2H), 1.58-1.57 (d, 3H); MS (EI) para $C_{30}H_{31}BrF_2N_4O_3$: 614 (MH^+).

[00614] ETAPA 3: Una mezcla de N-[1-(4-bromo-2,6-difluorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida (348 mg, 0.57 mmol), éster pinacol del ácido 3,6-dihidro-2H-piridin-1-terc-butoxicarbonil-4-borónico (228 mg, 0.74 mmol), complejo [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II) con diclorometano (28 mg, 5 mol %), carbonato de potasio (234 mg, 1.7 mmol), y N,N-dimetilformamida (4.5 mL) primero se desgasifica con nitrógeno por 10 minutos, después se agita a 80°C por 18 horas. La mezcla de reacción se enfría a temperatura ambiente, diluida con acetato de etilo (45 mL), se lava con 5% solución acuosa de cloruro de litio (2x 20 mL), se seca sobre sulfato de sodio, se filtra y se concentra. El producto crudo se purifica por cromatografía instantánea (65-95% de acetato de etilo en hexanos) para dar 4-(3,5-difluoro-4-{1-[({6-[3-endo-({[2-metil-3-

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(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino]etil}fenil)-3,6-dihidropiridin-1(2H)-carboxilato de 1,1-dimetiletilo (290 mg, 71% de rendimiento). ^{1}HNMR (400MHz, $CDCl_3$): 8.59 (d, 1H), 7.90 (dd, 1H), 7.21 (dd, 1H), 6.94-6.88 (m, 4H), 6.60 (d, 1H), 6.53 (d, 1H), 6.20 (d, 1H), 6.06 (br, 1H), 5.78-5.74 (m, 1H), 4.61 (br, 2H), 4.27 (q, 1H), 4.07 (br, 2H), 3.85 (s, 3H), 3.62 (tr, 2H), 2.42 (br, 2H), 2.36-2.31 (m, 2H), 2.29 (s, 3H), 2.22-2.20 (m, 2H), 2.03-1.97 (m, 2H), 1.85 (br, 1H), 1.81 (br, 1H), 1.62 (d, 3H), 1.49 (s 9H); MS (EI) para $C_{40}H_{47}F_2N_5O_5$: 716 (MH^+).

[00615] ETAPA 4: Una mezcla de 4-(3,5-difluoro-4-{1-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino]etil}fenil)-3,6-dihidropiridin-1(2H)-carboxilato de 1,1-dimetiletilo (133 mg, 0.19 mmol), 10% de paladio en carbón vegetal (Tipo Degussa, 100 mg), ácido acético (100 uL, 1.0 mmol), y metanol (20 mL) se agita en un aparato de hidrogenación Parr a 30 psi por 6 horas. La mezcla de reacción se filtra, se concentra, re-disuelve en una 1:1 mezcla (6 mL) de metanol y cloruro de hidrógeno a 4M en dioxano, y se agita a temperatura ambiente durante la noche. La mezcla de reacción se basifica con amoníaco a 2M en metanol, se concentra, y purifica por HPLC de fase inversa

preparatoria (eluyente de acetonitrilo acuoso amortiguado con acetato de amonio). Las fracciones que contienen el producto se combinan, y liofilizan para dar un sólido (58 mg, 0.094 mmol) el cual se disuelve en metanol (4 mL) que contiene y cloruro de hidrógeno a 4M en dioxano (49 uL, 0.20 mmol), después se evapora a sequedad lo cual proporciona clorhidrato de N-[1-(2,6-difluoro-4-piperidin-4-ilfenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. (65 mg, 51% de rendimiento). ^{1}HNMR (400MHz, d_4-metanol): 8.40 (d, 1H), 8.34 (dd, 1H), 7.37(d, 1H), 7.23 (dd, H), 7.01 (d, 1H), 6.94-6.90 (m, 3H), 5.48 (q, 1H), 4.80 (br, 2H), (4.10 (tr, 1H), 3.84 (s, 3H), 3.47 (br, 2H), 3.16 (m, 2H), 3.93 (m, 2H), 2.37-2.33 (m, 4H), 2.24-2.15 (m, 2H), 2.20 (s, 3H), 2.06 (d, 2H), 1.94-1.89 (m, 2H), 1.65 (d, 2H); MS (EI) para $C_{35}H_{41}F_2N_5O_3$: 618 (MH^+).

[00616] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se prepara el compuesto (12B). Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00617] (12B): N-[1-(2-fluoro-4-piperidin-4-ilfenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 12 iniciando con 4-bromo-2-fluoroacetofenona en la

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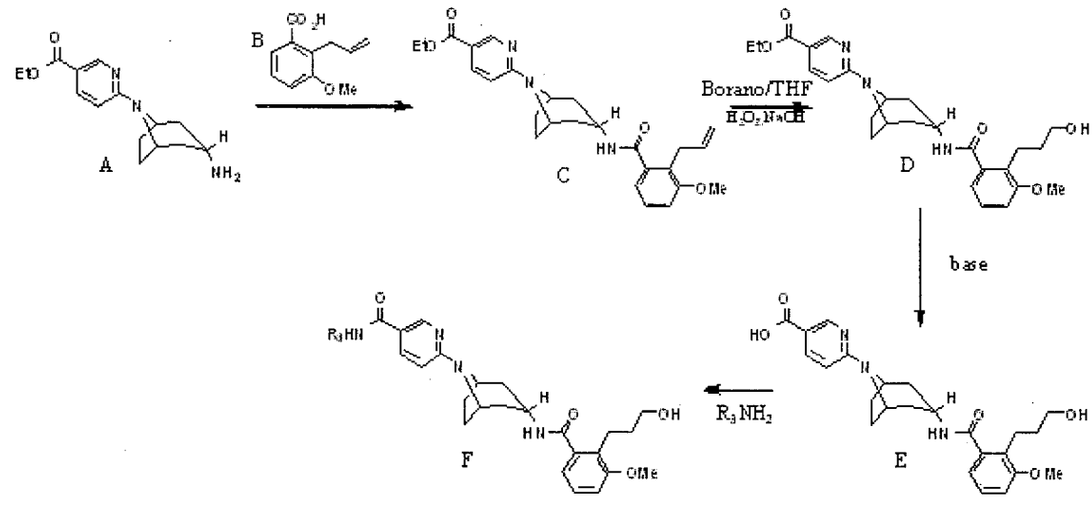
etapa 1. ^{1}H-NMR (400MHz, d_4-metanol): 8.44 (s, 1H), 8.38 (d, 1H), 7.40 (m, 2H), 7.24 (dd, 1H), 7.19 (d, 1H), 7.02 (dd, 2H), 6.91 (d, 1H), 5.41 (q, 1H), 4.79 (br, 2H), 4.11 (tr, 1H), 3.84 (s, 3H), 3.48 (d, 2H) 3.14 (m, 2H), 2.90 (m, 2H), 2.38-2.35 (m, 4H), 2.24-2.15 (m, 4H), 2.21 (s, 3H), 2.10-2.20 (m, 2H), 1.92-1.87 (m, 2H), 1.57 (d, 3H); MS (EI) para $C_{35}H_{42}FN_5O_3$: 600 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 13:



[00618] El esquema de reacción 13 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 13, en donde R_3 es como se define en la especificación.

[00619] En el esquema de reacción 13, el compuesto (B) se agrega al compuesto (A) bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el

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compuesto (C). El compuesto (C) después se convierte al intermediario (D) por hidroboración. De este modo, (C) primero se trata con borano en THF seguido por reacción con peróxido de hidrógeno en la presencia de una base adecuada tal como hidróxido de sodio. El carboxilato del compuesto (D) después se hidroliza por una base, tal como KOH, para llegar a un compuesto (E). Después se agrega R_3NH_2 al compuesto (E) bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (F).

[00620] EJEMPLO 13: 6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida.

[00621] ETAPA 1: Una solución de clorhidrato 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxilato de etilo (sintetizado en el Ejemplo 1) (2.60 g, 6.69 mmol), ácido 3-(metiloxi)-2-prop-2-en-1-ilbenzoico (sintetizado en la preparación del reactivo 19) (1.28 g, 6.69 mmol), HATU (2.54 g, 6.69 mmol), y diisopropiletilamina (3.46 g, 26.76 mmol) en DMF (10 mL) se agita a temperatura ambiente por 18 h. La mezcla de reacción se diluye con acetato de etilo (250 mL), se lava con bicarbonato de sodio saturado (100 mL), 5% de cloruro de litio (2 x 100 mL), y salmuera (100 mL), se

seca sobre sulfato de sodio, se filtra y se concentra para dar 6-[3-endo-({[3-(metiloxi)-2-prop-2-en-1-ilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo crudo (3.52 g) como un aceite marrón. MS (EI) para $C_{26}H_{31}N_3O_4$: 450 (MH^+).

[00622] ETAPA 2: A una solución de 6-[3-endo-({[3-(metiloxi)-2-prop-2-en-1-ilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (213 mg, 0.40 mmol) en THF (5 mL) se agrega una solución 1.0 M de complejo borano THF en THF (0.40 mL, 0.40 mmol) a 0 °C. Después de remover el baño helado, la mezcla se agita a temperatura ambiente por 4 h. Se agrega solución 1.0 M de complejo borano THF en THF adicional (0.40 mL, 0.40 mmol) y la agitación se continúa por 18 h. Se agrega otra solución 1.0 M de complejo borano THF en THF (0.40 mL, 0.40 mmol) y la mezcla se agita por 24 h adicionales. Después se agrega agua (1.0 mL) seguido por 10% de hidróxido de sodio (1.0 mL), y 30% peróxido de hidrógeno (2.2 mL). La mezcla de reacción se agita a temperatura ambiente por otros 90 min, después se enfría a 0 °C, y (3.40 g, 21.5 mmol) se agrega cuidadosamente tiosulfato de sodio. Se remueve el baño helado y la mezcla se agita a temperatura ambiente por 30 min. La mezcla se acidifica a pH3 con ácido clorhídrico 1N, y se extrae con acetato de etilo (3 x 40 mL). Las capas orgánicas se lavan

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con salmuera (20 mL), se secan sobre sulfato de sodio, se filtran y se concentran para proporcionar 6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo crudo (258 mg). MS (EI) para $C_{26}H_{33}N_3O_5$: 468 (MH^+).

[00623] ETAPA 3: Una suspensión de 6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (240 mg, 0.51 mmol) e hidróxido de potasio (58 mg, 1.02 mmol) en metanol (6 mL) y agua (2 mL) se agita a 60 °C por 2 h. Después del enfriamiento a temperatura ambiente, se agrega agua a la mezcla resultante, y el pH se ajusta a 5 con ácido clorhídrico acuoso a 1N. La extracción con acetato de etilo (3 x 30 mL), secado sobre sulfato de sodio después la filtración y concentración proporciona ácido 6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico crudo (120 mg, 53% de rendimiento). MS (EI) para $C_{24}H_{29}N_3O_5$: 440 (MH^+).

[00624] ETAPA 4: Una solución de ácido 6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (35 mg, 0.08 mmol), N-metilmorfolina (26 µl, 0.24 mmol), bencilamina (10 µl, 0.08 mmol) y HATU (30 mg, 0.08 mmol) en dimetilformamida

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(1 mL) se agita a 40 °C por 15 h. La mezcla se enfría a temperatura ambiente y se diluye con acetato de etilo. La porción orgánica se lava con 5% de cloruro de litio acuoso, 20% ácido cítrico acuoso, salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra. La purificación por HPLC de fase inversa preparatoria (eluyente de acetonitrilo acuoso amortiguado con 0.1% ácido trifluoroacético) proporciona 6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}-amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida como la sal de trifluoroacetato (17 mg, 38% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): 8.98 (br s, 1H), 8.56 (s, 1H), 8.30 (d, 1H), 8.14 (d, 1H), 7.35-7.31 (m, 5H), 7.26-7.21 (m, 2H), 7.05-7.02 (m, 2H), 6.85 (d, 1H), 4.63 (br s, 2H), 4.47 (d, 2H), 3.90-3.83 (m, 1H), 3.80 (s, 3H), 3.35 (t, 2H), 2.64-2.59 (m, 2H), 2.28-1.90 (m, 8H), 1.68-1.60 (m, 2H). MS (EI) para $C_{31}H_{36}N_4O_4$: 529 (MH^+).

[00625] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se prepara el compuesto (13B). Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00626] (13B): 6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida. Preparada de conformidad con el método del ejemplo 13 usando amoníaco en la etapa 4. ^{1}H NMR

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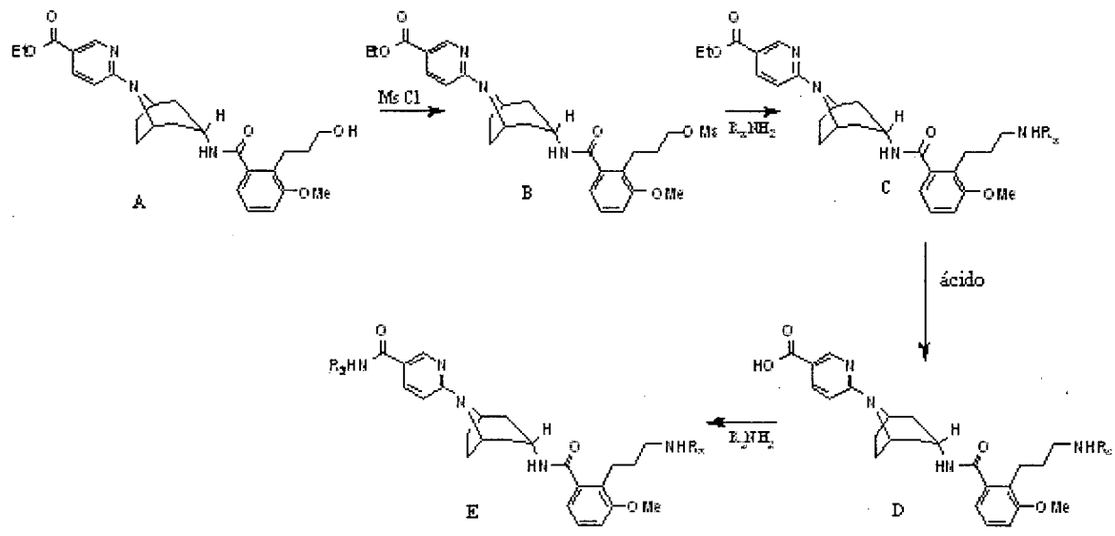
(400 MHz, d_4-MeOH): 8.62 (d, 1H), 8.34-8.31 (m, 1H), 7.99 (dd, 1H), 7.25 (t, 1H), 7.03 (d, 1H), 6.91 (d, 1H), 6.76 (d, 1H), 4.61 (br s, 2H), 4.04-3.97 (m, 1H), 3.84 (s, 3H), 3.51 (t, 2H), 2.75 (t, 2H), 2.35-2.07 (m, 6H), 1.92 (d, 2H), 1.85-1.76 (m, 2H); MS (EI) para $C_{24}H_{30}N_4O_4$: 439 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 14:



[00627] El esquema de reacción 14 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 14, en donde R_3 es como se define en la especificación y R_x es alquilo.

[00628] En el esquema de reacción 14, se agrega MsCl al compuesto (A) bajo condiciones de reacción apropiadas para llegar a un compuesto (B). Al compuesto (B) se agrega R_xNH_2 bajo condiciones de reacción apropiadas para llegar a un compuesto (C). El carboxilato del compuesto (C) después se

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hidroliza con una base para llegar a un compuesto (D). Al compuesto (D) se agrega R_3NH_2 bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (E).

[00629] EJEMPLO 14: 6-[3-endo-({[2-{3-[(1-metiletil)amino]propil}-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida.

[00630] ETAPA 1: Una solución de 6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (sintetizado en el Ejemplo 13) (90 mg, 0.19 mmol, ejemplo 13, etapa 2), trietilamina (51 mg, 0.50 mmol), y cloruro de mesilo (29 mg, 0.26 mmol) en diclorometano (5 mL) se agita a temperatura ambiente por 2.5 h. La mezcla de reacción se concentra y se agrega isopropilamina (5 mL). La mezcla resultante se agita a 50 °C por 17 h y después se concentra. El residuo se divide entre acetato de etilo (50 mL) y bicarbonato de sodio saturado (50 mL). Las capas se separan y la capa orgánica se lava con salmuera (20 mL), se seca sobre sulfato de sodio, después se filtra y se concentra para dar 6-[3-endo-({[2-{3-[(1-metiletil)amino]propil}-3-

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(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato etilo crudo (87 mg, 89% de rendimiento) como un aceite amarillo. MS (EI) para $C_{29}H_{40}N_4O_4$: 509 (MH^+).

[00631] ETAPA 2: Una suspensión de 6-[3-endo-({[2-{3-[(1-metiletil)amino]-propil}-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (83 mg, 0.16 mmol) e hidróxido de potasio (18 mg, 0.32 mmol) en metanol (3 mL) y agua (1 mL) se agita a 60 °C por 1 h. Después del enfriamiento a temperatura ambiente, se evapora algo del metanol, se agrega agua a la mezcla resultante y el pH se ajusta a 7 con ácido clorhídrico acuoso a 1N. La mezcla resultante se concentra y purifica por HPLC preparatoria (0.1% ácido trifluoroacético-acetonitrilo acuoso) para proporcionar sal de trifluoroacetato del ácido 6-[3-endo-({[2-{3-[(1-metiletil)amino]propil}-3-(metiloxi)fenil]-carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (39 mg, 41% de rendimiento) como un aceite incoloro. MS (EI) para $C_{27}H_{36}N_4O_4$: 481 (MH^+).

[00632] ETAPA 3: Una solución de sal de trifluoroacetato del ácido 6-[3-endo-({[2-{3-[(1-metiletil)amino]propil}-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (39 mg, 0.08 mmol), bencilamina (10

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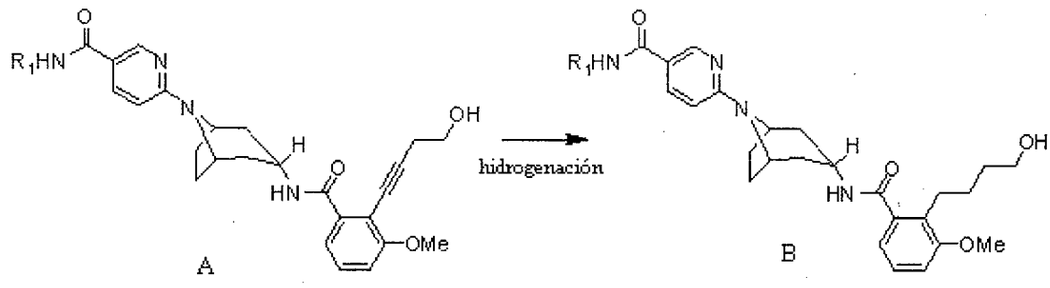
mg, 0.09 mmol), HATU (31 mg, 0.08 mmol), y diisopropiletilamina (26 mg, 0.20 mmol) en DMF (2 mL) se agita a temperatura ambiente por 5 h. La mezcla de reacción se purifica por HPLC de fase inversa preparatoria (0.1% ácido trifluoroacético-acetonitrilo acuoso) para proporcionar sal de trifluoroacetato 6-[3-endo-({[2-{3-[(1-metiletil)amino]-propil}-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida (25 mg, 45% de rendimiento). ^{1}H NMR (400 MHz, metanol-d_4): 8.57 (d, 1H), 8.46 (d, 1H), 8.26 (dd, 1H), 7.35 (m, 5H), 7.26 (m, 1H), 7.19 (d, 1H), 7.14 (d, 1H), 7.02 (d, 1H), 4.70 (br s, 2H), 4.57 (s, 2H), 4.10 (m, 1H), 3.88 (s, 3H), 3.25 (m, 1H), 2.88 (t, 2H), 2.81 (t, 2H), 2.39-2.20 (m, 6H), 2.10 (m, 2H), 1.26 (d, 6H); MS (EI) para $C_{34}H_{43}N_5O_3$: 570 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 15:



[00633] El esquema de reacción 15 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 15, en donde R_1 es como se define en la especificación.

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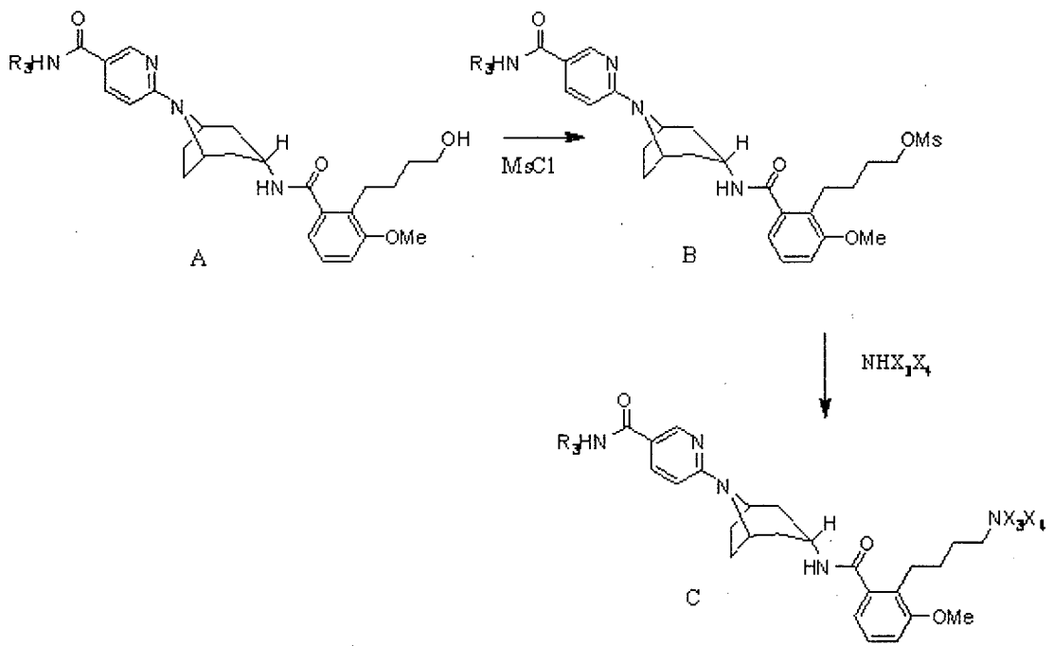
[00634] En el esquema de reacción 15, el compuesto (A) se hidrogena, como tal se coloca bajo un balón de hidrógeno o en un recipiente de presión bajo una atmósfera de hidrógeno en la presencia de un catalizador adecuado tal como paladio en carbono, para llegar a un compuesto (B).

[00635] EJEMPLO 15: 6-[3-endo-({[2-(4-hidroxibutil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida.

[00636] ETAPA 1: 6-[3-endo-({[2-(4-hidroxibut-1-in-1-il)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida (sintetizado en el Ejemplo 3) (0.069 g, 0.152 mmol) en metanol (20 ml) se agita bajo un balón de hidrógeno durante la noche a temperatura ambiente. La mezcla se filtra a través de Celite y la torta filtrada se enjuaga con acetato de etilo (2x10ml). Lo filtrado se seca sobre sulfato de sodio anhidro, se filtra y la solución se concentra. El residuo sólido se purifica por HPLC de fase inversa preparatoria (fase móvil de acetonitrilo acuoso amortiguado con 0.1% de acetato de amonio) y las fracciones puras combinadas se liofilizan para proporcionar 6-[3-endo-({[2-(4-hidroxibutil)-3-(metiloxi)fenil]carbonil}-amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida como un polvo blanco (0.047 g; 68% de rendimiento). ^{1}H NMR (400 MHz, d_4-

MeOH): 8.56 (d, 1H), 8.34 (d, 1H), 8.10 (dd, 1H), 7.24 (t, 1H), 7.02 (d, 1H), 6.96-6.88 (m, 2H), 4.65 (br s, 2H), 4.06-3.99 (m, 1H), 3.53 (t, 2H), 2.73 (t, 2H), 2.37-2.10 (m, 6H), 1.98 (d, 2H), 1.66-1.50 (m, 4H); MS (EI) para $C_{25}H_{32}N_4O_4$: 453 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 16:



[00637] El esquema de reacción 16 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 16, en donde R_3 es como se define en la especificación y X_3 y X_4 son cada uno independientemente H o alquilo.

[00638] En el esquema de reacción 16, se agrega MsCl al compuesto (A) bajo condiciones de reacción apropiadas para llegar a un compuesto (B). Al compuesto (B) se agrega NHX_3X_4

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bajo condiciones de reacción apropiadas para llegar a un compuesto (C).

[00639] EJEMPLO 16: 6-{3-endo-[({2-[4-(dimetilamino)butil]-3-(metiloxi)fenil}carbonil)amino]-8-azabiciclo[3.2.1]oct-8-il}piridin-3-carboxamida.

[00640] ETAPA 1: A una solución agitada de 6-[3-endo-({[2-(4-hidroxibutil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida (sintetizado en el Ejemplo 15) (0.038 g, 0.0823 mmol) en diclorometano (3 ml) se agrega trietilamina (0.034 ml, 0.250 mmol) seguido por cloruro de metansulfonilo (0.008 ml; 0.110 mmol) y la mezcla de reacción se agita a temperatura ambiente durante la noche. Se agregan más trietilamina (0.034 ml, 0.250 mmol) y cloruro de metansulfonilo (0.008 ml; 0.110 mmol) a la solución y la mezcla se agita a temperatura ambiente por dos horas adicionales. La mezcla se evapora por rotatorio y al residuo se agrega dimetilamina (4ml, solución 2 M en tetrahidrofurano 2 mmol). La solución resultante se agita en un recipiente de tubo sellado a 60 °C por 2h, se enfría a temperatura ambiente y se concentra. El residuo se purifica por HPLC de fase inversa preparatoria (0.1% de acetato de amonio en fase móvil de acetonitrilo acuoso) y las fracciones puras combinadas se liofilizan para proporcionar 6-{3-endo-[({2-[4-(dimetilamino)butil]-3-(metiloxi)fenil}carbonil)amino]-8-

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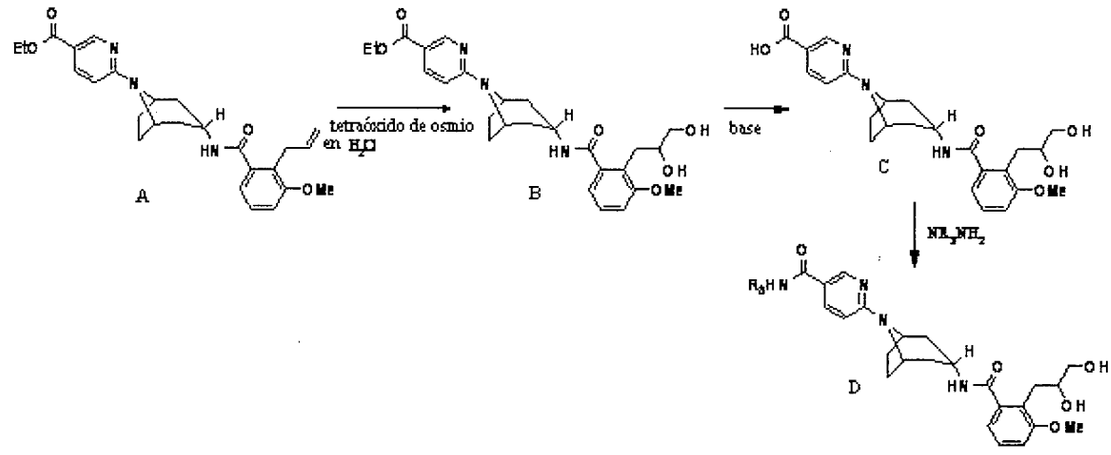
azabiciclo[3.2.1]oct-8-il}piridin-3-carboxamida (0.006 g; 15% de rendimiento). ^{1}H NMR (400 MHz, d_4-MeOH): 8.62 (d, 1H), 8.01 (dd, 1H), 7.28 (t, 1H), 7.05 (d, 1H), 6.94 (d, 1H), 6.78 (d, 1H), 4.62 (br s, 2H), 4.05-3.95 (m, 1H), 3.24-3.17 (m, 2H), 3.11 (t, 2H), 2.85 (s, 6H), 2.37-2.08 (m, 6H), 1.91 (d, 2H), 1.80-1.60 (m, 4H); MS (EI) para $C_{27}H_{37}N_5O_3$: 480 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 17:



[00641] El esquema de reacción 17 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 17, en donde R_3 es como se define en la especificación.

[00642] En el esquema de reacción 17, el compuesto (A) se hidroxila con un agente de oxidación, tal como tetraóxido de osmio, bajo condiciones de reacción apropiadas para formar el compuesto (B). El carboxilato del compuesto (B) después se hidroliza con una base, tal como KOH, para formar el compuesto (C). El ácido carboxílico de este modo formado se

convierte a carboxamida (D) por tratamiento con una amina R_3NH_2, o amoníaco en el caso de R_3 seleccionado por ser hidrógeno, en la presencia de un agente de acoplamiento adecuado tal como HATU.

[00643] EJEMPLO 17: 6-[3-endo-({[2-(2,3-dihidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida.

[00644] ETAPA 1: A una solución agitada de 6-[3-endo-({[3-(metiloxi)-2-prop-2-en-1-ilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (sintetizado en el Ejemplo 13) (0.210 g, 0.470 mmol) y N-óxido 4-metilmorfolina (0.137 g; 1.17 mmol) en una mezcla de acetona (0.8 ml) y agua (0.2 ml) se agrega una cantidad catalítica de tetraóxido de osmio (0.020 ml, 4% en peso de solución en agua). La mezcla de reacción se agita a 40 °C por 5 h y después se apaga por adición de una solución acuosa 10% de bisulfito de sodio (0.5 ml). La fase acuosa se extrae con acetato de etilo (2x2ml) y la capa orgánica se seca sobre sulfato de sodio anhidro y se concentra bajo vacío para dar 6-[3-endo({[2-(2,3-dihidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (0.191 g; 85% de rendimiento). MS (EI) para $C_{26}H_{33}N_3O_6$: 484 (MH^+).

[00645] ETAPA 2: A una solución agitada de 6-[3-endo({[2-(2,3-dihidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (0.191 g, 0.395 mmol) en metanol (4.5 ml) se agrega hidróxido de potasio (0.044 g; 0.79 mmol) en agua (1.5ml) y la mezcla de reacción se agita a 60 °C por 3h. El solvente parcialmente se evapora y la solución se acidifica a pH 4 por adición de ácido clorhídrico acuoso 1.5 M. La fase acuosa se extrae con acetato de etilo (2x5ml) y las capas orgánicas combinadas se secan sobre sulfato de sodio anhidro, se filtran y se concentran para dar ácido 6-[3-({[2-(2,3-dihidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (0.117 g; 65% de rendimiento). MS (EI) para $C_{24}H_{29}N_3O_6$: 454 (M-H).

[00646] ETAPA 3: Una solución agitada de ácido 6-[3-({[2-(2,3-dihidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (0.117 g, 0.257 mmol) y HATU en dimetilformamida se satura con NH_3(g) por 0.5h, y la mezcla de reacción se agita en un tubo sellado a temperatura ambiente durante la noche. La mezcla cruda se purifica por HPLC de fase inversa preparatoria (0.1% eluyente de acetonitrilo acuoso amortiguado con acetato de amonio) y las fracciones puras combinadas se liofilizan para proporcionar 6-[3-endo-({[2-(2,3-dihidroxipropil)-3-

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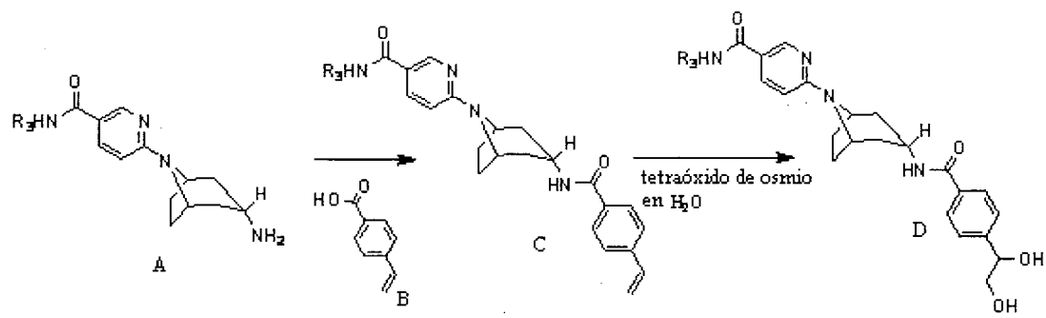
(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida (0.047 g, 40% de rendimiento). ^{1}H NMR (400 MHz, d_4-MeOH): 8.89-8.85 (m, 1H), 8.62 (d, 1H), 7.98 (dd, 1H), 7.30 (t, 1H), 7.07 (d, 1H), 7.03 (d, 1H), 6.74 (d, 1H), 4.60 (br s, 2H), 4.07-3.94 (m, 2H), 3.87 (s, 3H), 3.56-3.52 (m, 2H), 3.03 (dd, 1H), 2.71-2.63 (m, 1H), 2.36-1.92 (m, 8H); MS (EI) para $C_{24}H_{30}N_4O_5$: 454 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 18:



[00647] El esquema de reacción 18 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 18, en donde R_3 es como se define en la especificación.

[00648] En el esquema de reacción 18, el compuesto (B) se agrega al compuesto (A) bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (C). El compuesto (C) después se hidroxila con un agente de oxidación, tal como tetraóxido de osmio, bajo condiciones de reacción apropiadas para formar el compuesto

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(D).

[00649] EJEMPLO 18: 6-[3-endo-({[4-(1,2-dihidroxietil)fenil]carbonil}-amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida

[00650] ETAPA 1: A una solución agitada de ácido 4-vinilbenzoico (0.036 mg; 0.244 mmol) y N-metilmorfolina (0.098 g, 0.976 mmol) en dimetilformamida (1 ml) se agrega HOAt (0.490 ml; solución 0.5 M en dimetilformamida, 0.244 mmol), HATU (0.093 g, 0.244 mmol) y 6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida (sintetizado en el Ejemplo 2) (0.100 g, 0.244 mmol). La mezcla de reacción se agita a temperatura ambiente durante la noche seguido por adición de agua (3ml) y lo sólido resultante se recolecta por filtración y se seca bajo vacío para dar 6-(3-endo{[(4-ethenilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida (0.081; 71% de rendimiento). MS (EI) para $C_{29}H_{30}N_4O_2$: 467 (MH^+).

[00651] ETAPA 2: A una solución agitada de 6-(3-endo{[(4-ethenilfenil)carbonil]-amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida (0.081 g, 0.174 mmol) y N-óxido 4-metilmorfolina (0.053 g; 0.452 mmol) en una mezcla de

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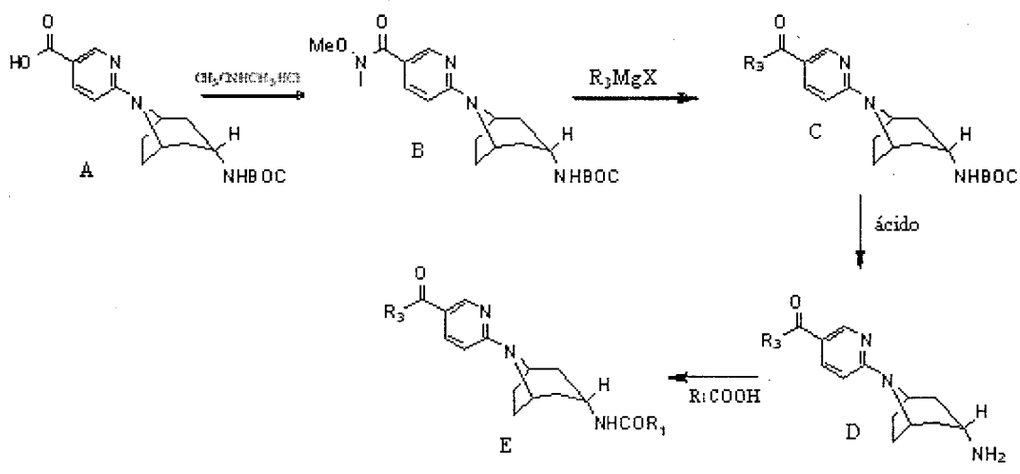
acetona (0.5 ml) y agua (0.13 ml) se agrega una cantidad catalítica de tetraóxido de osmio (0.010 ml, 4% en peso de solución en agua). La mezcla de reacción se agita a 40°C durante la noche y después se apaga por adición de a 10% solución acuosa de bisulfito de sodio (0.5 ml). La fase acuosa se extrae con acetato de etilo (2x 2 ml) y la capa orgánica se seca sobre sulfato de sodio anhidro después se filtra y se concentra. El residuo se purifica por HPLC de fase inversa preparatoria (0.05% ácido trifluoroacético amortiguado con fase móvil de acetonitrilo acuoso) y las fracciones puras combinadas se liofilizan para proporcionar 6-[3-endo-({[4-(1,2-dihidroxietil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida (0.052 g; 49% de rendimiento) como la sal de trifluoroacetato. MS (EI) para $C_{29}H_{32}N_4O_4$: 499 (M-H).

ESQUEMA DE REACCIÓN SINTÉTICA 19:



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[00652] El esquema de reacción 19 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 19, en donde R_3 y R_1 son como se definen en la especificación.

[00653] En el esquema de reacción 19, se agrega $CH_3ONHCH_3.HCl$ clorhidrato de N,O-dimetilhidroxilamina al compuesto (A) bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar compuesto (B). Al compuesto (B) se agrega R_3MgX, (un reactivo Grignard), en donde X representa un halógeno, bajo condiciones de reacción apropiadas para llegar a un compuesto (C). El compuesto (C) después se desprotege con un ácido, tal como HCl, para remover el BOC y llegar al compuesto (D). Al compuesto (D) se agrega R_1COOH bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (E).

[00654] EJEMPLO 19: N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-etilpiperidin-4-il)amino]bencen-1,4-dicarboxamida.

[00655] ETAPA 1: Una mezcla de ácido 6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}-amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxílico (7.96 g, 22.91 mmol, ejemplo 2, etapa 1), clorhidrato de N,O-dimetilhidroxilamina (2.23 g,

22.91 mmol), HATU (8.71 g, 22.91 mmol), y diisopropil-etilamina (11.84 g, 91.64 mmol) en DMF (50 mL) se agita a temperatura ambiente por 3 h. La mezcla de reacción se vierte en agua (250 mL), se filtra y la torta filtrada se lava con agua (2 x 100 mL) después se seca para dar [8-(5-{[metil(metiloxi)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo (8.55 g, 96% de rendimiento). ^{1}H NMR (400 MHz, DMSO-d_6): 8.46 (d, 1H), 7.79 (dd, 1H), 6.88 (br s, 1H), 6.69 (d, 1H), 4.49 (br s, 2H), 3.60 (s, 3H), 3.44 (m, 1H), 3.22 (s, 3H), 2.12 (m, 2H), 1.98 (m, 2H), 1.90 (m, 2H), 1.74 (d, 2H), 1.39 (s, 9H). MS (EI) para $C_{20}H_{30}N_4O_4$: 391 (MH^+).

[00656] ETAPA 2: A una suspensión de [8-(5-{[metil(metiloxi)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo (3.97 g, 10.17 mmol) en THF (70 mL) se agrega por goteo una solución 3M de bromuro metilmagnesio en éter (17 mL, 51.00 mmol) a 0 °C. Se remueve el baño helado y la solución se agita por 1 h. La solución se vierte en cloruro de amonio saturado (200 mL), extraída con acetato de etilo (3 x 100 mL) y las capas orgánicas se lavan con salmuera (100 mL), se secan sobre sulfato de sodio después se filtran y se concentran. La cromatografía en columna en sílice (hexanos:acetato de etilo 1:1) proporciona [8-(5-acetilpiridin-2-il)-8-

azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo (2.55 g, 73% de rendimiento). ^{1}H NMR (400 MHz, metanol-d_4): 8.71 (d, 1H), 8.03 (dd, 1H), 6.71 (d, 1H), 4.60 (br s, 2H), 3.59 (m, 1H), 2.49 (s, 3H), 2.20-2.04 (m, 6H), 1.81 (d, 2H), 1.44 (s, 9H).

[00657] ETAPA 3: A una solución de [8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo (2.00 g, 5.79 mmol) en metanol (5 mL) se agrega una solución de ácido clorhídrico en dioxano 4N (5 mL) y la mezcla de reacción se somete a reflujo por 2 min. Después del enfriamiento a temperatura ambiente la mezcla se concentra, se neutraliza con bicarbonato de sodio acuoso saturado, extraído con acetato de etilo (7 x 50mL), se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar 1-[6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il]etanona (1.11 g, 78% de rendimiento). ^{1}H NMR (400 MHz, metanol-d_4): 8.70 (d, 1H), 8.01 (dd, 1H), 6.70 (d, 1H), 4.62 (br s, 2H), 3.01 (m, 1H), 2.48 (s, 3H), 2.29-2.06 (m, 6H), 1.60 (d, 2H). MS (EI) para $C_{14}H_{19}N_3O$: 246 (MH^+).

[00658] ETAPA 4: A una solución de 1-[6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il]etanona (135 mg, 0.55 mmol) y ácido 4-(aminocarbonil)-3-[(1-{[(1,1-dimetiletil)-oxi]carbonil}piperidin-4-il)amino]benzoico (200 mg, 0.55

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mmol) en DMF (5 mL) se agregan HATU (418 mg, 1.1 mmol) y diisopropiletilamina (142 mg, 1.1 mmol) a temperatura ambiente. La mezcla de reacción se agita a temperatura ambiente por 30 min. La solución se vierte en solución de cloruro de sodio acuoso saturado (30 mL), extraída con acetato de etilo (3 x 30 mL), se seca sobre sulfato de sodio después se filtra y se concentra para proporcionar (4-{[5-({[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]aminocarbonil)-2-(aminocarbonil)fenil]amino}-pipiperidin-1-carboxilato de 1,1-dimetiletilo (285 mg, 87% de rendimiento). ^{1}H NMR (400 MHz, metanol-d_4): 8.70 (d, 1H), 8.01 (d, 1H), 7.96 (s, 3H), 7.65 (d, 1H), 7.1 (s, 1H), 6.9 (d, 1H), 6.70 (d, 1H), 4.65 (s, 1H), 4.0 (m, 3H), 3.65 (m, 1H), 3.1 (br s, 2H), 2.48 (s, 3H), 2.39-2.0 (m, 10H), 1.50 (s, 9H). MS (EI) para $C_{32}H_{42}N_6O_5$: 591 (MH^+).

[00659] ETAPA 5: A una solución de (4-{[5-({[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]aminocarbonil)-2-(aminocarbonil)fenil]amino}pipiperidin-1-carboxilato de 1,1-dimetiletilo (285 mg, 0.483 mmol) en metanol (2 mL) se agrega cloruro de hidrógeno en solución de dioxano (2M, 0.6 mL) a temperatura ambiente. La mezcla de reacción se agita a 45°C por 2 h. Después del enfriamiento a temperatura ambiente la mezcla se concentra. El residuo se tritura con acetato de etilo después se seca para dar N4-[8-

(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(piperidin-4-ilamino)bencen-1,4-dicarboxamida como la sal de clorhidrato. ^{1}H NMR (400 MHz, metanol-d_4): 8.55 (s, 1H), 8.30 (m, 2H), 7.70 (d, 2H), 7.65 (d, 1H), 7.22 (d, 1H), 7.18 (s, 1H), 7.00 (d, 1H), 4.06 (s, 1H), 3.92 (s, 1H), 3.48 (m, 2H), 3.24 (m, 2H), 2.39-2.18 (m, 12H), 1.70 (m, 2H); MS (EI) para $C_{27}H_{34}N_6O_3$: 491 (MH^+).

[00660] ETAPA 6: A una solución de N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(piperidin-4-ilamino)bencen-1,4-dicarboxamida (130 mg, 0.28 mmol) en metanol se agregan acetaldehído (12 mg, 0.28 mmol), cianoborohidruro de sodio (18 mg, 0.28 mmol) y ácido acético (17 mg, 0.28 mmol) a temperatura ambiente. La mezcla de reacción se agita a temperatura ambiente por 2 h. Después la mezcla de reacción se vierte en agua (250 mL), extraída con acetato de etilo (2 x 50 mL), se seca sobre sulfato de sodio, se filtra y se concentra a un volumen de 10 mL. Lo precipitado de este modo formado se recolecta por filtración para dar N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-etilpiperidin-4-il)amino]bencen-1,4-dicarboxamida (16 mg, 12% de rendimiento). ^{1}H NMR (400 MHz, metanol-d_4): 8.70(s, 1H), 8.06 (d, J = 9.2Hz, 1H), 7.69 (d, J = 8.2Hz, 1H), 7.14(s, 1H), 6.98(d, J = 8.2Hz, 1H), 6.77(d, J = 9.2Hz, 1H), 4.70(br,s,2H), 4.02(m, 1H), 3.82-3.45 (m, 2H),

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3.20-3.05 (m, 6H), 3.00(s, 6H), 2.53(s, 3H), 2.40-2.1(m, 10H), 2.05(m, 2H), 1.34(t, J = 7.2Hz, 3H). MS (EI) para $C_{29}H_{38}N_6O_3$: 519 (MH^+).

[00661] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [(19B)-(19(BE)]. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00662] (19B): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(piperidin-4-ilamino)-bencen-1,4-dicarboxamida. Preparada en el Ejemplo 19 etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.55 (s, 1H), 8.30 (m, 2H), 7.70 (d, 2H), 7.65 (d, 1H), 7.22 (d, 1H), 7.18 (s, 1H), 7.00 (d, 1H), 4.06 (s, 1H), 3.92 (s, 1H), 3.48 (m, 2H), 3.24 (m, 2H), 2.39-2.18 (m, 12H), 1.70 (m, 2H). MS (EI) para $C_{27}H_{34}N_6O_3$: 491 (MH^+).

[00663] (19C): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({2-[(1-metiletil)oxi]-etil}amino)bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-({2-[(1-metiletil)oxi]etil}amino)benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6) 8.73 (d, 1H), 8.32 (t, 1H), 8.20 (d, 1H), 7.95 (dd, 1H), 7.91 (br

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s, 1H), 7.68 (d, 1H), 7.32 (br s, 1H), 7.01 (s, 1H), 6.91 (d, 1H), 6.76 (d, 1H), 4.65 (br s, 2H), 3.82 (br s 1H), 3.58 (m, 3H), 3.25 (m, 2H), 2.43 (s, 3H), 2.20 (m, 2H), (2.18 (m, 6H), 1.08 (d, 6H). MS(EI) para $C_{27}H_{35}N_5O_4$: 494 (MH^+).

[00664] (19D): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-metiletil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(1-metiletil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.75 (s, 1H), 8.20 (dd, 1H), 8.14 (dd, 1H), 7.98 (dd, 1H), 7.92 (bs, 1H), 7.67 (d, 1H), 7.27 (s, 1H), 7.00 (s, 1H), 6.86 (dd, 1H), 6.79 (dd, 1H), 4.64 (bs, 2H), 3.85 (bs, 1H), 3.69 (m, 1H), 2.46 (s, 3H), 2.23 (d, 2H), 2.09-1.95 (m, 6H), 1.20 (d, 6H). MS (EI) para $C_{25}H_{31}N_5O_3$: 450 (MH^+).

[00665] (19E): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-etilpropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(1-etilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.26 (d, 1H), 8.23 (d, 1H), 7.96 (dd, 1H), 7.92 (bs, 1H), 7.66 (d, 1H), 7.26 (bs, 1H), 6.95 (s,

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1H), 6.81 (dd, 2H), 4.63 (bs, 1H), 3.85 (bs, 1H), 3.32 (m, 1H), 2.44 (s, 3H), 2.25 (dd, 2H), 2.04 (m, 6H), 1.97 (m, 1H), 1.54 (m, 4H), 0.90 (t, 6H). MS (EI) para $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00666] (19F): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2-metilpropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(2-metilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.39 (t, 1H), 8.21 (d, 1H), 7.96 (dd, 1H), 7.95 (bs, 1H), 7.65 (dd, 1H), 7.30 (bs, 1H), 6.96 (s, 1H), 6.87 (d, 1H), 6.79 (d, 1H), 4.64 (bs, 1H), 3.85 (bs, 1H), 2.99 (t, 2H), 2.46 (s, 3H), 2.25 (d, 2H), 2.04 (m, 4H), 1.97 (m, 4H), 0.95 (d, 6H). MS (EI) para $C_{26}H_{33}N_5O_3$: 464 (MH^+).

[00667] (19G): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2-dimetilpropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(2,2-dimetilpropil)-amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.73 (s, 1H), 8.51 (bs, 1H), 8.19 (d, 1H), 7.98 (m, 2H), 7.69 (dd, 1H), 7.31 (bs, 1H), 7.02 (s, 1H), 6.87 (dd, 1H), 6.83 (dd, 1H), 4.65 (bs, 2H), 3.84 (bs,

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1H), 2.95 (s, 2H), 2.46 (s, 3H), 2.23 (d, 2H), 2.02 (m, 6H), 0.98 (s, 9H). MS (EI) para $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00668] (19H): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(tetrahidrofuran-2-ilmetil)amino]bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(tetrahidrofuran-2-ilmetil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.49 (s, 1H), 8.30 (d, 1H), 8.24 (d, 1H), 7.95 (bs, 1H), 7.70 (dd, 1H), 7.46 (s, 1H), 7.32 (s, 2H), 7.20 (s, 1H), 7.05 (s, 1H), 6.92 (d, 1H), 4.06 (m, 1H), 3.91 (bs, 1H), 3.79 (m, 1H), 3.71 (m, 1H), 3.66 (m, 1H), 3.49 (m, 1H), 3.30 (m, 1H), 3.18 (m, 1H), 2.55 (s, 3H), 2.34 (d, 2H), 2.13 (m, 6H), 1.99 (m, 1H), 1.85 (m, 2H), 1.65 (m, 1H). MS (EI) para $C_{27}H_{33}N_5O_4$: 492 (MH^+).

[00669] (19I): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2-aminoetil)amino]bencen-1,4-dicarboxamida. Preparada como la sal de HCl de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-{[2-({[(1,1-dimetiletil)oxi]carbonil}amino)etil]amino}benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de la etapa 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.23 (m, 2H), 7.96 (dd, 2H),

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7.68 (dd, 1H), 7.32 (bs, 1H), 7.02 (s, 1H), 6.91 (dd, 1H), 6.80 (dd, 1H), 4.65 (bs, 2H), 3.90 (bs, 1H), 3.20 (m, 2H), 2.85 (t, 2H), 2.45 (s, 3H), 2.22 (d, 2H), 2.05 (m, 4H), 1.96 (m, 2H). MS (EI) para $C_{24}H_{30}N_6O_3$: 451 (MH^+).

[00670] (19J): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-metilpropil)-amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(1-metilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.21 (m, 2H), 7.97 (dd, 1H), 7.92 (bs, 1H), 7.66 (d, 1H), 7.27 (bs, 1H), 6.97 (s, 1H), 6.84 (dd, 1H), 6.79 (dd, 1H), 4.64 (bs, 2H), 3.85 (bs, 1H), 3.50 (m, 1H), 2.45 (s, 3H), 2.25 (d, 2H), 2.04 (m, 4H), 1.96 (m, 2H), 1.54 (m, 2H), 1.16 (d, 3h), 0.98 (t, 3H). MS (EI) para $C_{26}H_{33}N_5O_3$: 464 (MH^+).

[00671] (19K): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-propilbutil)amino]-bencen-1,4-dicarboxamida. Preparada como la sal de HCl de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(1-propilbutil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.48 (d, 1h), 8.40 (d, 1H), 7.88 (d, 1H), 7.52 (s, 1H), 7.40 (m, 2H), 4.81 (bs, 2H), 4.13 (m, 1H), 3.62 (q,

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1H), 2.57 (s, 3H), 2.43 (m, 2H), 2.31 (m, 6H), 1.60 (m, 4H), 1.43 (m, 4H), 0.94 (t, 6H); MS (EI) para $C_{29}H_{39}N_5O_3$: 506 (MH^+).

[00672] (19L): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1,2-dimetilpropil)-amino]bencen-1,4-dicarboxamida. Preparada como la sal de HCl de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(1,2-dimetilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.51 (d, 1H), 8.39 (dd, 1H), 8.08 (d, 1H), 7.90 (s, 1H), 7.81 (dd, 1H), 7.39 (d, 1H), 4.14 (m, 1H), 3.74 (m, 1H), 2.57 (s, 3H), 2.44 (m, 2H), 2.37 (m, 2H), 2.31 (m, 4H), 2.21 (m, 1H), 1.11 (m, 9H); MS (EI) para $C_{27}H_{35}N_5O_3$: 478 (MH^+).

[00673] (19M): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1,2,2-trimetilpropil)-amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(1,2,2-trimetilpropil)-amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.74 (d, 1H), 8.06 (dd, 1H), 7.64 (d, 1H), 7.12 (s, 1H), 6.84 (d, 1H), 6.76 (d, 1H), 4.70 (bs, 2H), 4.01 (t, 1H), 3.45 (quar, 1H), 2.51 (s, 3H), 2.26 (m, 4H), 2.19 (m, 2H), 2.01 (d, 2H), 1.15 (d, 3H), 1.00 (s, 9H). MS (EI) para

$C_{28}H_{37}N_5O_3$: 492 (MH^+).

[00674] (19N): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({1-[(metiloxi)metil]-propil}amino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-({1-[(metiloxi)metil]propil}amino)benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.74 (d, 1H), 8.06 (dd, 1H), 7.63 (d, 1H), 7.11 (s, 1H), 6.90 (d, 1H), 6.76 (d, 1H), 4.70 (bs, 2H), 4.01 (t, 1H), 3.61 (m, 1H), 3.52 (dd, 1H), 3.42 (dd, 1H), 3.36 (s, 3H), 2.51 (s, 3H), 2.26 (m, 4H), 2.18 (m, 2H), 2.01 (m, 2H), 1.76 (m, 1H), 1.59 (m, 1H), 1.00 (t, 3H). MS (EI) para $C_{27}H_{35}N_5O_4$: 494 (MH^+).

[00675] (19O): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-{[(1S)-1-metil-propil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-{[(1S)-1-metilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.74 (d, 1H), 8.24 (d, 1H), 8.06 (dd, 1H), 7.63 (d, 1H), 7.06 (s, 1H), 6.88 (dd, 1H), 6.76 (d, 1H), 4.69 (bs, 2H), 4.01 (m, 1H), 3.56 (m, 1H), 2.50 (s, 3H), 2.26

(m, 4H), 2.19 (m, 2H), 2.00 (m, 2H), 1.61 (m, 2H), 1.22 (m, 3H), 0.98 (t, 3H). MS (EI) para $C_{26}H_{33}N_5O_3$: 464 (MH^+).

[00676] (19P): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({3-[(1-metiletil)-amino]propil}amino)bencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-({3-[(1-metiletil)amino]-propil}amino)benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.74 (d, 1H), 8.06 (dd, 1h), 7.67 (d, 1H), 7.12 (s, 1H), 6.97 (d, 1H), 6.77 (d, 1H), 4.70 (bs, 2H), 4.01 (m, 1H), 3.38 (t, 2H), 3.08 (t, 2H), 2.51 (s, 3H), 2.23 (m, 6H), 1.99 (m, 4H), 1.89 (s, 3H), 1.31 (d, 6H); MS (EI) para $C_{28}H_{38}N_6O_3$: 507 (MH^+).

[00677] (19Q): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(trans-4-hidroxiciclohexil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(trans-4-hidroxiciclohexil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.27 (m, 2H), 7.97 (dd, 1H), 7.91 (br s, 1H), 7.66 (d, 1H), 7.27 (br s, 1H), 6.96 (s, 1H), 6.83 (d, 1H), 6.79 (d, 1H), 4.64 (br s, 2H), 4.60 (d, 1H), 3.85 (br s, 1H), 3.48 (m, 1H), 2.45 (s, 3H), 2.26 (m,

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2H), 2.02 (m, 9H), 1.84 (m, 2H), 1.25 (m, 4H). MS (EI) para $C_{28}H_{35}N_5O_4$: 506 (MH^+).

[00678] (19R): N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-metil-3-(metiloxi)-benzamida. Preparado de conformidad con el método del ejemplo 19 usando ácido 2-metil-3-metoxibenzoico en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.25 (d, 1H), 7.96 (dd, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.86 (d, 1H), 6.78 (d, 1H), 4.62 (br s, 2H), 3.86 (m, 1H), 3.80 (s, 3H), 2.45 (s, 3H), 2.22 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.98 (m, 2H), 1.89 (d, 2H). MS (EI) para $C_{23}H_{27}N_3O_3$: 394 (MH^+).

[00679] (19S): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(ciclopropilmetil)-amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(ciclopropilmetil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.74 (d, 1H), 8.26 (t, 1H), 8.18 (d, 1H), 7.96 (dd, 1H), 7.93 (br s, 1H), 7.67 (d, 1H), 7.29 (br s, 1H), 6.99 (d, 1H), 6.89 (dd, 1H), 6.79 (d, 1H), 4.64 (br s, 2H), 3.84 (m, 1H), 3.03 (m, 2H), 2.45 (s, 3H), 2.22 (m, 2H), 2.11-1.92 (m, 6H), 1.11 (m, 1H), 0.52 (m, 2H), 0.24 (m, 2H). MS (EI) para $C_{26}H_{31}N_5O_3$: 462 (MH^+).

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[00680] (19T): N4-{8-[5-(ciclopentilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando cloruro de ciclopentilmagnesio en la etapa 2 y ácido 4-(aminocarbonil)-3-[(ciclopropilmetil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, DMSO-d_6): 8.77 (d, 1H), 8.26 (t, 1H), 8.13 (d, 1H), 8.00 (dd, 1H), 7.94 (br s, 1H), 7.67 (d, 1H), 7.30 (br s, 1H), 6.99 (d, 1H), 6.89 (dd, 1H), 6.79 (d, 1H), 4.64 (br s, 2H), 3.85 (m, 1H), 3.70 (m, 1H), 3.03 (m, 2H), 2.22 (m, 2H), 2.12-1.92 (m, 6H), 1.85 (m, 2H), 1.72 (m, 2H), 1.60 (m, 4H), 1.11 (m, 1H), 0.51 (m, 2H), 0.24 (m, 2H). MS (EI) para $C_{30}H_{37}N_5O_3$: 516 (MH^+).

[00681] (19U): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(butilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 3-(butilamino)-4-(aminocarbonil)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (s, 1H), 8.27-8.20 (m, 2H), 7.97 (dd, 1H), 7.94 (br s, 1H), 7.67 (d, 1H), 7.30 (d, 1H), 6.97 (d, 1H), 6.87 (dd, 1H), 6.79 (d, 1H), 4.63 (br s, 2H), 3.87-3.81 (m, 1H), 3.16 (q, 2H), 2.45 (s, 3H), 2.27-2.20 (m, 2H), 2.10-1.92 (m, 6H), 1.62-1.54

(m, 2H), 1.44-1.33 (m, 2H),0.93 (t, 3H). MS (EI) para $C_{26}H_{33}N_5O_3$: 464 (MH^+).

[00682] (19V): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({4-(metiloxi)-3-[(2-morfolin-4-iletil)oxi]fenil}amino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-({4-(metiloxi)-3-[(2-morfolin-4-iletil)oxi]fenil}-amino)benzoico (sintetizado de conformidad con el reactivo de la preparación 40) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 9.93 (s, 1H), 8.73 (d, 1H), 8.20 (d, 1H), 8.13 (br s, 1H), 7.95 (dd, 1H), 7.76 (d, 1H), 7.56 (br s, 1H), 7.41 (d, 1H), 7.00 (dd, 1H), 6.92 (d, 1H), 6.85-6.81 (m, 2H), 6.76 (d, 1H), 4.59 (br s, 2H), 4.06 (t, 2H), 3.83-3.77 (m m, 1H), 3.74 (s, 3H), 3.56 (t, 4H), 3.50 (s, 1H), 2.68 (t, 2H), 2.44 (s, 3H), 2.34-2.31 (m, 1H), 2.14-2.07 (m, 2H), 2.04-1.85 (m, 7H), 1.23 (br s, 1H). MS (EI) para $C_{35}H_{42}N_6O_6$: 643 (MH^+).

[00683] (19W): 2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-metilbutanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando bromuro de isobutil magnesio en la etapa 2 y ácido 4-(aminocarbonil)-3-(ciclopropilmetilamino)benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.75

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(s, 1H), 8.29-8.24 (m, 1H), 8.19 (s, 1H), 8.01-7.91 (m, 2H), 7.70-7.65 (d, 1H), 7.35-7.26 (br. s, 1H), 6.99 (s, 1H), 6.92-6.86 (d, 1H), 6.81-6.76 (d, 1H), 4.71-4.53 (br. s, 2H), 3.88-3.81 (m, 1H), 3.06-3.00 (m, 2H), 2.77-2.71 (d, 2H), 2.26-2.19 (m, 2H), 2.17-1.91 (m, 7H), 1.15-1.06 (m, 1H), 0.95-0.90 (d, 6H), 0.55-0.48 (m, 2H), 0.28-0.21 (m, 2H). MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00684] (19X): 2-[(ciclopropilmetil)amino]-N4-{8-[5-(4,4,4-trifluorobutanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando bromuro de trifluoropropilmagnesio en la etapa 2 y ácido 4-(aminocarbonil)-3-(ciclopropilmetilamino)benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.78 (s, 1H), 8.29-8.24 (m, 1H), 8.19 (s, 1H), 8.04-8.00 (d, 1H), 7.94 (s, 1H), 7.69-7.65 (d, 1H), 7.29 (s, 1H), 6.99 (s, 1H), 6.91-6.87 (d, 1H), 6.82-6.78 (d, 1H), 4.73-4.55 (br. s, 2H), 3.88-3.81 (m, 1H), 3.23-3.16 (m, 2H), 3.06-3.01 (m, 2H), 2.68-2.55 (m, 2H), 2.27-2.19 (m, 2H), 2.11-1.93 (m, 6H), 1.15-1.06 (m, 1H), 0.55-0.48 (m, 2H), 0.27-0.21 (m, 2H). MS (EI) para $C_{28}H_{32}F_3N_5O_3$: 544 (MH^+).

[00685] (19Y): N4-[8-(5-butanoilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(ciclopropil-metil)amino]bencen-1,4-dicarboxamida. Preparada como la sal

de clorhidrato, de conformidad con el método del ejemplo 19 usando bromuro de propilmagnesio en la etapa 2 y ácido 4-(aminocarbonil)-3-(ciclopropilmetilamino)benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.53 (s, 1H), 8.29-8.24 (m, 1H), 7.74-7.70 (d, 1H), 7.33-7.27 (d, 1H), 7.09 (s, 1H), 7.02-6.97 (d, 1H), 4.86-4.75 (br. s, 2H), 3.98-3.92 (m, 1H), 3.09-3.06 (d, 2H), 2.97-2.92 (m, 2H), 2.39-2.32 (m, 2H), 2.24-2.09 (m, 6H), 1.71-1.61 (m, 2H), 1.18-1.06 (m, 1H), 0.99-0.92 (m, 3H), 0.58-0.51 (m, 2H), 0.31-0.24 (m, 2H). MS (EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00686] (19Z): N4-{8-[5-(ciclobutilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 19 usando bromuro de ciclobutilmagnesio en la etapa 2 y ácido 4-(aminocarbonil)-3-(ciclopropilmetilamino)benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.64 (s, 1H), 8.28-8.23 (m, 1H), 8.18 (s, 1H), 7.95-7.81 (m, 2H), 7.70-7.65 (d, 1H), 7.33-7.26 (br. s, 1H), 6.98 (s, 1H), 6.90-6.87 (d, 1H), 6.81-6.76 (d, 1H), 4.70-4.55 (br. s, 2H), 4.05-3.95 (m, 1H), 3.89-3.81 (m, 1H), 3.06-3.00 (m, 2H), 2.27-2.15 (m, 6H), 2.12-1.91 (m, 6H),

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1.83-1.73 (m, 2H), 1.14-1.06 (m, 1H), 0.55-0.48 (m, 2H), 0.28-0.21 (m, 2H); MS (EI) para $C_{29}H_{35}N_5O_3$: 502 (MH^+).

[00687] (19AA): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(ciclohexilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(ciclohexilamino)benzoico (sintetizado de conformidad con el reactivo de la prep 40) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.74 (d, 1H), 8.05 (dd, 1H), 7.62 (d, 1H), 7.07 (d, 1H), 6.87 (dd, 1H), 6.75 (d, 1H), 4.69 (br s, 2H), 4.01 (m, 1H), 3.44 (m, 1H), 2.50 (s, 3H), 2.30-2.14 (m, 6H), 2.09-1.96 (m, 1H), 1.82-1.75 (m, 2H), 1.68-1.61 (m, 1H), 1.50-1.26 (m, 5H). MS (EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00688] (19AB): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(ciclopentilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(ciclopentilamino)benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.74 (d, 1H), 8.06 (dd, 1H), 7.63 (d, 1H), 7.09 (d, 1H), 6.89 (dd, 1H), 6.76 (d, 1H), 4.69 (br s, 2H), 4.01 (m, 1H), 3.91 (m, 1H), 2.51 (s, 3H), 2.30-2.15 (m, 6H), 2.10-1.96 (m, 4H), 1.81-1.52 (m, 6H). MS (EI) para $C_{27}H_{33}N_5O_3$: 476 (MH^+).

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[00689] (19AC): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(etilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(etilamino)benzoico (sintetizado de conformidad con el reactivo de la prep 40) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.17 (d, 1H), 8.09 (t, 1H), 7.96 (dd, 1H), 7.91 (br s, 1H), 7.67 (d, 1H), 7.28 (br s, 1H), 6.98 (d, 1H), 6.89 (dd, 1H), 6.79 (d, 1H), 4.64 (br s, 2H), 3.85 (m, 1H), 3.18 (m, 2H), 2.45 (s, 3H), 2.25-2.20 (m, 2H), 2.11-1.94 (m, 6H), 1.21 (t, 3H). MS (EI) para $C_{24}H_{29}N_5O_3$: 436 (MH^+).

[00690] (19AD): N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-5-[(1-etilpropil)amino]-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-2-metil-5-(pentan-3-ilamino)benzoico (sintetizado de conformidad con el reactivo de la prep 42) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.57 (br s, 1H), 8.37 (d, 1H), 8.16 (d, 1H), 7.88 (br s, 1H), 7.51 (s, 1H), 7.18 (m, 2H), 6.59 (s, 1H), 4.42 (m, 2H), 3.89 (m, 1H), 3.23 (m, 1H), 2.52 (m, 2H), 2.36-2.31 (m, 2H), 2.19 (s, 3H), 2.15-2.01 (m ,4H), 2.08 (s, 3H), 1.52 (m, 4H), 0.88 (t, 6H). MS (EI) para $C_{28}H_{37}N_5O_3$: 492 (MH^+).

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[00691] (19AE): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino}-benzoico (sintetizado de conformidad con el reactivo de la prep 40) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.49 (d, 0.5H), 8.37 (dd, 0.5H), 7.97 (dd, 0.5H), 7.87 (d, 0.5H), 7.74 (d, 1H), 7.45 (s, 1H), 7.34 (dd, 1H), 7.09-6.96 (m, 4H), 4.81 (br s, 1H), 4.70 (br s, 1H), 4.34 (m, 2H), 4.05 (m, 1H), 3.88 (s, 3H), 3.58 (m, 3H), 3.02 (s, 6H), 2.56 (s, 1.5H), 2.32-2.12 (m, 8H), 1.54 (s, 1.5H). MS (EI) para $C_{33}H_{40}N_6O_5$: 601 (MH^+).

[00692] (19AF): N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-5-[(1-etilpropil)amino]-2-fluorobencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-2-fluoro-5-(pentan-3-ilamino)benzoico (sintetizado de conformidad con el reactivo de la prep 45) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.54 (m, 1H), 8.47 (d, 1H), 8.39 (dd, 1H), 7.59 (d, 1H), 7.37 (d, 1H), 7.15 (d, 1H), 4.79 (br s, 2H), 4.18 (m, 1H), 3.37 (m, 1H), 2.57 (s, 3H), 2.46-2.18 (m, 8H), 1.72-1.51 (m, 4H), 0.95 (t, 6H). MS (EI) para $C_{27}H_{34}FN_5O_3$: 496

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(MH^+).

[00693] (19AG): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(piperidin-1-ilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(piperidin-1-ilamino)benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, $CDCl_3$): 8.79 (d, 1H), 8.33 (d, 1H), 8.05 (dd, 1H), 7.80 (d, 1H), 7.42 (d, 1H), 6.99 (dd, 1H), 6.72 (d, 1H), 6.55 (d, 1H), 4.71 (br s, 2H), 4.28 (q, 1H), 2.74 (br s, 4H), 2.52 (s, 3H), 2.38-2.25 (m, 4H), 2.22-2.15 (m, 2H), 1.95-1.87(m, 2H), 1.73-1.63 (m, 6H). MS (EI) para $C_{27}H_{34}N_6O_3$: 491 (MH^+).

[00694] (19AH): N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-metil-5-(pentilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-2-metil-5-(pentilamino)benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.64 (d, 1H), 8.49 (d, 1H), 8.39 (dd, 1H), 7.74 (s, 1H), 7.36 (d, 1H), 7.16 (s, 1H), 4.79 (br s, 2H), 4.15 (q, 1H), 3.30 (m, 2H enmascarado por el solvente), 2.57 (s, 3H), 2.43-2.33 (m, 7H), 2.30-2.17 (m, 4H), 1.77-1.70 (m, 2H), 1.46-1.36 (m, 4H), 0.95 (t, 3H); MS (EI) para $C_{28}H_{37}N_5O_3$: 492

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(MH^+).

[00695] (19AI): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-il]-2-(pirrolidin-3-ilamino)bencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(1-{[(1,1-dimetiletil)oxi]carbonil}pirrolidin-3-il)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de la etapa 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.74 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 2.0, 9.2Hz, 1H), 7.71 (d, J = 8.0Hz, 1H), 7.08(s, 1H), 7.05 (dd, J = 1.2, 8.0Hz, 1H), 6.77 (d, J = 9.2Hz, 1H), 4.70 (s, 1H), 4.33(m, 1H), 4.02 (s, 1H), 3.58-3.40 (m, 4H), 2.51 (s, 3H), 2.40(m, 1H), 2.12-2.36 (m, 4H), 2.10-1.98 (m, 2H). MS (EI) para $C_{26}H_{32}N_6O_3$: 479 (MH^+).

[00696] (19AJ): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-il]-2-[(piperidin-3-ilmetil)amino]bencen-1,4-dicarboxamida. Preparada como la sal de HCl de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-{[(1-{[(1,1-dimetiletil)oxi]carbonil}piperidin-3-il)metil]amino}benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de la etapa 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.50(s, 1H), 8.39 (d, J = 9.2Hz, 1H), 7.69 (d, J = 8.4Hz, 1H), 7.37(d, J = 9.2 Hz, 1H), 7.14 (s, 1H),

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7.00 (m, 1H), 4.80 (br, s, 1H), 4.10(br, s, 1H), 3.72 (m, 2H), 3.50-3.10 (m, 6H), 2.99-2.76 (m, 4H), 2.43-2.0(m, 4H). MS (EI) para $C_{28}H_{36}N_6O_3$: 505 (MH^+).

[00697] (19AK): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-il]-2-[(pirrolidin-3-ilmetil)amino]bencen-1,4-dicarboxamida. Preparada como la sal de HCl de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-{[(1-{[(1,1-dimetiletil)oxi]-carbonil}pirrolidin-3-il)metil]amino}benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de la etapa 6. ^{1}H NMR (400 MHz, metanol-d_4): 8.50(s, 1H), 8.39 (d, J = 9.2Hz, 1H), 7.69 (d, J =8.4Hz, 1H), 7.38(d, J = 9.2 Hz, 1H), 7.19 (s, 1H), 7.00 (m, 1H), 4.82 (br, s, 1H), 4.07(br, s, 1H), 3.72 (m, 1H), 3.50-3.30 (m, 6H), 3.05 (m, 1H), 2.78(m, 1H), 2.60(s, 3H), 2.42-2.20(m, 8H), 1.85(m, 1H), 1.40(m, 2H). MS (EI) para $C_{27}H_{34}N_6O_3$: 491 (MH^+).

[00698] (19AL): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-il]-2-[(3-{[2-(dimetilamino)etil]oxi}fenil)amino]bencen-1,4-dicarboxamida. Preparada como la sal de acetato, de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-[(3-{[(2-dimetilamino)etil]oxi}fenil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz,

metanol-d_4): 8.70 (s, 1H), 8.29 (s, 1H), 8.11 (d, J = 6.0Hz, 1H), 7.73 (m, 2H), 7.38-6.6 (m, 6H), 4.70 (br,s,2H), 4.46 (br, s, 1H), 4.07 (m, 1H), 3.82-3.45 (m, 3H), 3.05 (m, 2H), 3.00 (s, 6H), 2.86 (m, 2H), 2.53 (s, 3H), 2.20 (m, 4H), 2.05 (m, 2H). MS (EI) para $C_{32}H_{38}N_6O_4$: 571 (MH^+).

[00699] (19AM): 2-[(ciclopropilmetil)amino]-N4-[8-(5-propanoilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando cloruro de etilmagnesio en la etapa 2 y ácido 4-(aminocarbonil)-3-(ciclopropilmetilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}HNMR (400 MHz, DMSO-d_6): 8.76 (s, 1H), 8.27-8.18 (m, 1H), 7.99-7.93 (m, 1H), 7.68-7.66 (d, 1H), 7.23 (s, 1H), 6.98 (s, 1H), 6.89 (d, 1H), 6.78 (d, 1H), 4.64 (s, 2H), 3.84 (s, 1H), 3.05 (t, 2H), 2.92 (t, 2H), 2.22-2.21 (m, 2H), 2.08-1.97 (m, 6H), 1.11-1.04 (m, 5H), 0.53-0.49 (m, 2H), 0.26-0.24 (m, 2H). MS (EI) para $C_{27}H_{33}N_5O_3$: 476 (MH^+).

[00700] (19AN): 2-[(ciclopropilmetil)amino]-N4-{8-[5-(2-metilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada como la sal de HCl de conformidad con el método del ejemplo 19 usando cloruro de isopropilmagnesio en la etapa 2 y ácido 4-(aminocarbonil)-3-(ciclopropilmetilamino)benzoico (sintetizado de conformidad

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con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}HNMR (400MHz, DMSO-d_6): 8.63 (s,1H), 8.25 (d, 1H), 8.16 (d, 1H), 7.96 (s, 1H), 7.70-7.68 (m, 1H), 7.32-7.30 (m, 1H), 7.12-7.10 (m, 1H), 6.93 (s, 1H), 6.90 (d, 1H), 4.77 (s, 2H), 3.89 (s, 1H), 3.16-3.01 (m, 2H), 2.28 (s, 6H), 2.11-2.07 (m, 2H), 2.05-2.04 (m, 6H), 1.12 (s, 1H), 1.08-1.06 (m, 4H), 0.53-0.5 (m, 2H), 0.27-0.24 (m, 2H). MS (EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00701] (19AO): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(etilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-ciano-5-[(trans-4-hidroxiciclohexil)amino]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la prep 41) en la etapa 3 seguido por hidrólisis de nitrilo como se describe en el Ejemplo 11 etapa 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.28 (d, 1H), 7.98-7.95 (m, 2H), 7.83 (br s, 1H), 7.47 (s, 1H), 7.16 (br s, 1H), 6.78 (d, 1H), 6.61 (s, 1H), 4.64 (br s, 2H), 4.57 (d, 1H), 3.87-3.82 (m, 1H), 3.51-3.42 (m, 1H), 3.26-3.17 (m ,1H), 2.45 (s, 3H), 2.32-2.26 (m, 2H), 2.19 (s, 3H), 2.08-1.91 (m, 8H), 1.86-1.80 (m, 2H), 1.32-1.15 (m, 4H). MS (EI) para $C_{29}H_{37}N_5O_4$: 520 (MH^+).

[00702] (19AP): N4-[8-(5-Acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(ciclopropilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del

ejemplo 19 usando ácido 4-(aminocarbonil)-3-(ciclopropilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 40) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.32 (br, 1H), 8.25 (d, 1H), 7.97 (dd, 2H), 7.68 (d, 1H), 7.41 (d, 1H), 7.34 (br, 1H), 6.93 (dd, 1H), 6.79 (d, 1H), 4.64 (br, 2H), 3.87 (br, 1H), 2.45 (s, 3H), 2.32-2.23 (m, 2H), 2.12-1.92 (m, 7H), 0.79-0.73 (m, 2H), 0.50-0.43 (m, 2H). MS (EI) para $C_{25}H_{29}N_5O_3$: 448 (MH^+).

[00703] (19AQ): N4-[8-(5-Acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(tetrahidrofuran-3-ilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(tetrahidrofuran-3-ilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.75 (d, 1H), 8.38 (d, 1H), 8.23 (d, 1H), 8.01-7.94 (m, 2H), 7.70 (d, 1H), 7.36 (br s, 1H), 6.97 (s, 1H), 6.92 (dd, 1H), 6.80 (d, 1H), 4.64 (br s, 2H), 4.18-4.10 (m, 1H), 3.94-3.72 (m, 4H), 3.56 (dd, 1H), 2.45 (s, 3H), 2.30-2.19 (m, 3H), 2.12-1.92 (m, 6H), 1.82-1.72 (m, 1H). MS (EI) para $C_{26}H_{31}N_5O_4$: 478 (MH^+).

[00704] (19AR): N4-[8-(5-Acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2,3,3,3-pentafluoropropil)amino]bencen-1,4-dicarboxamida. Preparada

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como la sal de clorhidrato, de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(2,2,3,3,3-pentafluoropropilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.72-8.60 (m, 2H), 8.28 (d, 1H), 8.14-8.07 (m, 2H), 7.74 (d, 1H), 7.51 (br s, 1H), 7.20 (s, 1H), 7.12-7.03 (m, 1H), 7.03 (dd, 1H), 4.78 (br s, 2H), 4.28 (br t, 2H), 3.90 (br s, 1H), 2.51 (s, 3H), 2.35-2.24 (m, 2H), 2.18-1.97 (m, 6H). MS (EI) para $C_{25}H_{26}F_5N_5O_3$: 540 (MH^+).

[00705] (19AS): N-[8-(5-Acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-metil-5-{[4-(trifluoro-metil)ciclohexil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-2-metil-5-(4-(trifluorometil)ciclohexil-amino)benzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.96 (dd, 1H), 7.90 (br s, 1H), 7.52 (s, 1H), 7.25 (br s, 1H), 6.78 (d, 1H), 6.60 (s, 1H), 4.62 (br s, 2H), 3.88-3.81 (m, 1H), 3.77-3.70 (m, 1H), 2.45 (s, 3H), 2.40-2.30 (m, 1H), 2.29-2.21 (m, 2H), 2.19 (s, 3H), 2.12-1.95 (m, 4H), 1.95-1.85 (m, 4H), 1.77-1.57 (m, 4H), 1.54-1.40 (m, 2H). MS (EI) para $C_{30}H_{36}F_3N_5O_3$: 572 (MH^+).

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[00706] (19AT): N4-[8-(5-Acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2,3,3,4,4,4-heptafluorobutil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(2,2,3,3,4,4,4-heptafluorobutilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.67 (t, 1H), 8.24 (d, 1H), 8.09 (br s, 1H), 7.97 (dd, 1H), 7.74 (d, 1H), 7.51 (s, 1H), 7.19 (s, 1H), 7.03 (dd, 1H), 6.79 (d, 1H), 4.65 (br s, 2H), 4.32 (td, 2H), 3.87 (br s, 1H), 2.46 (s, 3H), 2.29-2.20 (m, 2H), 2.13-1.90 (m, 6H). MS (EI) para $C_{26}H_{26}F_7N_5O_3$: 588 (MH^+).

[00707] (19AU): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-aminobencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-aminobenzoico (sintetizado de conformidad con el reactivo de la preparación 43) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.16 (d, 1H), 7.96 (dd, 1H), 7.84 (br s, 1H), 7.60 (d, 1H), 7.22 (br s, 1H), 7.07 (d, 1H), 6.80 (m, 4H), 4.63 (br s, 2H), 3.84 (s, 1H), 2.45 (s, 3H), 2.24 (m, 2H), 2.09-1.91 (m, 6H). MS (EI) para $C_{22}H_{25}N_5O_3$: 408 (MH^+).

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[00708] (19AV): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(tetrahidro-2H-piran-4-ilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(tetrahidro-2H-piran-4-ilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO):8.74 (d, 1H), 8.31 (d, 1H), 8.23 (d, 1H), 7.98-7.95 (m, 2H), 7.69 (d, 1H), 7.32 (br s, 1H), 7.00 (s, 1H), 6.87 (dd, 1H), 6.79 (d, 1H), 4.63 (br s, 2H), 3.88-3.86 (m, 3H), 3.66-3.56 (m, 1H), 3.45 (t, 2H), 2.46 (s, 3H), 2.24 (d, 2H), 2.07-1.92 (m, 8H), 1.46-1.36 (m, 2H). MS (EI) para $C_{27}H_{33}N_5O$: 492 (MH^+).

[00709] (19AW): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(fenilamino)bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(fenilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 10.13(br s, 1H), 8.64 (s, 1H), 8.31 (d, 1H), 8.19 (s, 1H), 8.07 (d, 1H), 7.80 (d, 1H), 7.65 (s, 1H), 7.64 (s, 1H), 7.35-7.31 (m, 2H), 7.25 (d, 2H), 7.11 (dd, 1H), 7.04-7.00 (m, 2H), 4.71 (br s, 2H), 3.84 (br s, 1H), 2.49 (s, 3H), 2.22 (d, 2H), 2.09-2.00 (m, 6H). MS (EI) para $C_{28}H_{29}N_5O_3$:

484 (MH^+).

[00710] (19AX): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(fenilmetil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 3-(fenilmetil)-4-(aminocarbonil)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 10.13(br s, 1H), 8.72-8.68 (m, 2H), 8.13 (br s, 1H), 7.99-7.94 (m, 2H), 7.69 (d, 1H), 7.37 (br s, 1H), 7.32 (br s, 4H), 7.24 (br s, 1H), 6.91-6.88 (m, 2H), 6.77 (d, 1H), 4.59 (br s, 2H), 4.48 (d, 2H), 3.79 (br s, 1H), 2.44 (s, 3H), 2.09 (d, 2H), 2.02-1.88 (m, 6H). MS (EI) para $C_{29}H_{31}N_5O_3$: 498 (MH^+).

[00711] (19AY): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(3S)-tetrahidrofuran-3-ilamino]bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 19 usando ácido (S)-4-(aminocarbonil)-3-(tetrahidrofuran-3-ilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (s, 1H), 8.29 (s, 1H), 8.14 (d, 1H), 8.00 (br s, 1H), 7.72 (d, 1H), 7.37 (br s, 1H), 7.13 (d, 1H), 6.97 (s, 1H), 6.93 (d, 1H), 4.81 (br s, 2H), 4.16 (br s, 1H), 3.90-3.75 (m, 4H), 3.57 (d, 1H), 2.52 (s, 3H), 2.35-2.19 (m, 4H), 2.09 (br s, 6H), 1.76

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(m, 1H). MS (EI) para $C_{26}H_{31}N_5O_4$: 478 (MH^+).

[00712] (19AZ): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2,2-trifluoroetil)-amino]bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(2,2,2-trifluoroetilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.64 (s, 2H), 8.24 (d, 1H), 8.12-8.05 (m, 2H), 7.73 (d, 1H), 7.51 (br s, 1H), 7.23 (s, 1H), 7.04 (d, 2H), 4.74 (br s, 2H), 4.26-4.15 (m, 2H), 3.89 (br s, 1H), 2.51 (s, 3H), 2.31-2.22 (m, 2H), 2.16-1.99 (m, 6H). MS (EI) para $C_{27}H_{33}N_5O$: 490 (MH^+).

[00713] (19BA): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(3R)-tetrahidrofuran-3-ilamino]bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 19 usando ácido (R)-4-(aminocarbonil)-3-(tetrahidrofuran-3-ilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.50 (s, 1H), 8.34 (d, 1H), 8.23 (d, 1H), 8.02 (br s, 1H), 7.72 (d, 1H), 7.36 (br s, 1H), 7.33 (d, 1H), 6.98 (s, 1H), 6.94 (d, 1H), 4.87 (br s, 2H), 4.19-4.13 (m, 1H), 3.92-3.87 (m, 2H), 3.86-3.73 (m, 2H), 3.59 (dd, 1H), 2.55 (s, 3H), 2.38-2.21 (m, 4H),

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2.18-2.07 (m, 6H), 1.82-1.73 (m, 1H). MS (EI) para $C_{26}H_{31}N_5O_4$: 478 (MH^+).

[00714] (19BB): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(propilamino)bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(propilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (s, 1H), 8.39 (s, 1H), 8.22-8.15 (m, 1H), 7.98 (br s, 1H), 7.74-7.67 (m, 1H), 7.34 (br s, 1H), 7.25 (br s, 1H), 7.01 (s, 1H), 6.94-6.88 (m, 1H), 4.54 (br s, 2H), 3.90 (s, 1H), 3.18-3.10 (m, 2H), 2.54 (s, 3H), 2.35-2.27 (m, 2H), 2.15-2.06 (m, 6H), 1.65-1.56 (m, 2H), 0.99-0.92 (m, 3H). MS (EI) para $C_{25}H_{31}N_5O_3$: 450 (MH^+).

[00715] (19BC): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-azetidin-1-ilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 3-(azetidin-1-il)-4-(aminocarbonil)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (s, 1H), 8.39 (s, 1H), 8.22-8.15 (m, 1H), 7.98 (br s, 1H), 7.74-7.67 (m, 1H), 7.34 (br s, 1H), 7.25 (br s, 1H), 7.01 (s, 1H), 6.94-6.88 (m, 1H), 4.54 (br s, 2H), 3.90 (s, 1H), 3.18-

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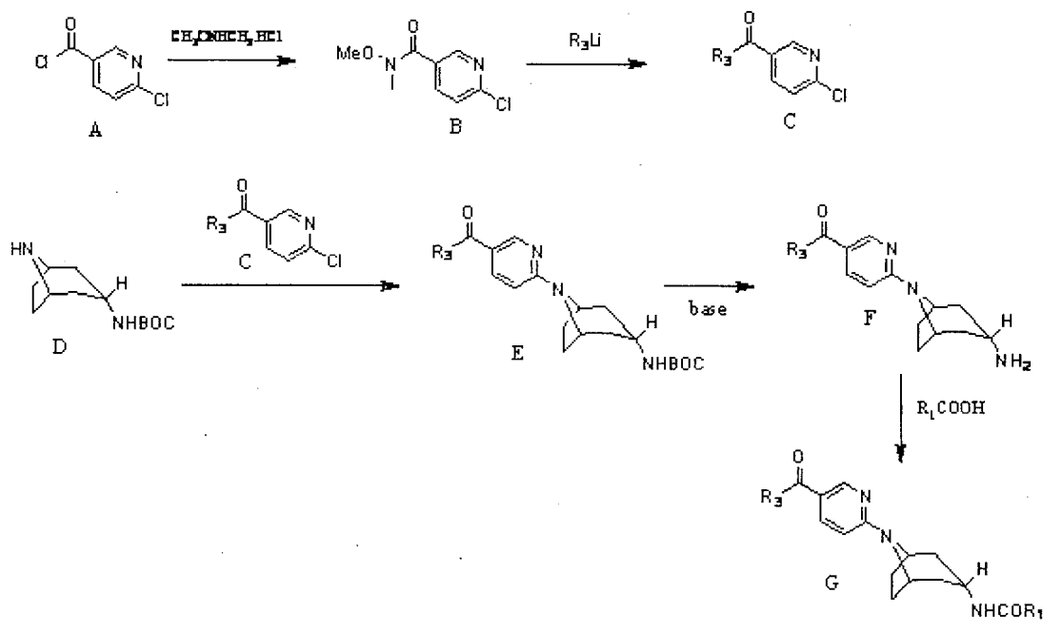
3.10 (m, 2H), 2.54 (s, 3H), 2.35-2.27 (m, 2H), 2.15-2.06 (m, 6H), 1.65-1.56 (m, 2H), 0.99-0.92 (m, 3H). MS (EI) para $C_{25}H_{29}N_5O_3$: 448 (MH^+).

[00716] (19BD): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-bromobencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 3-bromo-4-(aminocarbonil)benzoico (sintetizado de conformidad con el reactivo de la preparación 44) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.37 (d, 1H), 8.02 (d, 1H), 7.98-7.95 (m, 2H), 7.82 (dd, 1H), 7.70 (br s, 1H), 7.50 (d, 1H), 6.80 (d, 1H), 4.65 (br s, 2H), 3.89-3.83 (m, 1H), 2.46 (s, 3H), 2.20-2.19 (m, 2H), 2.14-1.92 (m, 6H). MS (EI) para $C_{22}H_{23}BrN_4O_3$: 471, 473 (MH^+).

[00717] (19BE): N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(3,3,3-trifluoropropil)-amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 19 usando ácido 4-(aminocarbonil)-3-(3,3,3-trifluoropropilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 4, después de la omisión de las etapas 5 y 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.74 (d, 1H), 8.38-8.34 (m, 1H), 8.26 (d, 1H), 7.99-7.95 (m, 2H), 7.70 (d, 1H), 7.36 (br s, 1H), 6.97 (s, 1H), 6.93 (dd, 1H), 6.89 (d, 1H), 4.64 (br s, 2H), 3.89-3.83 (m, 1H), 3.48 (q, 2H), 2.68-2.58 (m, 2H), 2.45 (s, 3H), 2.28-

2.21 (m, 2H), 2.11-1.91 (m, 6H). MS (EI) para $C_{25}H_{28}F_3N_5O_3$: 504 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 20:



[00718] El esquema de reacción 20 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 20, en donde R_3 y R_1 son como se definen en la especificación.

[00719] En el esquema de reacción 20, se agrega $CH_3ONHCH_3.HCl$ clorhidrato N,O-dimetilhidroxilamina al compuesto (A) bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar compuesto (B). Al compuesto B se agrega R_3Li bajo condiciones de reacción apropiadas para llegar a un compuesto (C). Al compuesto (D) se agrega el compuesto (C) en la presencia de una base débil, tal como fosfato de potasio

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tribásico, y condiciones de reacción tribásico para sufrir una reacción de sustitución nucleofílica aromática y llegar al compuesto (E). El compuesto (E) después se desprotege con un ácido, tal como HCl, para remover el BOC y llegar al compuesto (F). Al compuesto (F) se agrega R_1COOH bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (G).

[00720] EJEMPLO 20: N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida.

[00721] ETAPA 1: A una solución de cloruro de 6-cloronicotinoilo (2 g, 11.4 mmol) y dietilisopropilamina (5 mL, 28.5 mmol) en diclorometano (100 mL) se agrega clorhidrato de *N,O*-dimetilhidroxilamina (1.22 g, 12.5 mmol) a 0 °C. La solución se deja calentar a temperatura ambiente después se agita por 48 horas. La mezcla se lava con 20% ácido cítrico acuoso (2 x 100 mL), hidróxido de sodio acuoso 1N (2 x 100 mL), salmuera (100 mL), se seca sobre sulfato de sodio anhidro, se filtra y se concentra para proporcionar 6-cloro-*N*-metil-*N*-(metiloxi)piridin-3-carboxamida (2.05 g, 92% de rendimiento) como un aceite amarillo. ^{1}H NMR (400 MHz, d_6-DMSO): 8.65 (d, 1H), 8.08 (dd, 1H), 7.63 (d, 1H), 3.67 (s,

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3H), 3.30 (s, 3H); MS (EI) para $C_8H_9ClN_2O_2$: 201 (MH^+).

[00722] ETAPA 2: A una solución de ciclopropilbromuro (1.24 g, 10.24 mmol) en THF (10 mL) se agrega por goteo una solución 2.5M de n-butillitio en hexanos (4.0 mL, 10.00 mmol) a -78 °C y la mezcla de reacción se agita por 1 h a esta temperatura. Después una solución de 6-cloro-*N*-metil-*N*-(metiloxi)piridin-3-carboxamida (1.00 g, 4.98 mmol) en THF (5 mL) se agrega rápidamente a -78 °C, y se remueve el baño enfriante. La agitación se continúa por 1 h, después la solución se vierte en cloruro de amonio saturado (100 mL), extraída con acetato de etilo (3 x 50 mL) y las capas orgánicas se lavan con salmuera (50 mL), se secan sobre sulfato de sodio después se filtran y se concentran. La cromatografía en columna en sílice (hexanos:acetato de etilo 9:1 hasta 8:2) proporciona (6-cloropiridin-3-il)(ciclopropil)metanona (0.62 g, 68% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 9.04 (d, 1H), 8.22 (dd, 1H), 7.46 (d, 1H), 2.61 (m, 1H), 1.32 (m, 2H), 1.15 (m, 2H).

[00723] ETAPA 3: A una solución de clorhidrato 8-azabiciclo[3.2.1]oct-3-endo-ilcarbamato de 1,1-dimetiletilo (sintetizado en la preparación del reactivo 1) (795 mg, 3.03 mmol) y (6-cloropiridin-3-il)(ciclopropil)metanona (500 mg, 2.75 mmol) en dimetil éter dietilen glicol (5 mL) se agrega

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una solución acuosa de fosfato de potasio tribásico (1.75 g, 8.25 mmol en 5 mL de agua). La mezcla bifásica se agita a 125°C por 60 h. La mezcla se enfría a temperatura ambiente y se diluye con agua (25 mL). Lo precipitado de este modo formado se filtra, se lava varias veces con agua seguido por hexano caliente, y se seca para proporcionar 1,1-dimetil-etil{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato (943 mg, 96% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): 8.85 (d, 1H), 8.00 (dd, 1H), 6.89 (br s, 1H), 6.73 (d, 1H), 4.53 (br s, 2H), 3.44-3.40 (m, 1H), 2.80-2.73 (m, 1H), 2.15-2.08 (m, 2H), 2.00-1.87 (m, 4H), 1.78-1.71 (m, 2H), 1.37 (s, 9H), 0.94-0.88 (m, 4H); MS (EI) para $C_{21}H_{29}N_3O_3$: 372 (MH^+).

[00724] ETAPA 4: A una solución de 1,1-dimetiletil{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato (1.00 g, 2.69 mmol) en dioxano (18 mL) se agrega ácido sulfúrico concentrado (2.0 mL) y la mezcla se agita a temperatura ambiente por 30 min. La mezcla cuidadosamente se vierte en bicarbonato de sodio acuoso saturado (300 mL), y se extrae con 10% de metanol en cloroformo (3 x 100 mL). Las capas orgánicas combinadas se lavan con agua (50 mL), se secan sobre sulfato de sodio después se filtran y se concentran para dar [6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il](ciclopropil)-

metanona (0.71 g, 97% de rendimiento). ^{1}H NMR (400 MHz, d_4-metanol): 8.80 (d, 1H), 8.07 (dd, 1H), 6.72 (d, 1H), 4.63 (br s, 2H), 3.02 (m, 1H), 2.70 (m, 1H), 2.30-2.06 (m, 7H), 1.60 (d, 2H), 1.08 (m, 2H), 1.02 (m, 2H).

[00725] ETAPA 5: Una solución de [6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il](ciclopropil)metanona (100 mg, 0.37 mmol), HATU (210 mg, 0.55 mmol), ácido 4-(aminocarbonil)-2-metil-5-{[(1R)-1-metilpropil]amino}benzoico (sintetizado en la preparación del reactivo 41) (138 mg, 0.55 mmol), y diisopropiletilamina (256 µl, 1.47 mmol) en DMF (3 mL) se agita a temperatura ambiente por 2 h. La concentración y cromatografía en columna en sílice (diclorometano:metanol 100:0 después 95:5) seguido por trituración del residuo obtenido en la concentración de las fracciones puras combinadas con acetato de etilo, proporciona N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida (179 mg, 96% de rendimiento) como un polvo amarillo pálido. ^{1}H NMR (400 MHz, metanol-d_4): 8.84 (d, 1H), 8.11 (dd, 1H), 7.45 (s, 1H), 6.78 (d, 1H), 6.68 (s, 1H), 4.68 (br s, 2H), 4.02 (t, 2H), 3.77-3.67 (m, 1H), 3.25-3.19 (m, 2H), 2.76-2.70 (m, 1H), 2.32-2.25 (m, 7H), 2.18-2.14 (m, 2H), 1.97 (br s, 1H), 1.70-1.59 (m, 1H), 1.60-1.50 (m, 1H), 1.25-1.18 (m, 4H), 1.12-1.09 (m, 2H), 1.06-1.01 (m, 2H), 0.97 (t,

3H); MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00726] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [(20B)-(20BF)]. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00727] (20B): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-[(ciclopropilmetil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.26 (t, 1H), 8.18 (d, 1H), 8.05 (dd, 1H), 7.93 (br s, 1H), 7.67 (d, 1H), 7.29 (br s, 1H), 6.99 (d, 1H), 6.89 (dd, 1H), 6.81 (d, 1H), 4.64 (br s, 2H), 3.85 (m, 1H), 3.03 (m, 2H), 2.80 (m, 1H), 2.22 (m, 2H), 2.12-1.93 (m, 6H), 1.11 (m, 1H), 0.95 (m, 4H), 0.51 (m, 2H), 0.24 (m, 2H); MS (EI) para $C_{28}H_{33}N_5O_3$: 588 (MH^+).

[00728] (20C): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(1-etilpropil)amino]bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-[(1-etilpropil)amino]-benzoico (sintetizado de conformidad con el reactivo de la

preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.61 (d, 1H), 8.45 (dd, 1H), 8.42 (d, 1H), 7.73 (d, 1H), 7.39 (d, 1H), 7.23 (s, 1H), 7.06 (d, 1H), 4.81 (br s, 2H), 4.12 (m, 1H), 3.44 (m, 1H), 2.74 (m, 1H), 2.46-2.23 (m, 8H), 1.74-1.53 (m, 4H), 1.16 (m, 4H), 0.97 (t, 6H); MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00729] (20D): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(piridin-4-ilamino)bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-(piridin-4-ilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.64 (d, 1H), 8.55 (d, 1H), 8.42 (dd, 1H), 8.22 (d, 2H), 7.88 (m, 3H), 7.32 (d, 1H), 7.18 (d, 2H), 4.81 (br s, 2H), 4.14 (m, 1H), 2.74 (m, 1H), 2.43-2.20 (m, 8H), 1.15 (m, 4H); MS (EI) para $C_{29}H_{30}N_6O_3$: 511 (MH^+).

[00730] (20E): 2-(ciclopentilamino)-N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-(ciclopentilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.76 (s, 1H), 8.29 (d, 1H), 8.22 (d, 1H), 7.96 (br s, 1H), 7.69 (d, 1H),

7.31 (br s, 1H), 7.15 (br d, 1H), 7.02 (s, 1H), 6.87 (d, 1H), 4.80 (br s, 2H), 3.90 (m, 1H), 3.85 (m, 1H), 2.86 (m, 1H), 2.31 (m, 2H), 2.09 (m, 6H), 1.98 (m, 2H), 1.65 (m, 4H), 1.46 (m, 2H), 1.02 (d, 4H); MS (EI) para $C_{29}H_{35}N_5O_3$: 502 (MH^+).

[00731] (20F): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(cis-4-hidroxi-4-metilciclohexil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-[(cis-4-hidroxi-4-metilciclohexil)amino]-benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.88 (d, 1H), 8.23 (d, 2H), 8.06 (dd, 1H), 7.92 (br s, 1H), 7.67 (d, 1H), 7.29 (br s, 1H), 6.97 (s, 1H), 6.83 (d, 2H), 4.66 (br s, 2H), 3.85 (br s, 1H), 2.80 (m, 1H), 2.26 (m, 2H), 2.03 (m, 7H), 1.77 (m, 2H), 1.57 (m, 4H), 1.39 (m, 2H), 1.13 (s, 3H), 0.96 (m, 4H); MS (EI) para $C_{31}H_{39}N_5O_4$: 546 (MH^+).

[00732] (20G): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1R)-1,2-dimetilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-{[(1R)-1,2-dimetilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.85 (d, 1H), 8.11 (dd, 1H), 7.97 (d, 1H), 7.64 (d, 1H), 7.07 (s, 1H), 6.86 (d, 1H), 6.78 (d, 1H), 4.70 (br s, 2H), 4.02 (m, 1H), 3.53

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(m, 1H), 2.73 (m, 1H), 2.31-2.16 (m, 6H), 2.02 (m, 2H), 1.90 (m, 1H), 1.16 (d, 3H), 1.10 (m, 2H), 1.04 (m, 2H), 1.01 (d, 3H), 0.96 (d, 3H); MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00733] (20H): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-({2-[(1-metiletil)oxi]etil}amino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-({2-[(1-metiletil)oxi]etil}amino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. MS (EI) para $C_{29}H_{37}N_5O_4$: 520.6 (MH^+).

[00734] (20I): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[1-(trifluorometil)propil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-{[1-(trifluorometil)-propil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. MS (EI) para $C_{29}H_{34}F_3N_5O_3$: 558 (MH^+).

[00735] (20J): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(3,3,3-trifluoro-1-metilpropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-[(3,3,3-trifluoro-1-metilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. MS (EI) para

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$C_{29}H_{34}F_3N_5O_3$: 558 (MH^+).

[00736] (20K): 2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(2-metilpropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-[(2-metilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. MS (EI) para $C_{28}H_{34}BrN_5O_3$: 568 (MH^+).

[00737] (20L): 5-(ciclobutilamino)-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-[(ciclobutilamino)-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^1H NMR (400 MHz, DMSO-d_6): 8.90 (s, 1H), 8.32 (s, 1H), 8.05 (m, 1H), 8.04 (m, 1H), 7.84 (br, s, 1H), 7.50 (s, 1H), 7.22 (s, 1H), 6.80 (d, J = 9.2Hz, 1H), 6.46 (s, 1H), 4.64 (br s, 2H), 3.89 (m, 2H), 2.80 (m, 1H), 2.30 (m, 4H), 2.10-1.90 (m, 10H); MS (EI) para $C_{29}H_{35}N_5O_3$: 502 (MH^+).

[00738] (20M): N5-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-3-[(1-etilpropil)amino]-6-metilpiridin-2,5-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 6-(aminocarbonil)-5-[(1-etilpropil)amino]-2-metilpiridin-3-

carboxílico (sintetizado de conformidad con el reactivo de la preparación 49) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.84 (s, 1H), 8.11 (d, J = 8.80Hz), 7.97 (s, 2H), 7.09 (s, 1H), 6.78 (d, J = 8.80Hz, 1H), 4.69 (br, s, 2H), 4.04 (br, s, 1H), 3.32(m, 1H), 2.73 (m, 1H), 2.43 (s, 3H), 2.30-2.06 (m, 6H), 2.03-1.98 (m, 2H), 1.80-1.50 (m, 4H), 1.30 (m, 2H), 1.12-1.01(m, 4H), 0.96 (t, J = 7.2Hz, 6H); MS (EI) para $C_{29}H_{38}N_6O_3$: 519 (MH^+).

[00739] (20N): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-{[(1*S*)-1-metilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.84 (d, 1H), 8.11 (dd, 1H), 7.63 (d, 1H), 7.06 (s, 1H), 6.87 (dd, 1H), 6.78 (d, 1H), 4.69 (bs, 2H), 4.02 (t, 1H), 3.55 (q, 1H), 2.73 (m, 1H), 2.27 (m, 4H), 2.20 (m, 2H), 2.01 (m, 2H), 1.62 (m, 2H), 1.23 (d, 3H), 1.10 (m, 2H), 1.04 (m, 2H), 0.99 (t, 3H); MS (EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00740] (20O): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(1-metilpropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-[(1-metilpropil)amino]benzoico (sintetizado

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de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.84 (d, 1H), 8.11 (dd, 1H), 7.63 (d, 1H), 7.06 (s, 1H), 6.87 (dd, 1H), 6.78 (d, 1H), 4.71 (bs, 2H), 4.03 (t, 1H), 3.56 (q, 1H), 2.72 (m, 1H), 2.27 (m, 4H), 2.20 (m, 2H), 2.01 (m, 2H), 1.62 (m, 2H), 1.23 (d, 3H), 1.10 (m, 2H), 1.04 (m, 2H), 0.99 (t, 3H); MS (EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00741] (20P): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-{[(1*R*)-1-metilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.84 (d, 1H), 8.11 (dd, 1H), 7.63 (d, 1H), 7.06 (s, 1H), 6.84 (dd, 1H), 6.78 (d, 1H), 4.71 (bs, 2H), 4.02 (m, 1H), 3.56 (m, 1H), 2.73 (m, 1H), 2.27 (m, 4H), 2.20 (m, 2H), 2.00 (m, 2H), 1.62 (m, 2H), 1.23 (d, 3H), 1.10 (m, 2H), 1.04 (m, 2H), 0.99 (t, 3H); MS (EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00742] (20Q): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(2-metilpropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-[(2-metilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación

42) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (s, 1H), 8.27 (d, 1H), 8.19 (t, 1H), 8.04 (dd, 1H), 7.86 (bs, 1H), 7.49 (s, 1H), 7.19 (bs, 1H), 6.79 (d, 1H), 6.57 (s, 1H), 4.63 (bs, 2H), 3.85 (m, 1H), 3.32 (m, 1H), 2.93 (t, 2H), 2.80 (m, 1H), 2.27 (m, 2H), 2.19 (s, 3H), 2.04 (m, 4H), 1.93 (m, 2H), 0.94 (m, 10H); MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00743] (20R): 5-[(ciclopentilmetil)amino]-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-[(ciclopentilmetil)amino]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.26 (d, 1H), 8.12 (t, 1H), 8.04 (dd, 1H), 7.84 (bs, 1H), 7.48 (s, 1H), 7.17 (bs, 1H), 6.79 (d, 1H), 6.58 (s, 1H), 4.64 (bs, 2H), 3.85 (m, 1H), 3.32 (m, 1H), 3.02 (m, 2H), 2.26 (m, 2H), 2.19 (s, 3H), 2.04 (m, 4H), 1.92 (m, 2H), 1.73 (m, 2H), 1.60 (m, 2H), 1.52 (m, 2H), 1.24 (m, 2H), 0.95 (m, 4H); MS (EI) para $C_{31}H_{39}N_5O_3$: 530 (MH^+).

[00744] (20S): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[1-(1-metilciclopropil)etil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-{[1-(1-metilciclopropil)etil]amino}benzoico (sintetizado de

conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.27 (d, 1H), 8.17 (d, 1H), 8.04 (dd, 1H), 7.85 (s, 1H), 7.47 (s, 1H), 7.17 (bs, 1H), 6.79 (d, 1H), 6.56 (s, 1H), 4.63 (bs, 1H), 3.85 (m, 1H), 3.09 (t, 1H), 2.81 (m, 1H), 2.27 (m, 2H), 2.18 (s, 3H), 2.03 (m, 4H), 1.93 (m, 2H), 1.15 (d, 3H), 1.07 (s, 3H), 0.95 (m, 4H), 0.37 (m, 2H), 0.26 (m, 2H); MS (EI) para $C_{31}H_{39}N_5O_3$: 530 (MH^+).

[00745] (20T): 2-cloro-*N*-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-cloro-5-[(1-etilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 46) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.71 (d, 1H), 8.59 (d, 1H), 8.45 (dd, 1H), 7.68 (s, 1H), 7.38 (d, 1H), 6.76 (s, 1H), 4.77 (br s, 2H), 4.17-4.12 (m, 1H), 2.77-2.71 (m, 1H), 2.50-2.17 (m, 8H), 1.70-1.48 (m, 4H), 1.21-1.10 (m ,4H), 0.94 (t, 6H); MS (EI) para $C_{29}H_{36}ClN_5O_3$: 538 (MH^+).

[00746] (20U): 2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-(propilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-(propilamino)benzoico (sintetizado

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de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.42 (d, 1H), 8.33-8.28 (m, 1H), 8.04 (dd, 2H), 7.84 (s, 1H), 7.35 (br s, 1H), 6.79 (d, 1H), 6.59 (s, 1H), 4.63 (br s, 2H), 3.90-3.83 (m, 1H), 3.12-3.05 (m, 2H), 2.84-2.76 (m, 1H), 2.34-2.26 (m, 2H), 2.15-2.05 (m, 2H), 2.02-1.87 (m, 4H), 1.64-1.52 (m, 2H),1.00-0.90 (m, 2H); MS (EI) para $C_{29}H_{34}F_3N_5O_3$: 554, 556 (MH^+).

[00747] (20V): 2-(butilamino)-N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-(butilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.25-8.20 (m, 2H), 8.05 (dd, 1H), 7.94 (br s, 1H), 7.68 (d, 1H), 7.30 (br s, 1H), 6.97 (d, 1H), 6.87 (dd, 1H), 6.81 (d, 1H), 4.65 (br s, 2H), 3.86 (br s, 1H), 3.17 (q, 2H), 2.85-2.76 (m, 1H), 2.28-2.20 (m, 2H), 2.13-1.92 (m, 6H), 1.63-1.53 (m, 2H), 1.45-1.34 (m, 2H), 0.99-0.90 (m, 7H); MS (EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00748] (20W): *N*-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[2-metil-1-(trifluorometil)propil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-{[2-metil-1-

(trifluorometil)propil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.84 (d, 1H), 8.30 (d, 1H), 8.11 (dd, 1H), 7.53 (s, 1H), 6.87 (s, 1H), 6.78 (d, 1H), 4.69 (br s, 2H), 4.14-4.00 (m, 2H), 2.76-2.69 (m ,1H), 2.34-2.12 (m, 9H), 2.01-1.93 (m, 2H), 1.12-1.01 (m, 10H); MS (EI) para $C_{30}H_{36}F_3N_5O_3$: 572 (MH^+).

[00749] (20X): 2-bromo-*N*-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(2,2-dimetilpropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando 4-(aminocarbonil)-2-bromo-5-[(2,2-dimetilpropil)amino]benzoico ácido (sintetizado de conformidad con el reactivo de la preparación 50 en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.58 (t, 1H), 8.40 (d, 1H), 8.04 (m, 2H), 7.85 (s, 1H), 7.35 (s, 1H), 6.79 (d, 1H), 6.63 (s, 1H), 4.62 (br s, 2H), 3.89-3.84 (m, 1H), 3.17 (d, 1H), 2.90 (d, 1H), 2.84-2.77 (m, 1H), 2.34-2.28 (m, 2H), 2.14-1.87 (m, 6H), 0.99-0.92 (m, 13H); MS (EI) para $C_{29}H_{36}BrN_5O_3$: 582, 584 (MH^+).

[00750] (20Y): *N*-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[2-fluoro-1-(fluorometil)etil]amino}-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-{[2-fluoro-1-

(fluorometil)etil]amino}-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.37 (d, 1H), 8.28 (d, 1H), 8.04 (dd, 1H), 7.94 (s, 1H), 7.53 (s, 1H), 6.80 (d, 1H), 6.73 (s, 1H), 4.69-4.48 (m, 6H), 4.15-3.99 (m, 1H), 3.90-3.84 (m, 1H), 2.83-2.77 (m, 1H), 2.30-2.19 (m, 5H), 2.14-1.87 (m, 6H); MS (EI) para $C_{28}H_{33}F_2N_5O_3$: 526 (MH^+).

[00751] (20Z): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(trans-4-piperidin-1-ilciclohexil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-[(trans-4-(piperidin-1-ilciclohexil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 47) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.78 (s, 1H), 8.28 (s, 1H), 8.24-8.20 (d, 1H), 7.69-7.65 (d, 1H), 7.13 (s, 1H), 7.00-6.91 (m, 1H), 4.77-4.70 (br. s, 2H), 4.10-4.02 (m, 1H), 3.54-3.44 (m, 4H), 3.27-3.24 (m, 1H), 3.09-3.01 (m, 1H), 2.76-2.69 (m, 1H), 2.37-2.26 (m, 4H), 2.26-2.14 (m, 2H), 2.14-2.04 (d, 2H), 2.03-1.96 (d, 2H), 1.88-1.66 (m, 4H), 1.58-1.47 (m, 2H), 1.44-1.32 (m, 4H), 1.17-1.10 (m, 4H), 1.09-1.03 (m, 2H); MS (EI) para $C_{35}H_{46}N_6O_3$: 599 (MH^+).

[00752] (20AA): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1S)-1,2-dimetilpropil]amino}bencen-1,4-dicarboxamida. Preparada de

conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-{[(1S)-1,2-dimetilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (s, 1H), 8.40-8.34 (d, 1H), 8.23 (s, 1H), 8..07-8.02 (d, 1H), 7.96-7.89 (s, 1H), 7.70-7.63 (d, 1H), 7.31-7.24 (br. s, 1H), 6.97 (s, 1H), 6.85-6.78 (m, 2H), 4.72-4.53 (br. s, 2H), 3.88-3.81 (m, 1H), 3.52-3.43 (m, 1H), 2.85-2.77 (m, 1H), 2.31-2.19 (m, 4H), 2.12-1.92 (m, 6H), 1.91-1.82 (m, 1H), 1.12-1.05 (d, 3H), 0.99-0.92 (m, 5H), 0.91-0.85 (d, 2H); MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00753] (20AB): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(1-ciclopropiletil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-(1-ciclopropiletilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.84 (s, 1H), 8.14-8.09 (d, 1H), 7.65-7.60 (d, 1H), 7.08 (s, 1H), 6.92-6.86 (d, 1H), 6.81-6.75 (d, 1H), 4.76-4.64 (br. s, 2H), 4.05-3.98 (m, 1H), 3.28-3.20 (m, 1H), 2.77-2.68 (m, 1H), 2.33-2.15 (m, 6H), 2.05-1.96 (d, 2H), 1.30-1.26 (d, 3H), 1.14-1.07 (m, 2H), 1.06-0.95 (m, 3H), 0.55-0.45 (m, 2H), 0.37-0.22 (m, 2H); MS (EI) para $C_{29}H_{35}N_5O_3$: 502 (MH^+).

[00754] (20AC): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1R)-1,2-dimetilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-{[(1R)-1,2-dimetilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.84 (s, 1H), 8.14-8.09 (d, 1H), 7.45 (s, 1H), 6.80-6.75 (d, 1H), 6.68 (d, 1H), 6.81-6.75 (d, 1H), 4.75-4.63 (br. s, 2H), 4.05-3.98 (m, 1H), 3.47-3.40 (m, 1H), 2.77-2.68 (m, 1H), 2.34-2.21 (m, 7H), 2.20-2.11 (m, 2H), 2.04-1.86 (m, 3),1.17-1.12 (d, 3H), 1.11-1.08 (m, 2H), 1.06-1.02 (m, 2H), 1.01-0.98 (d, 3H), 0.96-0.92 (d, 2H); MS (EI) para $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00755] (20AD): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[2-metil-1-(1-metiletil)propil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-{[2-metil-1-(1-metiletil)propil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.84 (s, 1H), 8.15-8.07 (d, 1H), 7.45 (s, 1H), 6.82-6.73 (m, 2H), 4.75-4.63 (br. s, 2H), 4.05-3.98 (m, 1H), 3.38-3.34 (m, 3H), 3.12-3.05 (m, 1H), 2.74-2.67 (m, 1H), 2.35-2.11 (m, 6H), 2.04-1.86 (m, 2), 1.14-1.00 (m, 7H), 0.99-0.85 (m, 12H); MS (EI) para $C_{32}H_{45}N_5O_3$: 546 (MH^+).

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[00756] (20AE): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(dicicloropilmetil)amino]-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-(dicicloropilmetilamino)-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (s, 1H), 8.31-8.26 (d, 1H), 8.09-7.95 (m, 2H), 7.84 (s, 1H), 7.48 (s, 1H), 7.19 (s, 1H), 6.82-6.76 (d, 1H), 6.57 (s, 1H), 5.54-5.44 (m, 1H), 5.13-5.03 (m, 1H), 4.73-4.53 (m, 2H), 3.89-3.81 (m, 1H), 3.14-3.08 (m, 1H), 2.85-2.77 (m, 1H), 2.31-2.23 (m, 4H), 2.19 (s, 3H), 2.13-1.98 (m, 6H), 1.96-1.88 (m, 2H), 1.40-1.31 (m, 1H), 0.99-0.92 (m, 4H), 0.66-0.59 (m, 2H), 0.35-0.28 (m, 2H); MS (EI) para $C_{32}H_{39}N_5O_3$: 542 (MH^+).

[00757] (20AF): 2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(3,3,3-trifluoropropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-(3,3,3-trifluoropropilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.84 (s, 1H), 8.15-8.07 (d, 1H), 7.84 (s, 1H), 6.82-6.75 (d, 2H), 6.73 (s, 1H), 4.74-4.61 (br. s, 2H), 4.08-4.00 (m, 1H), 3.53-3.46 (m, 2H), 2.76-2.68 (m, 1H), 2.61-2.47 (m, 2H), 2.37-2.25 (m, 4H), 2.17-2.07 (m, 2H),

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2.03-1.94 (d, 2H), 1.14-1.07 (m, 2H), 1.06-0.99 (m, 2H); MS (EI) para $C_{27}H_{29}BrN_5O_3$: 609 (MH^+).

[00758] (20AG): 2-bromo-5-(ciclobutilamino)-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-(ciclobutilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (s, 1H), 8.46-8.43 (d, 1H), 8.40-8.36 (d, 1H), 8.07-8.02 (d, 2H), 7.85 (s, 1H), 7.42-7.37 (br. s, 1H), 6.82-6.77 (d, 1H), 6.47 (s, 1H), 4.72-4.54 (br. s, 2H), 3.95-3.83 (m, 2H), 2.84-2.76 (m, 1H), 2.43-2.26 (m, 4H), 2.13-2.04 (m, 2H), 2.03-1.96 (m, 2H), 1.93-1.87 (d, 2H), 1.85-1.71 (m, 4H), 1.00-0.91 (m, 4H); MS (EI) para $C_{28}H_{32}BrN_5O_3$: 567 (MH^+).

[00759] (20AH): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[(1R)-1,2,2-trimetilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-{[(1R)-1,2,2-trimetilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.32 (s, 1H), 8.30 (t, 1H), 8.04 (dd, 1H), 7.85 (s, 1H), 7.48 (s, 1H), 7.16 (s, 1H), 6.80 (d, 1H), 6.61 (s, 1H), 4.63 (br s, 1H), 3.82-3.88 (m, 1H), 3.35

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(s, 3H), 3.22-3.28 (m, 1H), 2.77-2.84 (m, 1H), 2.28 (d, 2H), 2.19 (t, 3H), 2.00-2.10 (m, 4H), 1.90-1.95 (m, 2H), 1.05 (d, 3H), 0.94 (s, 12H); MS (EI) para $C_{31}H_{41}N_5O_3$: 532 (MH^+).

[00760] (20AI): 2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-metiletil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-[(1-metiletil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.44 (d, 1H), 8.19 (d, 1H), 8.04 (dd, 2H), 7.83 (s, 1H), 7.35 (s, 1H), 6.79 (d, 1H), 6.61 (s, 1H), 3.85-3.88 (m, 1H), 3.60-3.64 (m, 2H), 2.78-2.82 (m, 1H), 2.31 (d, 2H), 1.88-2.11 (m, 6H), 1.12-1.18 (m, 7H), 0.93-0.97 (m, 4H); MS (EI) para $C_{27}H_{32}BrN_5O_3$: 555 (MH^+).

[00761] (20AJ): 2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-[(1-etilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.45 (d, 1H), 8.31 (d, 1H), 8.04 (dd, 2H), 7.83 (s, 1H), 7.33 (amplio s, 1H), 6.79 (d, 1H), 6.60 (s, 1H), 4.60 (amplio s, 2H), 3.85 (m, 1H), 3.28 (m,

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1H), 2.80 (m, 1H), 2.30 (m, 2H), 2.10 (m, 2H), 1.99 (m, 2H), 1.93 (d, 2H), 1.50 (m, 4H), 0.95 (m, 4H), 0.89 (t, 6H); MS (EI) para $C_{29}H_{36}N_5O_3Br$: 584 (MH^+).

[00762] (20AK): 2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-{[(1*R*)-1-metilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.44 (d, 1H), 8.26 (d, 1H), 8.04 (dd, 2H), 7.83 (s, 1H), 7.34 (amplio s, 1H), 6.79 (d, 1H), 6.60 (s, 1H), 4.60 (amplio s, 2H), 3.87 (m, 1H), 3.45 (m, 1H), 2.81 (m, 1H), 2.32 (m, 2H), 2.10 (m, 2H), 1.99 (m, 2H), 1.93 (d, 2H), 1.50 (m, 2H), 1.12 (d, 3H), 0.89 (m, 7H); MS (EI) para $C_{28}H_{34}N_5O_3$: 570 (MH^+).

[00763] (20AL): 2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1R)-1,2-dimetilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-{[(1R)-1,2-dimetilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H NMR (400 MHz, DMSO- d_6): 8.85 (d, 1H), 8.42 (m, 2H), 8.06 (d, 1H), 8.02 (d, 1H), 7.83 (s, 1H), 7.31 (bs, 1H), 6.78 (d, 1H),

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6.62 (s, 1H), 4.62 (bs, 2H), 3.86 (m, 1H), 3.40 (m, 1H), 2.81 (m, 1H), 2.32 (m, 2H), 2.08 (m, 2H), 1.98 (m, 2H), 1.90 (m, 2H), 1.83 (m, 1H), 1.06 (d, 3H), 0.94 (m, 7H), 0.87 (m, 3H); MS (EI) para $C_{29}H_{36}BrN_5O_3$: 584 (MH^+).

[00764] (20AM): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-aminocarbonil-2-metil-5-[(1-etilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.31 (d, 1H), 8.07-8.02 (m, 2H), 7.85 (br s, 1H), 7.48 (s, 1H), 7.17 (br s, 1H), 6.79 (d, 1H), 6.57 (s, 1H), 4.62 (br s, 2H), 3.88-3.82 (m, 1H), 3.27-3.18 (m, 1H), 2.84-2.76 (m, 1H), 2.32-2.23 (m, 2H), 2.18 (s, 3H), 2.13-1.88 (m, 6H), 1.62-1.41 (m, 4H), 0.99-0.92 (m, 4H), 0.88 (t, 6H); MS (EI) para $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00765] (20AN): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(2,2,3,3,3-pentafluoropropil)amino]bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-(2,2,3,3,3-pentafluoropropilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.65 (br s, 1H), 8.41-8.34 (m, 2H),

7.72 (d, 1H), 7.28 (br s., 1H), 7.25 (br s, 1H), 7.10 (dd, 1H), 4.78 (br s, 2H), 4.19-4.08 (m, 3H), 2.78-2.70 (m, 1H), 2.44-2.16 (m, 8H), 1.20-1.08 (m, 4H); MS (EI) para $C_{27}H_{28}F_5N_5O_3$: 566 (MH^+).

[00766] (20AO): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]-2-fluorobencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-aminocarbonil-2-fluoro-5-[(1-etilpropil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 45) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.89 (d, 1H), 8.37 (d, 1H), 8.07-8.01 (m, 2H), 7.98 (br s, 1H), 7.56 (d, 1H), 7.40 (br s, 1H), 6.80 (d, 1H), 6.72 (d, 1H), 4.63 (br s, 2H), 3.93-3.86 (m, 1H), 3.29-3.20 (m, 1H), 2.84-2.76 (m, 1H), 2.30-2.21 (m, 2H), 2.12-1.86 (m, 6H), 1.61-1.37 (m, 4H), 0.99-0.91 (m, 4H), 0.87 (t, 6H); MS (EI) para $C_{29}H_{36}FN_5O_3$: 522 (MH^+).

[00767] (20AP): 5-amino-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 5-amino-4-(aminocarbonil)-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 43) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.87 (d, 1H), 8.28 (d, 1H), 8.07 (dd, 1H), 7.79 (br s, 1H), 7.43 (s, 1H), 7.16 (br s, 1H), 6.85 (d, 1H), 6.67 (s, 1H), 4.65 (br s, 2H), 3.88-3.81 (m,

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1H), 2.85-2.77 (m, 1H), 2.29-2.22 (m, 2H), 2.17 (s, 3H), 2.14-1.86 (m, 6H), 0.99-0.93 (m, 4H); MS (EI) para $C_{25}H_{29}N_5O_3$: 448 (MH^+).

[00768] (20AQ): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[(1S)-1-metilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-3-{[(1S)-1-metilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.85 (d, 1H), 8.12 (dd, 1H), 7.45 (s, 1H), 6.78 (d, 1H), 6.69 (s, 1H), 4.69 (br s, 2H), 4.02 (t, 1H), 3.51-3.43 (m, 1H), 2.76-2.70 (m, 1H), 2.33-2.25 (m, 7H), 2.19-2.14 (m, 2H), 2.01-1.95 (m, 3H), 1.69-1.62 (m, 1H), 1.59-1.52 (m, 1H), 1.22 (d, 3H), 1.13-1.09 (m, 2H), 1.06-1.02 (m, 2H), 0.98 (t, 3H); MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00769] (20AR): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-ciclopropiletil)amino]-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-(1-ciclopropiletilamino)-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H NMR (400 MHz, metanol-d_4): 8.85 (d, 1H), 8.12 (dd, 1H), 7.45 (s, 1H), 6.79 (d, 1H), 6.69 (s, 1H), 4.69 (brs, 2H), 4.02 (t, 1H), 3.20-3.13 (m,

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1H), 2.77-2.70 (m, 1H), 2.33-2.13 (m, 9H), 2.01-1.95 (m, 3H), 1.27 (d, 3H), 1.12-0.95 (m, 5H), 0.52-0.47 (m, 2H), 0.33-0.24 (m, 2H); MS (EI) para $C_{30}H_{37}N_5O_3$: 515 (MH^+).

[00770] (20AS): 2-bromo-5-(ciclopentilamino)-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-(ciclopentilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H NMR (DMSO-d_6): 8.89 (s, 1H), 8.44 (d, 1H), 8.33 (d, 1H), 8.06-8.05 (m, 2H), 7.83 (s, 1H), 7.34 (s, 1H), 6.79 (s, 1H), 6.63 (s, 1H), 4.63 (s, 2H), 3.88 (s, 1H), 3.88-3.77 (m, 1H), 2.95-2.93 (m, 1H), 2.41 (d, 2H), 2.21-1.98 (m, 8H), 1.66-1.59 (m, 4H), 1.46-1.41 (m, 2H), 0.95-0.93 (m, 4H); MS (EI) para $C_{29}H_{34}BrN_5O_3$: 581 (MH^+).

[00771] (20AT): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-(propilamino)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-(propilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H NMR (DMSO-d_6): 8.89 (s, 1H), 8.30 (d, 1H), 8.07 (t, 2H), 7.87 (s, 1H), 7.49 (s, 1H), 7.21 (s, 1H), 6.82 (d, 1H), 6.58 (s, 1H), 4.64 (s, 2H), 3.86-3.85 (m, 1H), 3.09 (t, 2H), 2.83-2.82 (m, 1H), 2.20-2.18 (m, 2H), 2.16 (s, 3H),

2.09-1.94 (m, 6H), 1.62-1.57 (m, 2H), 0.98-0.91 (m, 7H); MS (EI) para $C_{28}H_{35}N_5O_3$: 490(MH^+).

[00772] (20AU): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]-2-(trifluorometil)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-[(1-etilpropil)amino]-2-(trifluorometil)-benzoico (sintetizado de conformidad con el reactivo de la preparación 51) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.82 (d, 1H), 8.50 (d, 1H), 8.20 (br s, 1H), 8.04 (dd, 1H), 7.96 (d, 1H), 7.40 (br s, 1H), 6.79 (d, 1H), 6.64 (s, 1H), 4.63 (br s, 2H), 3.89-3.81 (m, 1H), 3.45-3.33 (m, 1H), 2.84-2.76 (m, 1H), 2.30-2.20 (m, 2H), 2.14-1.92 (m, 4H), 1.88 (d, 2H), 1.66-1.43 (m, 4H), 0.99-0.92 (m, 4H), 0.89 (t, 6H); MS (EI) para $C_{30}H_{36}F_3N_5O_3$: 572 (MH^+).

[00773] (20AV): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(3,3,3-trifluoropropil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-(3,3,3-trifluoropropil-amino)benzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.32 (d, 1H), 8.16 (t, 1H), 8.04 (dd, 1H), 7.89 (br s, 1H), 7.52 (s, 1H), 7.26 (br s, 1H), 6.80 (d, 1H), 6.60 (s, 1H), 4.62 (br s, 2H), 3.91-3.83 (m, 1H), 3.43 (q, 2H),

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2.85-2.76 (m, 1H), 2.69-2.53 (m, 2H), 2.32-2.23 (m, 2H), 2.21 (s, 3H), 2.15-1.96 (m, 4H), 1.91 (d, 2H), 1.00-0.91 (m, 4H); MS (EI) para $C_{28}H_{32}F_3N_5O_3$: 544 (MH^+).

[00774] (20AW): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1R)-1-metilpropil]amino}-2-(trifluorometil)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-{[(1R)-1-metilpropil]amino}-2-(trifluorometil)benzoico (sintetizado de conformidad con el reactivo de la preparación 52) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.78 (d, 1H), 8.49 (d, 1H), 8.19 (br s, 1H), 8.04 (dd, 1H), 7.96 (s, 1H), 7.41 (br s, 1H), 6.80 (d, 1H), 6.65 (s, 1H), 4.63 (br s, 2H), 3.89-3.82 (m, 1H), 3.58-3.49 (m, 1H), 2.85-2.76 (m, 1H), 2.28-2.20 (m, 2H), 2.14-2.03 (m, 2H), 2.03-1.95 (m, 2H), 1.88 (d, 2H), 1.63-1.47 (m, 2H), 1.17 (d, 3H), 0.99-0.88 (m, 7H); MS (EI) para $C_{29}H_{34}F_3N_5O_3$: 558 (MH^+).

[00775] (20AX): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etil-2-metilpropil)amino]-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-[(1-etil-2-metilpropil)amino]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H NMR (400 MHz, $CDCl_3$ p/ 20% de metanol-d_4): 8.87 (d, 1H), 8.09 (dd, 1H), 7.34 (s,

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1H), 7.21 (m, 1H) 6.66 (d, 1H), 6.62 (d, 1H), 4.67 (br s, 2H), 4.15 (m, 1H), 3.16 (m, 1H), 2.61 (m, 1H), 2.40-2.10 (br m, 8H), 1.92 (br d, 2H), 1.63 (m, 1H), 1.45 (m, 1H), 1.21 (m, 2H), 1.06 (m, 2H), 0.95 (m, 9H); MS (EI) para $C_{31}H_{41}N_5O_3$: 554 (M+Na).

[00776] (20AY): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-ciclopropilpropil)amino]-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-[(1-ciclopropilpropil)amino]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8..89 (d, 1H), 8.28 (d, 1H), 8.04 (m, 2H), 7.83 (br s, 1H), 7.47 (s, 1H), 7.30 (br s, 1H), 6.80 d, 1H), 6.56 (s, 1H), 4.63 (br s, 2H), 3.88 (s, 1H), 2.94 (m, 1H), 2.81 (m, 1H), 22.228 (d, 2), 2.13-1.97 (br m, 4H), 1.92 (br d, 2H), 1.60 (m, 2H), 0.98-0.85 (br m, 5H), 0.44-.35 (br m, 2H), 0.20 (m, 2H); MS (EI) para $C_{31}H_{39}N_5O_3$: 530 (MH^+).

[00777] (20AZ): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(3S)-tetrahidrofuran-3-ilamino]bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-[(3S)-tetrahidrofuran-3-ilamino]benzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa

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5. ^{1}H NMR de Free Base (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.30 (d, 1H), 8.15 (d, 1H), 8.04 (dd, 1H), 7.90 (br s, 1H), 7.51 (s, 1H), 7.25 (br s, 1H), 6.80 (d, 1H), 6.57 (s, 1H), 4.63 (br s, 2H), 4.09-4.02 (m, 1H), 3.89-3.71 (m, 4H), 3.58 (dd, 1H), 2.84-2.77 (m, 1H), 2.30-2.15 (m, 6H), 2.12-1.98 (m, 4H), 1.96-1.88 (m, 2H), 1.83-1.74 (m, 1H),0.99-0.91 (m, 4H); MS (EI) para $C_{29}H_{35}N_5O_4$: 518 (MH^+).

[00778] (20BA): N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(propilamino)bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-3-(propilamino)benzoico (sintetizado de conformidad con el reactivo de la preparación 39) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.83 (d, 1H), 8.24 (d, 1H), 8.12 (dd, 1H), 7.94 (br s, 1H), 7.68 (d, 1H), 7.31 (br s, 1H), 6.98 (d, 1H), 6.95 (br s, 2H), 6.88 (dd, 1H), 4.71 (br s, 2H), 3.90-3.84 (m, 1H), 3.13 (s, 1H), 2.88-2.80 (m, 2H), 2.30-2.23 (m, 2H), 2.12-1.99 (m, 6H), 1.66-1.56 (m, 2H), 1.00-0.93 (m, 2H); MS (EI) para $C_{27}H_{33}N_5O_3$: 476 (MH^+).

[00779] (20BB): 5-amino-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 5-amino-4-(aminocarbonil)-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 48) en la etapa

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5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.32 (d, 1H), 8.04 (dd, 1H), 7.75 (br s, 1H), 7.40 (s, 1H), 7.11 (br s, 1H), 7.79 (d, 1H), 6.64 (s, 1H), 6.52 (s, 2H), 4.63 (br s, 2H), 3.87-3.80 (m, 1H), 2.84-2.76 (m, 1H), 2.16 (s, 3H), 2.12-1.97 (m, 4H), 1.93-1.85 (m, 2H), 0.98-0.89 (m, 4H); MS (EI) para $C_{24}H_{29}N_5O_3$: 448 (MH^+).

[00780] (20BC): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(1-metiletil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-[(1-metiletil)amino]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (d, 1H), 8.29 (d, 1H), 8.04 (dd, 1H), 7.92 (d, 1H), 7.84 (br s, 1H), 7.48 (s, 1H), 7.18 (br s, 1H), 6.80 (d, 1H), 6.59 (s, 1H), 4.63 (br s, 2H), 3.89-3.82 (m, 1H), 3.64-3.56 (m, 1H), 2.84-2.76 (m, 1H), 2.30-2.23 (m, 2H), 2.19 (s, 3H), 2.12-1.98 (m, 4H), 1.98-1.89 (m, 2H), 1.18 (s, 1H), 1.17 (s, 1H), 1.00-0.91 (m, 4H); MS (EI) para $C_{28}H_{35}N_5O_3$: 490 (MH^+).

[00781] (20BD): 5-(ciclopentilamino)-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-(ciclopentilamino)-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación

42) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.29 (d, 1H), 8.05-8.02 (m, 2H), 7.85 (br s, 1H), 7.48 (s, 1H), 7.18 (br s, 1H), 6.79 (d, 1H), 6.62 (s, 1H), 4.63 (br s, 2H), 3.88-3.83 (m, 1H), 3.78-3.71 (m, 1H), 2.84-2.24 (m, 1H), 2.32-2.24 (m, 2H), 2.19 (s, 3H), 2.11-1.90 (m, 8H), 1.73-1.53 (m, 4H), 1.50-1.41 (m, 2H), 0.99-0.92 (m, 4H); MS (EI) para $C_{30}H_{37}N_5O_3$: 516 (MH^+).

[00782] (20BE): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(2,2-dimetilpropil)amino]-2-metilbencen-1,4-dicarboxamida.

Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-[(2,2-dimetilpropil)amino]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.29 (t, 1H), 8.24 (d, 1H), 8.04 (dd, 1H), 7.87 (br s, 1H), 7.49 (s, 1H), 7.18 (br s, 1H), 6.79 (d, 1H), 6.59 (s, 1H), 4.63 (br s, 2H), 3.88-3.82 (m, 1H), 2.89 (d, 2H), 2.84-2.77 (m, 1H), 2.29-2.22 (m, 2H), 2.18 (s, 3H), 2.14-1.97 (m, 4H), 1.95-1.88 (m, 2H), 1.98-0.90 (m, 13H); MS (EI) para $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00783] (20BF): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(ciclopropilmetil)amino]-2-metilbencen-1,4-dicarboxamida.

Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-(ciclopropilmetilamino)-2-

metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.24 (d, 1H), 8.05-8.03 (m, 2H), 7.85 (br s, 1H), 7.48 (s, 1H), 7.19 (br s, 1H), 6.78 (d, 1H), 6.57 (s, 1H), 4.63 (br s, 2H), 3.88-3.82 (m, 1H), 2.89 (t, 2H), 2.84-2.74 (m, 1H), 2.28-2.21 (m, 2H), 2.19 (s, 3H), 2.13-1.98 (m, 4H), 1.95-1.87 (m, 2H), 1.15-1.06 (m, 1H), 0.98-0.90 (m, 4H), 0.52-0.46 (m, 4H), 0.24-0.19 (m, 2H); MS (EI) para $C_{29}H_{35}N_5O_3$: 502 (MH^+).

[00784] (20BG): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(2,2-difluoro-1-metiletil)amino]-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-[(2,2-difluoro-1-metiletil)amino]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 42) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.90 (s, 1H), 8.24 (m, 2H), 8.06 (m, 1H), 7.94 (s, 1H), 7.52 (s, 1H), 7.30 (s, 1H), 6.81 (d, 1H), 6.73 (s, 1H), 6.11 (t, 1H), 4.63 (bs, 2H), 4.01 (m, 1H), 3.86 (s, 1H), 2.79 (m, 1H), 2.25 (m, 1H), 2.20 (s, 3H), 2.08 (m, 2H), 2.00 (m, 2H), 1.92 (m, 2H), 1.21 (m, 3H), 0.96 (m, 5H); MS (EI) para $C_{28}H_{33}F_2N_5O_3$: 526.3 (MH^+).

[00785] (20BH): 2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1,1-dimetiletil)amino]bencen-1,4-dicarboxamida.

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Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-[(1,1-dimetiletil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.52 (d, 1H), 8.48 (s, 1H), 8.03-8.06 (m, 2H), 7.82 (s, 1H), 7.36 (s, 1H), 6.78-6.80 (m, 2H), 4.63 (amplio s, 2H), 3.82-3.85 (m, 1H), 3.34 (s, 3H), 2.77-2.83 (m, 1H), 2.31 (d, 2H), 1.92-2.09 (m, 6H), 1.35 (s, 9H), 0.94-0.97 (m, 3H). MS (EI) para $C_{28}H_{34}BrN_5O_3$: 569 (MH^+).

[00786] (20BI): 5-amino-2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 5-amino-4-(aminocarbonil)-2-bromobenzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.85 (d, 1H), 8.42 (d, 1H), 8.04 (dd, 1H), 7.79 (s, 1H), 7.26 (bs, 1H), 6.85 (bs, 2H), 6.79 (d, 1H), 6.69 (s, 1H), 4.62 (bs, 2H), 3.86 (m, 1H), 2.82 (m, 1H) 2.30 (m, 2H), 2.10 (m, 2H), 2.00 (m 2H), 1.88 (m, 2H), 0.96 (m, 4H). MS (EI) para $C_{24}H_{26}BrN_5O_3$: 514 (MH^+).

[00787] (20BJ): 2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1S)-1,2-dimetilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-{[(1S)-

1,2-dimetilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.85 (d, 1H), 8.42 (m, 2H), 8.02 (2d, 2H), 7.81 (s, 1H), 7.30 (bs, 1H), 6.78 (d, 1H), 6.61 (s, 1H), 4.60 (bs, 2H), 3.87 (m, 1H), 3.40 (m, 1H), 2.80 (m, 1H), 2.31 (m, 2H), 2.08 (m, 2H), 1.98 (m, 2H), 1.90 (m, 2H), 1.82 (m, 1H), 1.06 (d, 3H), 0.94 (m, 7H), 0.87 (d, 3H). MS (EI) para $C_{29}H_{36}BrN_5O_3$: 584 (MH^+).

[00788] (20BK): 2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-bromo-5-[(ciclopropilmetil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.95-8.88 (s,1H), 8.45-8.38 (d,1H), 8.35-8.28 (m, 1H), 8.12-8.00 (d, 1H), 7.88-7.81 (s, 1H), 7.40-7.31 (s, 1H), 6.83-6.77 (d, 1H), 6.63-6.58 (s, 1H), 4.77-4.53 (br. s, 2H), 3.93-3.83 (m, 1H), 3.05-2.95 (m, 2H), 2.85-2.76 (m, 1H), 2.38-2.26 (d, 2H), 2.20-1.84 (m, 6H), 1.18-1.04 (m, 1H), 1.03-0.91 (m, 4H), 0.57-0.46 (m, 2H), 0.29-0.19 (m, 2H). MS (EI) para $C_{28}H_{32}BrN_5O_3$: 567 (MH^+).

[00789] (20BL): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1,1-dimetiletil)amino]-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con

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el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-[(1,1-dimetiletil)amino]-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.88-8.83 (s,1H), 8.17-8.08 (d,1H), 7.47-7.44 (s, 1H), 6.98-6.95 (s, 1H), 6.83-6.76 (d, 1H), 4.66-4.59 (m, 2H), 4.07-4.00 (m, 1H), 2.77-2.70 (m, 1H), 2.34-2.24 (m, 5H), 2.22-2.09 (m, 2H), 2.07-1.86 (m, 4H), 2.85-2.76 (m, 4H), 1.43-1.37 (s, 9H), 1.30-1.00 (m, 4H). MS (EI) para $C_{29}H_{37}N_5O_3$: 504 (MH^+).

[00790] (20BM): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-(2-metilpropil)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-(2-metilpropil)benzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.89 (s,1H), 8.26-8.25 (d,1H), 8.06-8.03 (m, 1H), 7.73 (s, 1H), 7.38 (s, 1H), 7.21 (s, 1H), 7.08 (s, 1H), 6.80 (d, 1H), 4.62 (br. s, 2H), 3.87-3.82 (m, 1H), 3.32-3.33 (m, 3H), 2.85-2.77 (m, 1H), 2.63-2.62 (d, 2H), 2.31 (s, 3H), 2.23-2.21 (m, 2H), 2.15-1.89 (m, 7H), 0.97-0.94 (m, 4H), 0.86-0.82 (d, 2H). MS (EI) para $C_{29}H_{36}N_4O_3$: 489 (MH^+).

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[00791] (20BN): 2-cloro-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-3-[(1-ciclopropiletil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-cloro-3-[(1-ciclopropiletil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 46) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.87(d, 1H), 8.44 (d, 1H), 8.04-8.01(m, 2H), 7.58(s, 1H), 7.45(d, 1H), 6.82(d, 1H), 6.78(d, 1H), 6.40(d, 1H), 4.59(s, 2H), 3.84(s, 1H), 2.75-2.70(m, 1H), 2.42(d, 2H), 2.01-1.91(m, 4), 1.80(d, 2H), 1.06 (d, 3H), 0.93-0.91(m, 4H), 0.79-0.74(m, 2H), 0.28-0.25 (m, 2H), 0.03-0.02 (m, 2H); MS(EI) para $C_{29}H_{34}ClN_5O_3$: 537(MH^+).

[00792] (20BO): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-(metiloxi)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-(metiloxi)benzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.62 (s, 1H), 8.32 (s, 1H), 8.03-8.02 (d, 1H), 7.64 (s, 1H), 7.62 (s, 1H), 7.59 (s, 1H), 6.98 (s, 1H), 7.80-6.76 (d, 1H), 4.63 (b, 2H), 4.04(s, 2H), 3.88 (b, 4H), 3.80-2.75 (m, 1H), 2.26 (s, 3H), 2.24-2.20(q, 1H), 2.15-1.95 (m, 3H), 2.26 (s, 3H), 1.89 (s, 1H), 1.86 (s, 1H), 0.96-0.89 (m, 4H); MS (EI) para $C_{26}H_{30}N_4O_4$: 463 (MH^+).

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[00793] (20BP): 5-bromo-3-cloro-N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-6-bromo-2-cloro-3-{[(1R)-1-metilpropil]amino}benzoico (sintetizado de conformidad con el método del reactivo de la preparación 50) en la etapa 5. ^{1}H-NMR (400 MHz, CD_3OD): 8.96(s, 1H), 8.64(s, 1H), 8.40(dd, 1H), 7.69(s, 1H), 7.31(d, 1H), 4.77(s, 2H), 4.16(t, 1H), 3.57-3.37(m, 1H), 2.74-2.67(m, 1H), 2.54-2.34(m, 3H), 2.19-2.09(m, 6H), 1.66-1.57(m, 1H), 1.54-1.44(m,1H), 1.32-1.21(m, 1H), 1.26-1.11(m, 6H), 1.00 (t, 2H); MS(EI) para $C_{28}H_{33}BrClN_5O_3$: 603 (MH^+).

[00794] (20BQ): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(metiloxi)-5-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-(metiloxi)-5-{[(1R)-1-metilpropil]amino}benzoico (sintetizado de conformidad con el método del reactivo de la preparación 50) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.92-8.89 (s,1H), 8.68-8.63 (d,1H), 8.08-8.02 (m, 2H), 7.67-7.62 (d, 1H), 7.38-7.33 (s, 2H), 7.13-7.10 (s, 1H), 6.82-6.77 (d, 1H), 4.77-4.55 (br. s, 2H), 4.08-4.01 (m, 1H), 3.91-3.88 (s, 3H), 3.42-3.32 (m, 1H), 2.84-2.77 (m, 1H), 2.22-2.06 (m, 6H), 1.87-1.78 (d, 2H),

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1.55-1.42 (m, 2H), 1.13-1.09 (d, 3H), 0.98-0.93 (m, 4H), 0.91-0.86 (m, 3H). MS (EI) para $C_{29}H_{37}N_5O_4$: 520 (MH^+).

[00795] (20BR): 3-cloro-N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-metil-2-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-cloro-6-metil-3-{[(1R)-1-metilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H-NMR (400 MHz, CD_3OD): 8.49(d, 1H), 8.62(d, 1H), 8.42(dd, 1H), 7.58(s, 1H), 7.32(dd, 1H), 4.78(s, 2H), 4.22(t, 1H), 3.62(q, 1H), 2.71-2.60(m, 1H), 2.50-2.37(m, 4H), 2.27(s, 3H), 2.25-2.08(m, 6H), 1.75-1.61(m, 2H), 1.57-1.47(m, 1H), 1.22-1.08(m, 6H), 1.00-0.9 (m, 2H); MS(EI) para $C_{29}H_{36}ClN_{53}$: 539 (MH^+).

[00796] (20BS): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}tiofen-2,5-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 5-(aminocarbonil)tiofen-2-carboxílico en la etapa 5. ^{1}H-NMR (400 MHz, CD_3OD): 8.83(s, 1H), 8.31(d, 1H), 8.22-8.12(m, 2H), 7.73-7.69(m, 2H), 7.61(s, 1H), 6.99 (d, 1H), 4.72(s, 2H), 3.88(s, 1H), 2.82-2.78(m, 1H), 2.31-1.97(m, 8H), 1.00-0.95(m, 4H); MS(EI) para $C_{22}H_{24}N_4O_3S$: 425 (MH^+).

[00797] (20BT): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(etilamino)-5-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-(etilamino)-5-{[(1R)-1-metilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.92-8.89 (s,1H), 8.45-8.41 (s,1H), 8.08-8.02 (d, 2H), 7.95-7.90 (s, 1H), 7.26-7.15 (m, 2H), 6.91-6.90 (s, 1H), 6.82-6.77 (d, 1H), 6.76-6.75 (s, 1H), 6.70-6.66 (s, 1H), 5.98-5.92 (m, 1H), 4.72-4.57 (m, 2H), 3.92-3.84 (m, 1H), 3.09-3.01 (m, 2H), 2.85-2.77 (m, 1H), 2.30-2.24 (m, 1H), 2.09-1.99 (m, 2H), 1.97-1.90 (m, 2H), 1.77-1.71 (m, 2H), 1.63-1.53 (m, 2H), 1.48-1.39 (m, 2H), 1.18-1.11 (m, 6H), 0.98-0.87 (m, 5H). MS (EI) para $C_{30}H_{40}N_6O_3$: 533 (MH^+).

[00798] (20BU): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(1-metilpropil)oxi]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-[(1-metilpropil)oxi]benzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.89-8.87 (s,1H), 8.36-8.33 (s,1H), 8.04-8.00 (d, 1H), 7.69-7.67 (s, 1H), 7.66-7.54 (d, 2H), 6.98-6.96 (s, 1H), 6.80-6.76 (d, 1H), 4.69-4.49 (m, 3H), 3.91-3.84 (m, 1H), 2.81-2.74 (m, 1H),

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2.28-2.20 (m, 5H), 2.13-1.95 (m, 4H), 1.92-1.85 (d, 2H), 1.79-1.60 (m, 4H), 1.32-1.27 (d, 3H), 0.96-0.88 (m, 5H). MS (EI) para $C_{29}H_{36}N_4O_4$: 505 (MH^+).

[00799] (20BV): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-etil-5-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-etil-5-{[(1R)-1-metilpropil]amino}benzoico (sintetizado de conformidad con el reactivo de la preparación 50) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): ^{1}H NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.32 (d, 1H), 8.01-8.06 (m, 2H), 7.88 (s, 1H), 7.49 (s, 1H), 7.17 (s, 1H), 6.79 (d, 1H), 6.53 (s, 1H), 4.63 (amplio s, 2H), 3.86 (s, 1H), 3.39-3.42 (m, 1H), 2.77-2.83 (m, 1H), 2.55 (d, 2H), 2.27 (d, 2H), 2.02-2.09 (m, 4H), 1.93 (d, 2H), 1.46-1.61 (m, 2H), 1.09-1.16 (m, 6H), 0.88-0.97 (m, 7H). MS (EI) para $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00800] (20BW): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-etil-2-metilbencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-5-etil-2-metilbenzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.32 (d, 1H), 8.03 (dd, 1H), 7.88 (s, 1H), 7.49 (s, 1H), 7.20 (s, 1H), 7.17 (s, 1H), 6.81 (d, 1H), 4.63 (amplio s, 2H), 3.85-3.91 (m, 1H), 3.35 (s, 5H), 2.77-2.84

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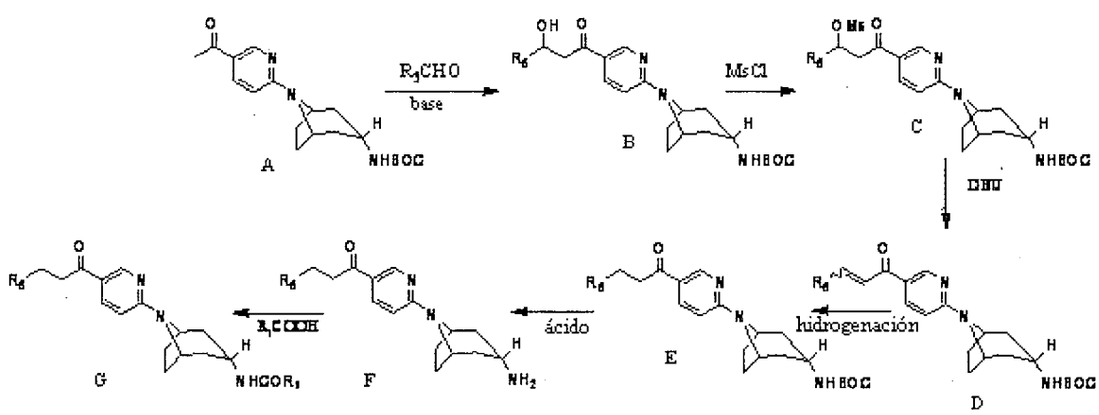
(m, 1H), 2.73 (q, 2H), 2.31 (s, 3H), 2.24 (d, 2H), 2.08-2.14 (m, 2H), 2.00-2.04 (m, 2H), 1.91 (d, 2), 1.16 (t, 3H), 0.93-0.98 (m, 4H). MS (EI) para $C_{27}H_{32}N_4O_3$: 461 (MH^+).

[00801] (20BX): N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[2-(metiloxi)etil]oxi}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 20 usando ácido 4-(aminocarbonil)-2-metil-5-{[2-(metiloxi)etil]oxi}benzoico (sintetizado de conformidad con el reactivo de la preparación 41) en la etapa 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.90 (d, 1H), 8.34 (d, 1H), 8.03 (dd, 1H), 7.72 (s, 1H), 7.71 (s, 1H), 7.65 (s, 1H), 7.04 (s, 1H), 6.80 (d, 1H), 4.63 (amplio s, 2H), 4.26-4.28 (m, 2H), 3.89-3.91 (m, 1H), 3.72-3.74 (m, 2H), 3.33 (d, 10H), 2.77-2.84 (m, 1H), 2.29 (s, 3H), 2.21-2.27 (m, 2H), 2.10-2.16 (m, 2H), 2.00-2.02 (m, 2H), 1.91 (s, 1H), 1.87 (s, 1H), 0.93-0.98 (m, 4H). MS (EI) para $C_{28}H_{34}N_4O_5$: 507 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 21:



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[00802] El esquema de reacción 21 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 21, en donde R_5 y R_1 son como se definen en la especificación.

[00803] En el esquema de reacción 21, se agrega al compuesto (A) R_5CHO y una base fuerte, tal como litio diisopropilamida, bajo condiciones de reacción apropiadas para formar el compuesto (B). Al compuesto (B) se agrega MsCl bajo condiciones de reacción apropiadas para llegar a un compuesto (C). Al compuesto (C) se agrega DBU bajo condiciones de reacción apropiadas para llegar a un compuesto (D). El compuesto (D) se reduce con un agente de reducción apropiado, tal como 10% de paladio en carbón vegetal, y bajo condiciones de reacción apropiada, para llegar a un compuesto (E). El compuesto (E) se desprotege bajo condiciones acídicas, tal como con HCl, para remover BOC y llegar al compuesto (F). Se agrega R_1COOH al compuesto (F) bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (G).

[00804] Ejemplo 21: 2-[(ciclopropilmetil)amino]-N4-(8-{5-[3-(1-metilpiperidin-4-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida acetato.

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[00805] ETAPA 1: Una solución de diisopropilamida de litio (0.87 mL, 2.0 M en tetrahidrofurano 1.74 mmol) se agrega por goteo a una mezcla de [8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo (300 mg, 0.87 mmol) en tetrahidrofurano a -78°C. Después de la agitación por 10 minutos, se agrega por goteo una solución de 4-formilpipiperidin-1-carboxilato de fenilmetilo (322 mg, 1.30 mmol) en tetrahidrofurano y se agita por 2 horas a -78°C. La mezcla de reacción se vierte en solución de cloruro de amonio acuoso saturado (50 mL), extraída con acetato de etilo (3 x 20 mL), y el extracto combinado se lava con agua (50 mL), después salmuera (20 mL), se seca sobre sulfato de sodio, se filtra después se concentra. El residuo se purifica por cromatografía instantánea (55% a 75% de acetato de etilo en hexanos) para dar 4-(3-{6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}-1-hidroxi-3-oxopropil)pipiperidin-1-carboxilato de fenilmetilo (360 mg, 70% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 8.75 (d, 1H), 7.99 (dd, 1H), 7.37-7.30 (m, 5H), 6.49 (dd, 1H), 5.13 (s, 2H), 4.97 (br, 1H), 4.63 (br, 1H), 4.26 (br, 2H), 3.96 (br, 1H), 3.79 (br, 1H), 3.56 (br, 1H), 3.08 (d, 1H), 2.89 (dd, 1H), 2.77 (2H), 2.26-2.02 (m, 6H), 1.93 (m, 1H), 1.79 (br, 1H), 1.76 (br, 1H), 1.73-1.59 (m, 3H), 1.45 (s, 9H), 1.34 (m, 2H); MS (EI) para $C_{33}H_{44}N_4O_6$: 593 (MH^+).

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[00806] ETAPA 2: Se agrega cloruro de metansulfonilo (29 uL, 0.72 mmol) a una mezcla de 4-(3-{6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}-1-hidroxi-3-oxopropil)pipiperidin-1-carboxilato de fenilmetilo (213 mg, 0.36 mmol) y trietilamina (51 µL, 0.72 mmol) en diclorometano (20 mL) a 0°C. La mezcla de reacción lentamente se calienta a temperatura ambiente. Después de la agitación por 18 horas, se lava con agua (20 mL), después solución bicarbonato de sodio acuoso saturado (20 mL), se seca sobre sulfato de sodio después se filtra y se concentra. El residuo se purifica por cromatografía instantánea (25% a 55% de acetato de etilo en hexanos) para dar 4-(3-{6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}-1-[(metilsulfonil)oxi]-3-oxopropil)pipiperidin-1-carboxilato de fenilmetilo (212 mg, 89% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 8.75 (d, 1H), 7.97 (dd, 1H), 7.37-7.33 (m, 5H), 6.49 (dd, 1H), 5.22 (s, 1H), 5.13 (br, 2H), 4.97 (br, 1H), 4.26 (br, 2H), 3.79 (br, 1H), 3.36 (dd, 1H), 3.04 (d, 1H), 3.00 (s, 3H), 2.77 (br, 2H), 2.25-2.04 (m, 9H), 1.78 (m, 2H), 1.73-1.59 (m, 3H), 1.69 (br, 1H), 1.45 (s, 9H), 1.34 (m, 2H); MS (EI) para $C_{34}H_{46}N_4O_8S$: 671 (MH^+).

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[00807] ETAPA 3: (82 *u*L, 0.27 mmol) se agrega a una solución de fenilmetilo 4-(3-{6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}-1-[(metilsulfonil)oxi]-3-oxopropil)pipiperidin-1-carboxilato de 1,8-Diazabiciclo[5.4.0]undec-7-eno (183 mg, 0.27 mmol) en diclorometano (20 mL) y la mezcla resultante se agita por una hora a temperatura ambiente. La mezcla se lava con solución de cloruro de amonio acuoso saturado (2x 20 mL), salmuera (20 mL), se seca sobre sulfato de sodio, se filtra después se concentra. El residuo se purifica por cromatografía instantánea (25% a 55% de acetato de etilo en hexanos) para dar 4-[(1E,*Z*)-3-{6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}-amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}-3-oxoprop-1-en-1-il]pipiperidin-1-carboxilato de fenilmetilo (147 mg, 94% de rendimiento). MS (EI) para $C_{33}H_{42}N_4O_5$: 575 (MH^+).

[00808] ETAPA 4: Una mezcla de 4-[(1E,*Z*)-3-{6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}-3-oxoprop-1-en-1-il]pipiperidin-1-carboxilato de fenilmetilo (107 mg, 0.19 mmol), 10% de paladio en carbón vegetal (Tipo Degussa, 110 mg), y ácido acético (23 µL, 0.37 mmol) en acetato de etilo (50 mL) se hidrogena a 1 atm por 18 horas. La mezcla se filtra y se concentra para dar {8-[5-(3-piperidin-4-

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ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo como la sal de acetato (91 mg, 97% de rendimiento). MS (EI) para $C_{25}H_{38}N_4O_3$: 443 (MH^+).

[00809] ETAPA 5: Se agrega triacetoxiborohidruro de sodio (96 mg, 0.45 mmol) a una mezcla de sal de acetato {8-[5-(3-piperidin-4-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endoil}carbamato de 1,1-dimetiletilo (91 mg, 0.18 mmol), formaldehído (73 µL, 37% de solución acuosa, 0.91 mmol) y ácido acético (55 *u*L, 0.92 mmol) en tetrahidrofurano (5 mL) a temperatura ambiente. Después de la agitación por una hora, se agrega una solución de cloruro de amonio acuoso saturado (5 mL) y se agita por 5 minutos. La mezcla de reacción se diluye con agua (15 mL), extraída con acetato de etilo (3 x 20 mL) y el extracto combinado se lava con agua (50 mL), después salmuera (20 mL), se seca sobre sulfato de sodio, se filtra, después se concentra para dar (8-{5-[3-(1-metilpiperidin-4-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)carbamato de 1,1-dimetiletilo (68 mg, 82% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 8.76 (d, 1H), 8.01 (dd, 1H), 6.49 (d, 1H), 4.99 (br, 1H), 4.63 (br, 2H), 3.78 (br, 1H), 3.53 (d, 2H), 2.89 (t, 2H), 2.76 (s, 3H), 2.66 (tr, 2H), 2.25-2.04 (m, 6H), 2.00-1.87 (m, 4H), 1.83-1.71 (m, 3H), 1.45 (s, 9H), 1.28 (m, 2H); MS (EI) para $C_{26}H_{40}N_4O_3$: 457 (MH^+).

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[00810] ETAPA 6: Una mezcla de (8-{5-[3-(1-metilpiperidin-4-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)carbamato de 1,1-dimetiletilo (60 mg, 0.13 mmol), metanol (1 mL) y cloruro de hidrógeno en dioxano (4 M, 1 mL) se agita a 60°C por 20 minutos. La mezcla de reacción se concentra para dar un sólido blanco, el cual se lava con hexano y se seca para dar sal clorhidrato de 1-[6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il]-3-(1-metilpiperidin-4-il)propan-1-ona (51 mg, 39% de rendimiento). MS (EI) para $C_{21}H_{32}N_4O$: 357 (MH^+).

[00811] ETAPA 7: Se agrega N,N-Diisopropiletilamina (101 uL, 0.66 mmol) a una mezcla de hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (53 mg, 0.14 mmol), y ácido 4-(aminocarbonil)-3-[(ciclopropilmetil)amino]-benzoico (sintetizado de conformidad con el reactivo de la preparación 39) (31 mg, 0.13 mmol) y la mezcla resultante se agita a temperatura ambiente por 30 minutos. Se agrega una solución de sal clorhidrato de 1-[6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il]-3-(1-metilpiperidin-4-il)propan-1-ona (51 mg, 0.13 mmol) en N,N-dimetilformamida (0.5 mL) y la agitación se continúa por 18 horas. La mezcla de reacción se diluye con metanol (1.5 mL), y se purifica por HPLC de fase inversa preparatoria (eluyente de acetonitrilo acuoso amortiguado con acetato de amonio) para dar 2-

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[(ciclopropilmetil)amino]-N4-(8-{5-[3-(1-metilpiperidin-4-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida como la sal de acetato, (54 mg, 66% de rendimiento). ^{1}H NMR (400 MHz, d_4-Metanol): 8.65 (d, 1H), 7.97 (dd, 1H), 7.54 (d, 1H), 6.96 (d, 1H), 6.82 (dd, 1H), 6.67 (d, 1H), 4.57, (Br, 2H), 3.89 (tr,1H), 3.04 (m, 2H), 2.95 (d, 2H), 2.87 (tr, 2H), 2.44 (s, 3H), 2.37 (tr, 2H), 2.21-2.01 (m, 6H), 1.91 (br, 1H), 1.88 (br, 1H), 1.80 (s, 3H), 1.78 (m, 1H), 1.58 (q, 4H), 1.38 (br, 1H), 1.22 (m, 2H), 1.02 (m, 1H), 0.47 (m, 2H), 0.20 (m, 2H); MS (EI) para $C_{33}H_{44}N_6O_3$: 573 (MH^+).

[00812] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [(21B)-(21H)]. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00813] (21B): 2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-hidroxi-4-metilpentanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 21 usando 2-metilpropanal en la etapa 1 y omitiendo las etapas 2 hasta 5. ^{1}H NMR (400 MHz, d_4-Metanol): 8.67 (d, 1H), 8.00 (dd, 1H), 7.55 (d, 1H), 6.97 (d, 1H), 6.84 (dd, 1H), 6.68 (d, 1H), 4.60, (Br, 2H), 3.90 (m,1H), 3.83 (m, 1H), 2.95 (d, 2H), 2.93 (m, 1H), 2.82 (dd, 1H), 2.21-2.01 (m, 6H), 1.93 (br, 1H),

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1.89 (br, 1H), 1.66 (m, 1H), 1.07 (m, 1H), 0.90 (d, 6H), 0.49 (m, 2H), 0.20 (m, 2H). MS (EI) para $C_{30}H_{39}N_5O_4$: 534 (MH^+).

[00814] (21C): 2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-fenilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 21 usando benzaldehído en la etapa 1 y omitiendo la etapa 5. ^1H NMR (400 MHz, d_4-Metanol): 8.67 (d, 1H), 7.97 (dd, 1H), 7.56 (d, 1H), 7.08 (m, 5H), 6.98 (d, 1H), 6.84 (dd, 1H), 6.67 (d, 1H), 4.59, (Br, 2H), 3.90 (m,1H), 3.93 (tr, 1H), 3.15 (tr, 2H), 3.00 (d, 2H), 2.92 (tr, 2H), 2.18-2.11 (m, 6H), 1.93 (br, 1H), 1.90 (br, 1H), 1.66 (m, 1H), 1.07 (m, 1H), 0.51 (m, 2H), 0.22 (m, 2H); MS (EI) para $C_{33}H_{37}N_5O_3$: 552 (MH^+).

[00815] (21D): 2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-hidroxi-3-fenilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 21 usando benzaldehído en la etapa 1 y omitiendo las etapas 2 hasta 5. ^1H NMR (400 MHz, d_4-Metanol): 8.64 (d, 1H), 7.97 (dd, 1H), 7.55 (d, 1H), 7.34 (m, 2H), 7.25 (m, 2H), 7.17 (m 1H), 6.96 (d, 1H), 6.84 (dd, 1H), 6.65 (d, 1H), 5.18 (dd, 1H), 4.60, (br, 2H), 3.92 (m,1H), 3.31 (dd, 1H), 3.06 (dd, 1H), 3.00 (d, 2H), 2.18-2.09 (m, 6H), 1.93 (br, 1H), 1.90 (br, 1H), 1.86 (br, 1H), 1.66 (m, 1H), 1.04 (m, 1H), 0.48 (m, 2H), 0.19 (m, 2H); MS (EI) para $C_{33}H_{37}N_5O_4$: 568 (MH^+).

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[00816] (21E): 2-[(ciclopropilmetil)amino]-N4-{8-[5-(4-metilpentanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 21 usando 2-metilpropanal en la etapa 1 y omitiendo la etapa 5. ^{1}H NMR (400 MHz, d_4-Metanol): 8.67 (d, 1H), 8.01 (dd, 1H), 7.55 (d, 1H), 6.98 (d, 1H), 6.83 (dd, 1H), 6.68 (d, 1H), 4.60, (br, 2H), 3.93 (m,1H), 3.00 (d, 2H), 2.83 (dd, 1H), 2.18-2.05 (m, 7H), 1.93 (br, 1H), 1.90 (br, 1H), 1.59-1.46 (m, 3H), 1.05 (m, 1H), 0.87 (d, 6H), 0.49 (m, 2H), 0.20 (m, 2H); MS (EI) para $C_{30}H_{39}N_5O_3$: 518 (MH^+).

[00817] (21F): N4-{8-[5-(3-ciclohexilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 21 usando ciclohexanocarbaldehído en la etapa 1 y omitiendo la etapa 5. ^{1}H NMR (400 MHz, d_4-Metanol): 8.67 (d, 1H), 7.99 (dd, 1H), 7.57 (d, 1H), 6.99 (d, 1H), 6.86 (dd, 1H), 6.68 (d, 1H), 4.61, (br, 2H), 3.91 (m,1H), 3.01 (d, 2H), 2.83 (dd, 1H), 2.12-2.10 (m, 6H), 1.95 (br, 1H), 1.91 (br, 1H), 1.76-1.59 (m, 5H), 1.51 (q, 2H), 1.05 (m, 5H), 0.87 (d, 2H), 0.51 (m, 2H), 0.23 (m, 2H); MS (EI) para $C_{33}H_{43}N_5O_3$: 558 (MH^+).

[00818] (21G): 5-[(1-etilpropil)amino]-2-metil-N-(8-{5-[3-(1-metilpiperidin-4-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada como la sal de clorhidrato, de conformidad con el

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método del ejemplo 21 usando ácido 4-aminocarbonil-2-metil-5-(pentan-3-ilamino)benzoico (preparado de conformidad con el reactivo de la preparación 42) en la etapa 7. ^{1}H NMR (400 MHz, Metanol-d_4): 8.56 (d, 1H), 8.42 (dd, 1H), 7.93 (s, 1H), 7.48 (s, 1H), 7.39 (d, 1H), 4.88-4.81 (m, 2H), 4.21-4.12 (m, 1H), 3.60-3.48 (m, 3H), 3.15-2.93 (m, 4H), 2.86 (s, 3H), 2.53-2.16 (m, 9H), 2.06 (d, 2H), 1.88-1.61 (m, 7H), 1.55-1.39 (m, 2H), 1.01 (t, 6H); MS (EI) para $C_{35}H_{50}N_6O_3$: 604 (MH^+).

[00819] (21H): 2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-piperidin-4-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparado de conformidad con el método del ejemplo 21 usando 4-formilpipiperidin-1-carboxilato de fenilmetilo en la etapa 1 y omitiendo la etapa 5. ^{1}H NMR (400 MHz, CD_3OD): 8.65 (s, 1H), 8.33-8.29 (s, 1H), 8.26-8.19 (d, 1H), 7.68-7.63 (d, 1H), 7.10-7.03 (d, 1H), 6.97-6.92 (d, 1H), 4.77-4.70 (m, 2H), 4.08-4.02 (m, 1H), 3.45-3.35 (m, 2H), 3.11-3.07 (d, 2H), 3.05-2.92 (m, 4H), 2.35-2.19 (m, 6H), 2.14-2.07 (d, 2H), 2.05-1.96 (d, 2H), 1.75-1.66 (m, 2H), 1.45-1.32 (m, 2H), 1.21-1.09 (m, 1H), 0.62-0.55 (m, 2H), 0.32-0.26 (m, 2H), 0.11-0.08 (m, 1H). MS (EI) para $C_{32}H_{42}N_6O_3$: 559 (MH^+).

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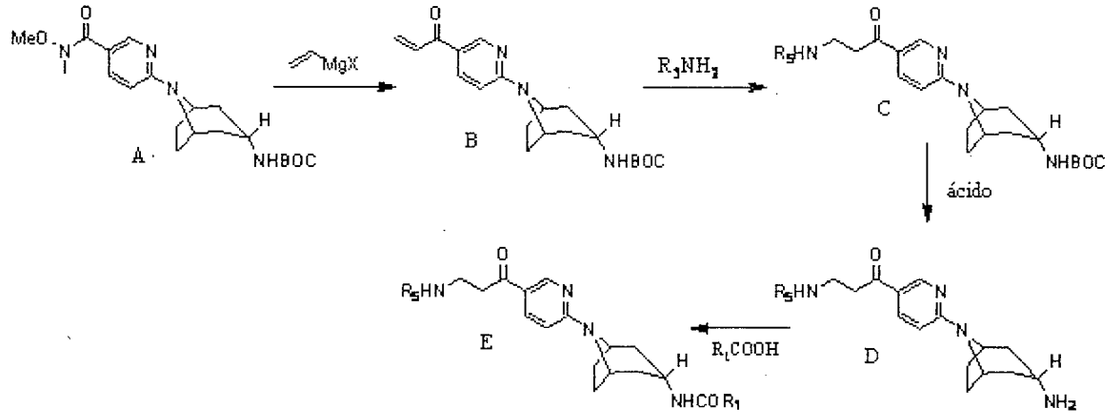
ESQUEMA DE REACCIÓN SINTÉTICA 22:



[00820] El esquema de reacción 22 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 22, en donde R_5 y R_1 son como se definen en la especificación.

[00821] En el esquema de reacción 22, se agrega un reactivo Grignard apropiado, tal como bromuro de vinil magnesio, al compuesto (A) bajo condiciones de reacción apropiadas para formar el compuesto (B). Al compuesto (B) se agrega R_5NH_2 bajo condiciones de reacción apropiadas para formar el compuesto (C). El compuesto (C) se desprotege con un ácido, tal como ácido trifluoroacético en diclorometano, para formar el compuesto (D). Al compuesto (D) se agrega R_1COOH bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (E).

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[00822] Ejemplo 22: 2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-piperidin-1-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida

[00823] ETAPA 1: Una solución de bromuro de vinil magnesio (1.0 M en tetrahidrofurano 6.5 mL) se agrega a una solución de [8-(5-{[metil(metiloxi)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo (sintetizado de conformidad con ejemplo 19 etapa 1) (0.5 g, 1.3 mmol) en tetrahidrofurano (20 mL) a 0°C y la mezcla resultante se agita a 0°C por una hora. La mezcla se vierte en solución de cloruro de amonio acuoso saturado (50 mL), extraída con acetato de etilo (3 x 20 mL) y el extracto combinado se lava con agua (50 mL), salmuera (20 mL) después se seca sobre sulfato de sodio, se filtra y se concentra. El residuo se purifica por cromatografía instantánea (50% a 65% de acetato de etilo en hexanos) para dar [8-(5-acriloilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo (180 mg, 39% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 8.81 (d, 1H), 8.09 (dd, 1H), 7.13 (dd, 1H), 6.55 (d, 1H), 6.43 (d, 1H), 5.85 (dd, 1H), 4.97 (br, 1H), 4.63 (b, 2H), 3.93 (m, 1H), 2.28-2.05 (m, 6H), 1.78 (d, 2H), 1.45 (s, 9H); MS (EI) para $C_{20}H_{27}N_3O_3$: 358 (MH^+).

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[00824] ETAPA 2: A una solución de [8-(5-acriloilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo (45 mg, 13 mmol) en tetrahidrofurano (2 mL) se agrega pipiperidina (13 *u*L, 13 mmol) y la mezcla resultante se agita a temperatura ambiente por 18 horas. La mezcla de reacción se concentra y el residuo se purifica por cromatografía instantánea (10% de metanol en diclorometano) para dar {8-[5-(3-piperidin-1-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo (41 mg, 74% de rendimiento). MS (EI) para $C_{25}H_{38}N_4O_3$: 443 (MH^+).

[00825] ETAPA 3: Una solución de {8-[5-(3-piperidin-1-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo (41 mg, 0.093 mmol) en 1:1 ácido trifluoroacético diclorometano (1 mL) se agita a temperatura ambiente por 15 min. La mezcla de reacción se concentra y el residuo se tritura con hexanos (3x 2 mL) y se seca in vacuo para dar 1-[6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il]-3-piperidin-1-ilpropan-1-ona como la sal de trifluoroacetato (42 mg, 100% de rendimiento). MS (EI) para $C_{20}H_{30}N_4O$: 343 (MH^+).

[00826] ETAPA 4: Se agrega N,N-Diisopropiletilamina (192 *u*L, 0.46 mmol) a una mezcla de hexafluorofosfato de O-(7-

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azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (38 mg, 0.10 mmol), y ácido 4-(aminocarbonil)-3-[(ciclopropilmetil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) (22 mg, 0.093 mmol) y la mezcla resultante se agita a temperatura ambiente por 30 minutos. Se agrega una solución de sal trifluoroacetato de 1-[6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il]-3-piperidin-1-ilpropan-1-ona (42 mg, 0.093 mmol) en N,N-dimetilformamida (0.5 mL) y la agitación se continúa por 18 horas. La mezcla de reacción se diluye con metanol (1.5 mL) y se purifica por HPLC de fase inversa preparatoria (eluyente de acetonitrilo acuoso amortiguado con acetato de amonio) para proporcionar 2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-piperidin-1-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida como la sal de acetato (4.6 mg, 12% de rendimiento). ^{1}H NMR (400MHz, D_4-Metanol): 8.67 (d, 1H), 7.97 (dd, 1H), 7.54(d, 1H), 6.96 (d, 1H), 6.82 (dd, 1H), 6.67 (d, 1H), 4.60 (br, 2H), 3.89 (tr, 1H), 3.07 (tr, 3H), 2.98 (d, 2H), 2.84 (br,3), 2.16-2.10 (m, 6H), 1.84 (m, 3H), 1.67 (m, 4H), 1.50(m, 2H), 1.07(m, 1H), 0.48 (m, 2H), 0.18 (m, 2H); MS (EI) para $C_{32}H_{42}N_6O_3$: 559 (MH^+).

[00827] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos [(22B)-(22I)]. Se obtienen comercialmente materiales de partida alternativos a menos que

se indique de otra manera.

[00828] (22B): 2-[(ciclopropilmetil)amino]-N4-{8-[5-(N,N-dimetil-beta-alanil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 22 usando dimetilamina en la etapa 2. ^{1}H NMR (400MHz, D_4-Metanol): 8.67 (d, 1H), 7.99 (dd, 1H), 7.54(d, 1H), 6.95 (d, 1H), 6.82 (dd, 1H), 6.68 (d, 1H), 4.61 (br, 2H), 3.90 (tr, 1H), 3.43-3.38 (m, 4H), 2.98 (d, 2H), 2.84 (s, 6H), 2.17-2.10 (m, 6H), 1.92 (m, 3H), 1.09 (m, 1H), 0.47 (m, 2H), 0.19 (m, 2H); MS (EI) para $C_{29}H_{38}N_6O_3$: 519 (MH^+).

[00829] (22C): 2-[(ciclopropilmetil)amino]-N4-(8-{5-[3-(metiloxi)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 22 usando metanol en la etapa 2. ^{1}H NMR (400MHz, D_4-Metanol): 8.67 (d, 1H), 7.98 (dd, 1H), 7.55 (d, 1H), 6.97 (d, 1H), 6.83 (dd, 1H), 6.68 (d, 1H), 4.61 (br, 2H), 3.90 (tr, 1H), 3.69 (tr, 2H), 3.25 (s, 3H), 3.06 (tr, 2H), 3.00 (d, 2H), 2.21-2.02 (m, 6H), 1.91 (m, 2H), 1.04 (m, 1H), 0.49 (m, 2H), 0.20 (m, 2H); MS (EI) para $C_{28}H_{35}N_5O_4$: 506 (MH^+).

[00830] (22D): 2-[(ciclopropilmetil)amino]-N4-(8-{5-[3-(etiloxi)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 22 usando etanol en la etapa 2. ^{1}H NMR (400MHz, $CDCl_3$): 8.81 (d, 1H), 8.06 (dd, 1H), 7.93 (b,

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1H), 7.45 (d, 1H), 7.09 (d, 1H), 6.75 (dd, 1H), 6.58 (d, 1H), 6.54 (d, 1H), 5.70 (br, 1H), 4.70 (br, 2H), 4.23 (q, 1H), 3.86 (tr, 1H), 3.54 (q, 2H), 3.14 (tr, 2H), 3.07 (tr, 2H), 2.39-2.23 (m, 4H), 2.09 (m, 2H), 1.89 (d, 2H), 1.20 (tr, 3H), 1.13 (m, 1H), 0.59 (m, 2H), 0.28 (m, 2H); MS (EI) para $C_{29}H_{37}N_5O_4$: 520 (MH^+).

[00831] (22E): 2-[(ciclopropilmetil)amino]-N4-(8-{5-[N-(4-fluorofenil)-beta-alanil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida Preparado de conformidad con el método del ejemplo 22 usando 4-fluoroanilina en la etapa 2. ^1H NMR (400MHz, D_4-Metanol): 8.74 (d, 1H), 8.06 (dd, 1H), 7.63 (b, 1H), 7.06 (d, 1H), 6.92 (dd, 1H), 6.86 (m, 21H), 6.75 (d, 1H), 6.65 (m, 2H), 4.57 (br, 2H), 3.90 (tr, 1H), 3.34 (m, 2H), 3.07 (tr, 2H), 3.02 (m 2H), 2.98 (d, 2H), 2.21-2.02 (m, 5H), 1.91 (m, 3H), 1.03 (m, 1H), 0.57 (m, 2H), 0.29 (m, 2H); MS (EI) para $C_{33}H_{37}FN_6O_3$: 585 (MH^+).

[00832] (22F): 2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-morfolin-4-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 22 usando morfolina en la etapa 2. ^1H NMR (400MHz, D_4-Metanol): 8.67 (d, 1H), 7.98 (dd, 1H), 7.54 (d, 1H), 6.96 (d, 1H), 6.82 (dd, 1H), 6.68 (d, 1H), 4.60 (br, 2H), 3.90 (tr, 1H), 3.61 (tr, 4H), 3.05 (tr, 2H), 3.00 (d, 2H), 2.71 (tr, 2H), 2.47 (br, 4H), 2.22-2.04 (m, 6H), 1.91

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(d, 2H), 1.06 (m, 1H), 0.48 (m, 2H), 0.19 (m, 2H); MS (EI) para $C_{31}H_{40}N_6O_4$: 561 (MH^+).

[00833] (22G): 2-[(ciclopropilmetil)amino]-N4-(8-{5-[3-(4-metilpiperazin-1-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 22 usando 1-metilpiperazina en la etapa 2. ^1H NMR (400MHz, D_4-Metanol): 8.69 (d, 1H), 7.99 (dd, 1H), 7.57 (d, 1H), 6.99 (d, 1H), 6.85 (dd, 1H), 6.70 (d, 1H), 4.63 (br, 2H), 3.93 (tr, 1H), 3.21 (m, 1H), 3.09 (tr, 2H), 3.02 (d, 2H), 2.71 (tr, 2H), 2.47 (br, 4H), 2.42 (s, 3H), 2.26-2.04 (m, 7H), 1.98-1.84 (m, 4H), 1.08 (m, 1H), 0.51 (m, 2H), 0.22 (m, 2H); MS (EI) para $C_{32}H_{43}N_7O_3$: 574 (MH^+).

[00834] (22H): 2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-pirrolidin-1-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 22 usando pirrolidina en la etapa 2. ^1H NMR (400MHz, D_4-Metanol): 8.69 (d, 1H), 8.00 (dd, 1H), 7.54 (d, 1H), 6.96 (d, 1H), 6.82 (dd, 1H), 6.70 (d, 1H), 4.61 (br, 2H), 3.90 (tr, 1H), 3.06-2.97 (m, 6H), 2.71 (tr, 2H), 2.47 (br, 4H), 2.42 (s, 3H), 2.19-2.08 (m, 6H), 1.82 (br, 2H),1.06 (m, 1H), 0.48 (m, 2H), 0.20 (m, 2H); MS (EI) para $C_{31}H_{40}N_6O_3$: 545 (MH^+).

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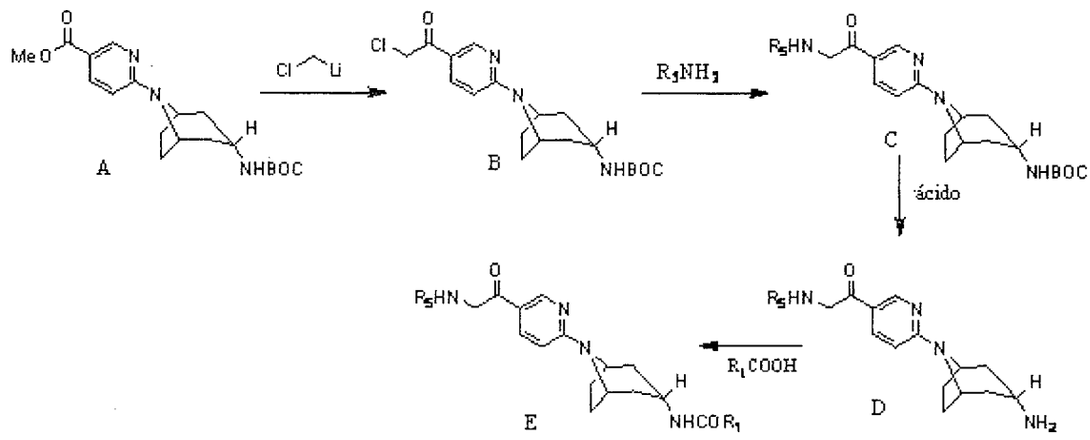
[00835] (22I): 2-[(ciclopropilmetil)amino]-N4-(8-{5-[3-(4-fenilpiperazin-1-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida. Preparada de conformidad con el método del ejemplo 22 usando 1-fenilpiperazina en la etapa 2. ^{1}H NMR (400MHz, D_4-Metanol): 8.80 (d, 1H), 8.10 (dd, 1H), 7.63 (d, 1H), 7.27 (m, 2H), 7.06 (d, 1H), 7.02 (d, 2H), 6.91 (m, 2H), 6.79 (d, 1H), 4.72 (br, 2H), 4.00 (tr, 1H), 3.47-3.32 (m, 11H), 3.08 (d, 2H), 2.32-2.15 (m, 6H), 2.02 (m, 3H), 1.14 (m, 1H), 0.58 (m, 2H), 0.29 (m, 2H); MS (EI) para $C_{37}H_{45}N_7O_3$: 636 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 23:



[00836] El esquema de reacción 23 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 23, en donde R_5 y R_1 son como se definen en la especificación.

[00837] En el esquema de reacción 23, se agrega cloroyodometano al compuesto (A) con una base, tal como

diisopropilamida de litio, bajo condiciones de reacción apropiadas para formar el compuesto (B). Al compuesto B se agrega R_5NH_2 bajo condiciones de reacción apropiadas para formar el compuesto (C). El compuesto (C) se desprotege con un ácido, tal como ácido trifluoroacético en diclorometano, para formar el compuesto (D). Al compuesto (D) se agrega R_1COOH bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (E).

[00838] EJEMPLO 23: 2-[(ciclopropilmetil)amino]-N4-{8-[5-(piperidin-1-ilacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida.

[00839] ETAPA 1: Una solución de diisopropilamida de litio (0.36 mL, 2.0 M en tetrahidrofurano 0.72 mmol) se agrega por goteo a una mezcla de 6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de metilo (sintetizado de conformidad con el método de ejemplo 1) (52 mg, 0.14 mmol) y cloroyodometano (42 *u*L, 0.56 mmol) en tetrahidrofurano (2 mL) a -78°C. Después de la agitación por 10 minutos, la mezcla de reacción se apaga con agua (10 mL), extraída con acetato de etilo (3 x 10 mL), y el extracto combinado se lava con agua (15 mL), después salmuera (15 mL), se seca sobre sulfato de

sodio, se filtra y se concentra. El residuo se purifica por cromatografía instantánea (25% a 65% de acetato de etilo en hexanos) para dar {8-[5-(cloroacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo (45 mg, 82% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 8.78 (d, 1H), 8.01 (dd, 1H), 6.53 (d, 1H), 4.95 (br, 1H), 4.85 (br, 1H), 4.55 (s, 2H), 3.80 (br, 1H), 2.27-2.04 (m, 6H), 1.85-1.75 (m, 2H), 1.43 (s, 9H); MS (EI) para $C_{19}H_{26}ClNO_3$: 380 (MH^+).

[00840] ETAPA 2: A una solución de {8-[5-(cloroacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato (44 mg, 0.12 mmol) en tetrahidrofurano (2 mL) se agrega pipiperidina (13 µL, 13 mmol), y la mezcla resultante se agita a temperatura ambiente por 18 horas. La mezcla se diluye con acetato de etilo (10 mL), se lava con agua (10 mL), después salmuera (10 mL) y se seca sobre sulfato de sodio. La solución orgánica se filtra y se concentra, después se seca in vacuo para proporcionar {8-[5-(piperidin-1-ilacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo (50 mg, 100% de rendimiento); MS (EI) para $C_{24}H_{36}N_4O_3$: 429 (MH^+).

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[00841] ETAPA 3: Una solución de {8-[5-(piperidin-1-ilacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo (50 mg, 0.12 mmol) en 1:1 ácido trifluoroacético diclorometano (1 mL) se agita a temperatura ambiente por 15 min. La mezcla de reacción se concentra, y el residuo se tritura con hexanos (3x2 mL) después se seca in vacuo para dar 1-[6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il]-2-piperidin-1-iletanona como la sal de trifluoroacetato (51 mg, 99% de rendimiento). MS (EI) para $C_{19}H_{28}N_4O$: 329 (MH^+).

[00842] ETAPA 4: Se agrega N,N-Diisopropiletilamina (78 *u*L, 0.58 mmol) a una mezcla de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (47 mg, 0.12 mmol), y ácido 4-(aminocarbonil)-3-[(ciclopropilmetil)amino]benzoico (sintetizado de conformidad con el reactivo de la preparación 39) (22 mg, 0.093 mmol) y la mezcla resultante se agita a temperatura ambiente por 30 minutos. Se agrega una solución de sal trifluoroacetato 1-[6-(3-endo-amino-8-azabiciclo[3.2.1]oct-8-il)piridin-3-il]-2-piperidin-1-iletanona (42 mg, 0.093 mmol) en N,N-dimetilformamida (0.5 mL) y la agitación se continúa por 18 horas. La mezcla de reacción se diluye con metanol (1.5 mL) y purifica por HPLC de fase inversa preparatoria (eluyente de acetonitrilo acuoso amortiguado con acetato de amonio) para

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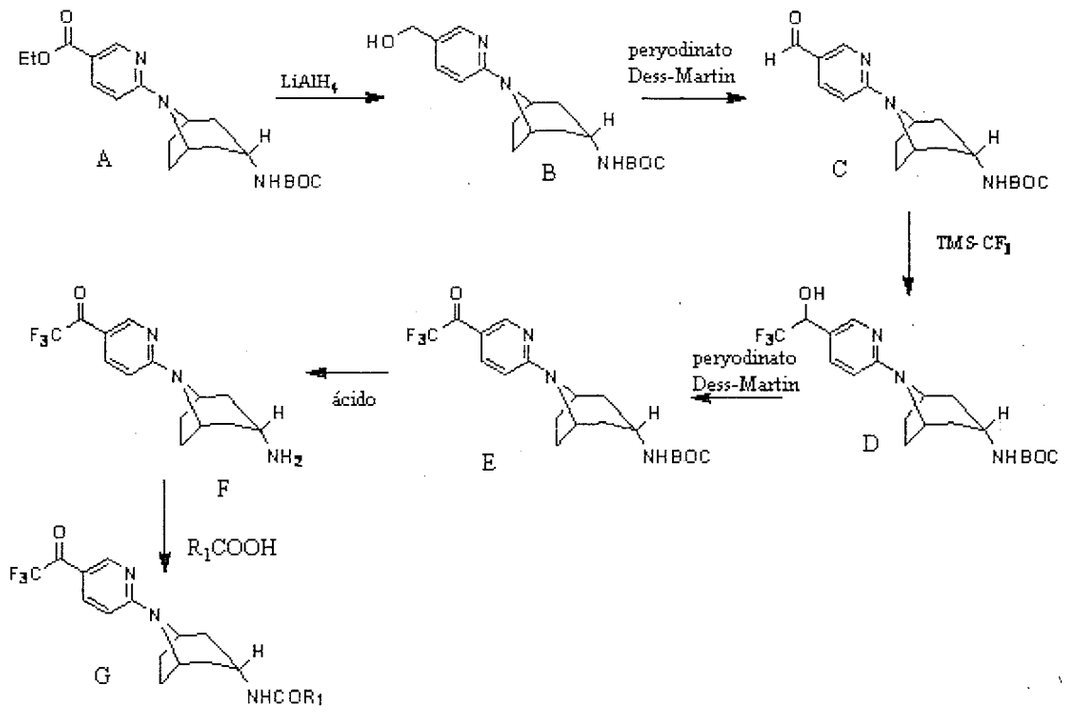
dar 2-[(ciclopropilmetil)amino]-N4-{8-[5-(piperidin-1-ilacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida como la sal de acetato (24.4 mg, 39% de rendimiento). ^{1}H NMR (400 MHz, d_4-Metanol): 8.69 (d, 1H), 7.98 (dd, 1H), 7.54 (d, 1H), 6.96 (d, 1H), 6.83 (dd, 1H), 6.67 (d, 1H), 4.55 (br, 2H), 3.90 (br, 3H), 2.98 (d, 2H), 2.62 (m, 4H), 2.20-2.07 (m, 6H), 1.92 (m, 2H), 1.61 (m, 4H), 1.45.

ESQUEMA DE REACCIÓN SINTÉTICA 24:



[00843] El esquema de reacción 24 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 24, en donde R_1 es como se define en la especificación.

[00844] En el esquema de reacción 24, se agrega $LiAlH_4$ al compuesto (A) bajo condiciones de reacción apropiadas para formar el compuesto (B). El compuesto (B) sufre oxidación del alcohol primario en un aldehído para formar el compuesto (C) por tratamiento con un agente de oxidación apropiado tal como peryodinato Dess-Martin. Después se agrega $TMS-CF_3$ al compuesto (C) bajo condiciones de reacción apropiadas para formar el compuesto (D). El compuesto (D) sufre oxidación del alcohol secundario en una cetona para formar el compuesto (E) por tratamiento con un agente de oxidación apropiado tal como peryodinato Dess-Martin. El compuesto (E) se desprotege con un ácido, tal como HCl, para formar el compuesto (F). Al compuesto (F) se agrega R_1COOH bajo condiciones de reacción apropiadas y con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (G).

[00845] EJEMPLO 24: 2-[(ciclopropilmetil)amino]-N4-{8-[5-(trifluoroacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida.

[00846] ETAPA 1: A una suspensión de 6-[3-endo-({[(1,1-dimetiletil)oxi]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxilato de etilo (sintetizado en el Ejemplo 1) (1.47 g, 3.92 mmol) en THF (25 ml) lentamente se agrega

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hidruro de aluminio y litio (1.96 ml, solución 2M en THF, 3.92 mmol) a 0 °C. La mezcla de reacción se agita a 0 °C por 4 horas y después se apaga por adición de agua (0.15 ml), seguido por 15% de hidróxido de sodio acuoso (0.15 ml) y después agua (0.45 ml). Después de ser agitada por 0.5 h a temperatura ambiente, la mezcla se diluye con acetato de etilo, se filtra a través de Celite, se lava con acetato de etilo y se concentra. La cromatografía en columna en sílice (diclorometano:metanol 30:1 a 15:1) proporciona {8-[5-(hidroximetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo (0.72 g, 55% de rendimiento). MS (EI) para $C_{18}H_{27}N_3O_3$: 334 (MH^+).

[00847] ETAPA 2: Una suspensión de {8-[5-(hidroximetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo (105 mg, 0.31 mmol) y peryodinato Dess-Martin (147 mg, 0.35 mmol) en diclorometano (5 mL) se agita a temperatura ambiente por 90 min. Se agregan una solución al 10% de tiosulfato de sodio (5 mL) y después bicarbonato de sodio saturado (5 mL) y la agitación se continúa por 30 min. Las capas se separan y la capa acuosa se extrae con diclorometano (2 x 20 mL). Las capas orgánicas combinadas se lavan con bicarbonato de sodio saturado (20 mL) y salmuera (20 mL), se secan sobre sulfato de sodio, y se concentran para dar [8-(5-formilpiridin-2-il)-8-

azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo crudo (100 mg, 96% de rendimiento) como una espuma incolora. ^{1}H NMR (400 MHz, $CDCl_3$): 9.76 (s, 1H), 8.55 (d, 1H), 7.92 (dd, 1H), 6.54 (d, 1H), 4.97 (d, 1H), 4.60 (br s, 2H), 3.81 (m, 1H), 2.20 (m, 4H), 2.08 (d, 2H), 1.80 (d, 2H).

[00848] ETAPA 3: A una solución de [8-(5-formilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]carbamato de 1,1-dimetiletilo (72 mg, 0.22 mmol) en DMF (1.5 mL) se agrega trimetil(trifluorometil)silano (154 mg, 1.09 mmol) y carbonato de cesio (85 mg, 0.26 mol), y la mezcla de reacción se agita a temperatura ambiente por 1 h. Se agrega acetato de etilo (30 mL), y la mezcla se lava con agua (3 x 10 mL) y salmuera (10 mL), se seca sobre sulfato de sodio, y se concentra. La cromatografía en columna en sílice (diclorometano:metanol 95:5) proporciona {8-[5-(2,2,2-trifluoro-1-hidroxietil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo (45 mg, 52% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 8.17 (d, 1H), 7.59 (dd, 1H), 6.55 (d, 1H), 4.98 (br s, 1H), 4.91 (m, 1H), 4.51 (br s, 2H), 3.78 (m, 1H), 2.51 (d, 1H), 2.24 (m, 2H), 2.16 (m, 2H), 2.03 (m, 2H), 1.70 (d, 2H), 1.45 (s, 9H); MS (EI) para $C_{19}H_{26}F_3N_3O_3$: 402 (MH^+).

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[00849] ETAPA 4: Una suspensión de {8-[5-(2,2,2-trifluoro-1-hidroxietil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo (41 mg, 0.10 mmol) y peryodinato Dess-Martin (52 mg, 0.12 mmol) en diclorometano (2 mL) se agita a temperatura ambiente por 3.5 h. Se agregan una solución al 10% de tiosulfato de sodio (2 mL) y después bicarbonato de sodio saturado (2 mL) y la agitación se continúa por 30 min. Las capas se separan y la capa acuosa se extrae con diclorometano (2 x 10 mL). Las capas orgánicas combinadas se lavan con salmuera (50 mL), se secan sobre sulfato de sodio, y se concentran para dar {8-[5-(trifluoroacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo crudo (40 mg, 98% de rendimiento) como un incoloro. MS (EI) para $C_{19}H_{24}F_3N_3O_3$: 400 (MH^+).

[00850] ETAPA 5: A una solución de {8-[5-(trifluoroacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}carbamato de 1,1-dimetiletilo (38 g, 0.10 mmol) en metanol (2 mL) se agrega una solución de cloruro de hidrógeno 4N en dioxano (2 mL), y la mezcla de reacción se somete a reflujo por 2 min. Después del enfriamiento a temperatura ambiente la mezcla se concentra y se seca in vacuo. Al residuo se agrega ácido 4-(aminocarbonil)-3-[(ciclopropilmetil)amino]benzoico (sintetizado de conformidad con el reactivo de la prep 39)

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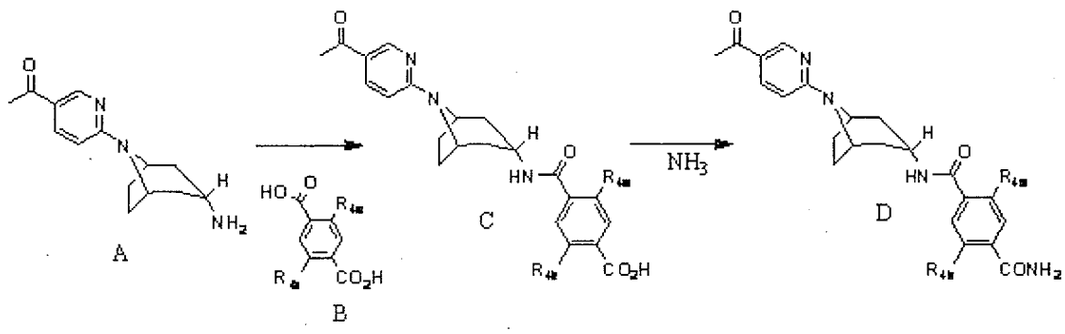
(23 mg, 0.10 mmol), HATU (38 mg, 0.10 mmol), DMF (1 mL), y diisopropiletilamina (76 mg, 0.58 mmol), y la mezcla se agita a temperatura ambiente por 16 h. La purificación por HPLC preparatoria (0.1% de acetato de amonio amortiguado con fase móvil de acetonitrilo acuoso) proporciona 2-[(ciclopropil-metil)amino]-N4-{8-[5-(trifluoroacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida (18 mg, 37% de rendimiento). ^{1}H NMR (400 MHz, DMSO-d_6): 8.77 (s, 1H), 8.26 (t, 1H), 8.23 (d, 1H), 7.99 (dd, 1H), 7.94 (br s, 1H), 7.67 (d, 1H), 7.30 (br s, 1H), 6.99 (d, 1H), 6.91 (m, 2H), 4.96 (br s, 1H), 4.56 (br s, 1H), 3.89 (m, 1H), 3.03 (t, 2H), 2.26 (m, 2H), 2.06 (m, 6H), 1.11 (m, 1H), 0.52 (m, 2H), 0.25 (m, 2H); MS (EI) para $C_{26}H_{28}F_3N_5O_3$: 516 (MH^+).

ESQUEMA DE REACCIÓN SINTÉTICA 25:



[00851] El esquema de reacción 25 generalmente describe la síntesis de todos los compuestos listados en el Ejemplo 25, en donde R_{4a} y R_{4b} son como se definen en la especificación.

[00852] En el esquema de reacción 25, el compuesto (B) se

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agrega al compuesto (A), con un reactivo de acoplamiento adecuado, tal como HATU, para condensar y formar la amida unida en el compuesto (C). Este esquema de reacción es aplicable cuando R_{4a} y R_{4b} son los mismos. Al compuesto (C) se agrega NH_3 (g) bajo condiciones de reacción apropiadas para formar el compuesto (D).

[00853] EJEMPLO 25: N-[8-(5-Acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2,5-dimetilbencen-1,4-dicarboxamida.

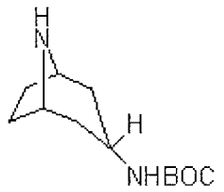
[00854] ETAPA 1: Se agrega ácido 2,5-Dimetiltereftálico (200 mg, 1.03 mmol) disuelto en DMF (5 mL) y HATU (392 mg, 1.03 mmol) y la mezcla se agita a ambiente por 15 minutos. Se agrega N,N-Diisopropiletilamina (0.7 mL, 3.99 mmol) y después de 5 minutos se agrega 1-[6-(3-endo-amino-8-azabiciclo-[3.2.1]oct-8-il)piridin-3-il]etanona (preparada en el Ejemplo 19 Etapa 3) (250 mg, 1.02 mmol) y la mezcla se agita a 50 °C por 15 h. La mezcla se enfría a temperatura ambiente y HATU (392 mg, 1.03 mmol) y se agregan N,N-diisopropiletilamina (0.2 mL, 1.14 mmol) y la mezcla se agita a ambiente por 15 minutos. gas amoníaco se burbujea en la solución y se forma un precipitado espeso. La mezcla se agita a 50 °C por 0.5 h y después se enfría a temperatura ambiente y se concentra. El residuo se trata con ácido clorhídrico acuoso 1N (~ 2mL) y DMSO. Se agrega agua y lo precipitado se recolecta por

filtración después se purifica adicionalmente por HPLC de fase inversa. Las fracciones puras se combinan y se concentra a un residuo acuoso. El residuo acuoso se basifica con bicarbonato de sodio y se extrae con acetato de etilo (2x). La porción orgánica combinada se seca sobre sulfato de magnesio después se filtra y se concentra para proporcionar N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2,5-dimetilbencen-1,4-dicarboxamida (77 mg, 0.183 mmol, 18% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.74 (d, 1H), 8.28 (d, 1H), 7.97 (dd, 1H), 7.71 (br s, 1H), 7.41 (br s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.79 (d, 1H), 4.62 (br s, 2H), 3.87 (br s, 1H), 2.45 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 2.27-2.18 (m, 2H), 2.15-1.94 (m, 4H), 1.89 (d, 2H); MS (EI) para $C_{24}H_{28}N_4O_3$: 421 (MH^+).

PREPARACIONES DE REACTIVO:

[00855] Los siguientes reactivos referidos en los ejemplos anteriores se elaboran como sigue. Los números de reactivo posteriores corresponden a los números de reactivos referidos en los ejemplos anteriores

PREPARACIÓN DEL REACTIVO 1: 8-azabiciclo[3.2.1]octan-3-endo-ilcarbamato de terc-butilo:



[00856] ETAPA 1: A un matraz de fondo redondo de 5 L se agrega 8-metil-8-azabiciclo[3.2.1]octan-3-endo-amina (432 g, 3.1 mol), 2 L de 1,4-dioxano seco, 675 mL de agua desionizada y 468 g de trietilamina seca. Se agrega bicarbonato de di-*terc-butilo* (solución en 1.2 L de dioxano) por goteo a la solución agitada a temperatura ambiente durante 16 h. La mezcla de reacción se concentra y el residuo resultante se suspende en 2.5 L de cloruro de metileno. Después se lava dos veces con 1 L de agua, se seca con sulfato de magnesio anhidro, se filtra, y los volátiles orgánicos se remueven por evaporación rotatoria para proporcionar 617 g (83%) de 8-metil-8-azabiciclo[3.2.1]octan-3-ilcarbamato de terc-butilo (mp 79-81 °C).

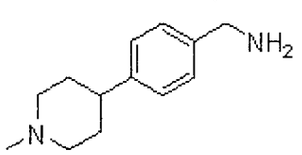
[00857] ETAPA 2: A un matraz de fondo redondo de 5 L se agrega 480 g (2.0 mol) de 8-metil-8-azabiciclo[3.2.1]octan-3-endo-ilcarbamato de terc-butilo, 2 L de tolueno, y 69 g (0.5 mol) de carbonato de potasio. Se agrega por goteo cloroformiato de 2,2,2-tricloroetilo (347 mL, 2.4 mol) a

temperatura ambiente durante 6 h y la reacción se calienta a temperatura de reflujo por 8 h. Después de que la solución se enfría a temperatura ambiente, se agrega 1.2 L de agua a la solución de reacción y se agita 0.5 h. La capa orgánica se separa y se lava con 1 L de salmuera, se seca con sulfato de magnesio anhidro, se filtra, y se concentra para proporcionar un aceite turbio. El aceite se tritura con 700 mL de una solución 3:2 etilo éter/hexanos para proporcionar 280 g (mp 131-135°C) de 3-endo-(terc-butoxicarbonilamino)-8-azabiciclo[3.2.1]octane-8-carboxilato de 2,2,2-tricloroetilo que se recolecta por filtración. El licor madre se concentra y se tritura adicionalmente para proporcionar una muestra menos pura de la diamina protegida Troc (129 g, mp 116-118°C).

[00858] ETAPA 3: A un matraz de fondo redondo de 5 L se agrega 360 g (0.9 mol) de 3-endo-(terc-butoxicarbonilamino)-8-azabiciclo[3.2.1]octane-8-carboxilato de 2,2,2-tricloroetilo, 2.8 L de metanol y 675 g (12.6 mol) de cloruro de amonio. La solución se calienta a reflujo y cuidadosamente se agrega 387 g (7.5 mol) de polvo de zinc en porciones pequeñas durante 0.5 h. Al completarse la adición del polvo de zinc, la reacción se calienta a temperatura de reflujo por 2 h, después se enfría a temperatura ambiente. La reacción se filtra a través de una almohadilla de Celite 545, y el metanol se remueve por evaporación rotatoria. Lo sólido

resultante se disuelve en 800 mL de cloruro de metileno y se agita con 600 mL de hidróxido de amonio concentrado por 0.5 h. La capa orgánica se separa, se lava con 600 mL de agua, se seca con sulfato de magnesio anhidro, se filtra, y se concentra para proporcionar un aceite. El residuo se disuelve en 200 mL de cloruro de metileno y después se filtra 1 L de éter de etilo. La solución resultante se congela a 0 °C y se agregan lentamente 215 mL de cloruro de hidrógeno 4N en dioxano, por goteo durante 0.5 h, asegurándose de mantener la temperatura de solución de reacción cercana a 0°C. Después de que la adición se completa, se agregan 200 mL de cloruro de metileno y 1.4 L de éter de etilo a la solución enfriada y se forma un precipitado blanco pálido. Lo sólido resultante se recolecta por filtración para proporcionar 173 g (85%) de sal clorhidrato de 8-azabiciclo[3.2.1]octan-3-endo-ilcarbamato terc-butilo.

PREPARACIÓN DEL REACTIVO 2: 4-(1-metilpiperidin-4-il)bencilamina:



[00859] ETAPA 1: A una solución de 4-piperidin-4-ilbenzamida (200 mg, 1.00 mmol), 37% de formaldehído acuoso (162 µL, 2.00 mmol), y ácido acético (86 uL, 1.5 mmol) en una

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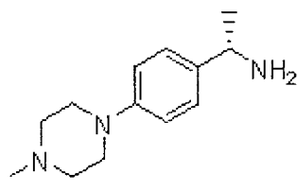
mezcla de diclorometano y metanol (2:1, 6 mL) se agrega triacetoxilborohidruro de sodio (318 mg, 1.5 mmol) en porciones durante quince minutos y la agitación se continúa por 2 hr a temperatura ambiente. La reacción después se apaga con agua y se ajusta a pH 9 con hidróxido de sodio 2N acuoso después extraído con diclorometano (2x 50 ml). Los extractos orgánicos se combinan y se secan sobre sulfato de sodio, se filtran y se concentran para dar 4-(1-metilpiperidin-4-il)benzamida (190 mg, 87 %). MS (EI) para $C_{13}H_{18}N_2O$: 218 (MH^+).

[00860] ETAPA 2: A una solución enfriada con hielo de 4-(1-metilpiperidin-4-il)benzamida (190 mg, 0.87 mmol) en tetrahidrofurano (5 mL) se agrega hidruro de aluminio y litio 1.0M en tetrahidrofurano (1.79 mL, 1.79 mmol) y la agitación se continúa durante la noche a temperatura ambiente. La mezcla de reacción se apaga agregando sulfato de sodio decahidratado hasta que la evolución de gas cesa. La suspensión se filtra a través de Celite y la torta filtrada se lava con una mezcla de acetato de etilo y cloroformo (2:1, 50mL). Lo filtrado se concentra para dar 4-(1-metilpiperidin-4-il)bencilamina (130 mg, 71%) como un aceite. ^1H NMR (400 MHz, $CDCl_3$): 7.23 (dd, 4H), 3.86 (s, 3H), 2.98 (m, 2H), 2.49 (m, 1H), 2.11 (m, 2H), 1.83 (m, 4H).

PREPARACIÓN DEL REACTIVO 3: (S)-1-[4-(4-metilpiperazin-1-il)fenil]etilamina:



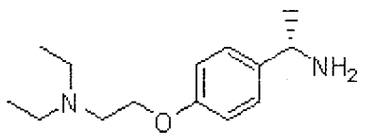
[00861] ETAPA 1: Una solución de (1S)-1-(4-bromofenil)etilamina (10g, 50 mmol) y dicarbonato de di-terc-butilo (13 g, 60 mmol) en diclorometano (80 mL) se agita a temperatura ambiente por 15 horas. La concentración de la mezcla de reacción proporciona un residuo sólido que después se suspende en éter de dietilo (100 mL). La mezcla se diluye con hexano (100 mL) y lo sólido se aísla por filtración, después se lava con hexano y se seca para proporcionar 14.4 g, 48 mmol (96%) de [(1S)-1-(4-bromofenil)etil]carbamato de 1,1-dimetiletilo. ^{1}H NMR (400 MHz, $CDCl_3$): 7.46-7.42 (m, 2H), 7.19-1.76 (m, 2H), 5.29 (s, 1H), 4.71 (br s, 1H), 1.43-1.39 (m, 12H). MS (EI) para $C_{13}H_{18}BrNO_2$: 301 (MH^+).

[00862] ETAPA 2: Una mezcla de [(1S)-1-(4-bromofenil)-etil]carbamato de 1,1-dimetiletilo (14.4 g, 48 mmol), tris(dibencilidenacetona)dipaladio(0) (4.6 g, 4.8 mmol), N-metilpiperazina (22 mL, 200 mmol), BINAP (1.4 g, 4.8 mmol) y fosfato de potasio tribásico en dimetiléter de etileno glicol (120 mL) se somete a reflujo por 15 horas. En enfriamiento a temperatura ambiente, la mezcla se diluye con acetato de

etilo (100 mL). La mezcla orgánica se extrae usando ácido clorhídrico acuoso 1N (3 x 100 mL). El pH de las porciones acuosas combinadas se ajustan a 10 y después se extraen usando acetato de etilo (3 x 100 mL). La porción orgánica combinada se lava con salmuera después se seca sobre sulfato de sodio anhidro. La filtración y concentración proporciona un residuo marrón el cual se purifica por cromatografía en columna de gel de sílice. Eluyendo con 0-20% de metanol en acetato de etilo, las fracciones purificadas se combinan y se concentran para proporcionar 12.9g, 40.5 mmol (84%) de {(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}carbamato de 1,1-dimetiletilo. ^{1}H NMR (400 MHz, d_6-DMSO): 7.16 (d, 2H), 6.84 (d, 2H), 4.54 (m, 1H), 3.07 (m, 4H), 2.42 (m, 4H) 2.21 (s, 3H), 1.38 (s, 9H), 1.25 (d, 3H). MS (EI) para $C_{18}H_{29}N_3O_2$: 320 (MH^+).

[00863] ETAPA 3: Una solución de {(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}carbamato de 1,1-dimetiletilo (2g, 6.3 mmol) y cloruro de hidrógeno 4N en dioxano (5 mL) en metanol (5 mL) se somete a reflujo por 2 min. Después del enfriamiento a temperatura ambiente la mezcla se concentra y se evapora rotatoriamente a partir de benceno, y se seca adicionalmente in vacuo para proporcionar 1.7 g, 5.9 mmol (95%) de diclorhidrato de (S)-1-[4-(4-metilpiperazin-1-il)fenil]etilamina. MS (EI) para $C_{13}H_{21}N_3$: 220 (MH^+).

PREPARACIÓN DEL REACTIVO 4: (S)-2-[4-(1-aminoetil)fenoxi]-N,N-dietiletilamina:



[00864] ETAPA 1: Una solución de (S)-1-(4-metoxifenil)etanamina (3.10 g, 20.5 mmol) en diclorometano (30 ml) se enfría a -78 °C y se agrega una solución de tribromuro de boro (3.88 ml, 41 mmol) en diclorometano (15 ml) por goteo. La mezcla de reacción se agita a -78 °C por dos horas y después a temperatura ambiente por 2 h. La solución después se enfría a 0 °C y se agrega agua (15 ml) seguido por carbonato de sodio acuoso saturado a pH 8. La mezcla parcialmente se concentra por evaporación rotatoria, después se agrega tetrahidrofurano (50 ml) seguido por dicarbonato de di-terc-butilo (4.47 g, 20.5 mmol) y la mezcla de reacción se agita a temperatura ambiente durante la noche. La capa acuosa se extrae con acetato de etilo (2x 150 ml) y las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio después se filtran y se concentran. El residuo se purifica por cromatografía en columna de gel de sílice usando hexanos:acetato de etilo 4:1 a 3:1 como eluyente para proporcionar [(1S)-1-(4-hidroxifenil)etil]carbamato de 1,1-dimetiletilo (2.90 g, 60 %

de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 7.10 (br s, 2H), 6.73 (d, 2H), 6.07 (br s, 1H), 4.91-4.51 (m, 2H), 1.56-1.25 (m, 12H).

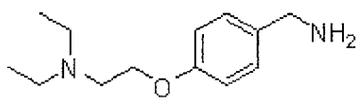
[00865] ETAPA 2: A una solución de [(1S)-1-(4-hidroxifenil)etil]carbamato de 1,1-dimetiletilo (2.90 g, 12.2 mmol) en dimetilformamida (25ml) se agregan carbonato de cesio (11.9 g, 36.6 mmol) y bromhidrato de 2-bromo-N,N-dietilamina (3.18 g, 12.2 mmol) y la mezcla de reacción se agita a 60 °C por 24h. La mezcla se divide entre acetato de etilo (150 ml) y agua (75ml) y la fase orgánica se lava con hidróxido de sodio 1M acuoso (50 ml), 5% de cloruro de litio acuoso (50ml), se seca sobre sulfato de sodio después se filtra y se concentra para dar [(1S)-1-(4-{[2-(dietilamino)etil]oxi}fenil)etil]carbamato de 1,1-dimetiletilo (0.920 g, 22% de rendimiento) como un aceite amarillo. MS (EI) para $C_{19}H_{32}N_2O_3$: 337 (MH^+).

[00866] ETAPA 3: Una solución de [(1S)-1-(4-{[2-(dietilamino)etil]oxi}fenil)etil]carbamato de 1,1-dimetiletilo (0.912 g, 2.7 mmol) en cloruro de hidrógeno 4N en dioxano (5 mL) y metanol (5 mL) se somete a reflujo por 2 min. Después del enfriamiento a temperatura ambiente la mezcla se concentra para proporcionar (S)-2-[4-(1-aminoetil)fenoxi]-N,N-dietiletilamina como la sal de

clorhidrato (0.830 g, 99% de rendimiento). MS (EI) para $C_{14}H_{24}N_2O$: 237 (MH^+).

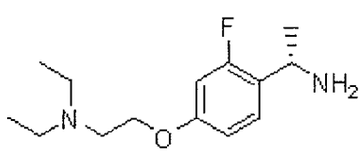
[00867] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes reactivos. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00868] 2-[4-(aminometil)fenoxi]-N,N-dietiletilamina:



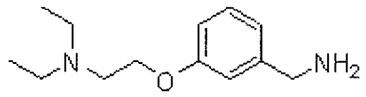
Sintetizado de conformidad con el método del reactivo de la preparación 4 usando 4-(aminometil)fenol en la etapa 1. ^1H NMR(CD_3OD): 7.45 (d, 2H), 7.10 (d, 2H), 4.40 (t, 2H), 4.06 (s, 2H), 3.70 (s, 2H), 3.65 (t, 2H), 3.32 (t, 2H), 1.39-1.36 (m, 6H). MS (EI) para $C_{13}H_{22}N_2O$: 223.

[00869] (S)-2-[4-(1-aminoetil)-3-fluorofenoxi]-N,N-dietiletilamina:



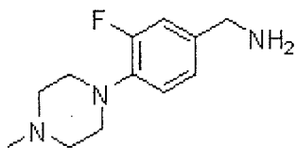
Sintetizado de conformidad con el método del reactivo de la preparación 4 usando (S)-4-(1-aminoetil)-3-fluorofenol en la etapa 1. MS (EI) para $C_{14}H_{23}FN_2O$: 255 (MH^+).

[00870] 2-[3-(aminometil)fenoxi]-N,N-dietiletilamina:



[00871] Sintetizado de conformidad con el método del reactivo de la preparación 4 usando 3-(aminometil)fenol en la etapa 1. ^{1}H NMR(DMSO-d_6): 6.05 (t, 2H), 5.85 (s, 2H), 5.75-5.72 (m, 2H), 3.05-3.03 (m, 2H), 2.28 (s, 2H), 2.28-2.01 (m, 2H), 1.95-1.93 (m, 10H). MS(EI) para $C_{13}H_{22}N_2O$: 223.

PREPARACIÓN DEL REACTIVO 5: [3-fluoro-4-(4-metilpiperazin-1-il)fenil]bencilamina:



[00872] ETAPA 1: A ácido 4-bromo-3-fluorobenzoico (2.00 g, 9.13 mmol) en metanol (12 ml) se agrega ácido sulfúrico (500 µl) y se calienta a 80°C por 18 h, después se enfría a temperatura ambiente y se concentra. El residuo se diluye con bicarbonato de sodio saturado y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio, se filtra, y después se concentra para proporcionar (2.07 g, 97%) de 4-bromo-3-fluorobenzoato de metilo, el cual se usa sin purificación adicional. ^{1}H NMR (400 MHz, CD_3OD): 7.80-7.73 (m, 3H), 3.91 (s, 3H). MS (EI) para $C_8H_6BrFO_2$: 234 (MH^+).

[00873] ETAPA 2: A 1-metilpiperazina (980 µl, 8.80 mmol) en tolueno (15 ml) se agrega tris(dibencilideno acetona)dipaladio (201 mg, 0.22 mmol), BINAP (550 mg, 0.88 mmol), y carbonato de cesio (4.30 g, 13.2 mmol). La mezcla se agita por 30 minutos antes de la adición de 4-bromo-3-fluorobenzoato de metilo (2.05 g, 8.80 mmol), después del cual, la temperatura se incrementa a 105°C y se agita por 18h adicionales. La mezcla se enfría y se filtra a través de Celite, se lava con acetato de etilo, y lo filtrado resultante se concentra in vacuo para proporcionar un aceite anaranjado. El residuo se purifica por cromatografía en columna eluyendo con 5% de metanol en diclorometano. Las fracciones puras se concentran para proporcionar (1.80 g, 81%) de 3-fluoro-4-(4-metilpiperazin-1-il)benzoato de metilo como un aceite incoloro. ^{1}H NMR (400 MHz, CD_3OD): 7.78-7.73 (d, 1H), 7.64-7.59 (d, 1H), 7.09-7.03 (m, 1H), 3.86 (s, 3H), 3.26-3.20 (m, 4H), 2.65-2.59 (m, 4H), 2.35 (s, 3H). MS (EI) para $C_{13}H_{17}FN_2O_2$: 253 (MH^+).

[00874] ETAPA 3: A 3-fluoro-4-(4-metilpiperazin-1-il)benzoato de metilo (1.80 g, 7.13 mmol) en metanol (40 ml) se agrega hidróxido de sodio 1 M (25 ml, 25.0 mmol). La solución se agita a 50°C por 3 h, punto en el cual la mezcla se concentra. El residuo se diluye con agua (10 ml) y el pH se ajusta a 6 con ácido clorhídrico 1 N. Lo precipitado

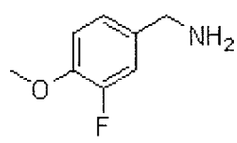
resultante se recolecta por filtración y se seca in vacuo para proporcionar (733 mg, 43%) de ácido 3-fluoro-4-(4-metilpiperazin-1-il)benzoico. ^{1}H NMR (400 MHz, CD_3OD): 7.73-7.68 (d, 1H), 7.62-7.57 (d, 1H), 7.03-6.97 (m, 1H), 3.26-3.20 (m, 4H), 2.83-2.76 (m, 4H), 2.47 (s, 3H). MS (EI) para $C_{12}H_{15}FN_2O_2$: 239 (MH^+).

[00875] ETAPA 4: A ácido 3-fluoro-4-(4-metilpiperazin-1-il)benzoico (250 mg, 1.05 mmol) en THF (10 ml) se agrega trietilamina (221 µl, 1.58 mmol) y cloroformiato de isobutilo (145 µl, 1.10 mmol). La mezcla se agita a 0°C por 1 hora, tiempo en el cual se agrega amoníaco acuoso concentrado (3 ml). La mezcla de reacción se agita por 3 horas después el volumen se reduce in vacuo. El residuo se diluye con agua y se extrae con acetato de etilo. La capa orgánica se lava con salmuera, se seca sobre sulfato de sodio anhidro, se filtra, y después se concentra para proporcionar (30.0 mg, 12%) de 3-fluoro-4-(4-metilpiperazin-1-il)benzamida, el cual se usa sin purificación adicional. MS (EI) para $C_{12}H_{16}FN_3O$: 238 (MH^+).

[00876] ETAPA 5: A 3-fluoro-4-(4-metilpiperazin-1-il)benzamida (300 mg, 1.33 mmol) en THF (10 ml) se agrega borohidruro de sodio (252 mg, 6.67 mmol), seguido por adición por goteo de trifluoruro eterato de boro (2.28 ml, 8.65 mmol) durante 5 minutos. La mezcla se agita a 70°C por 16 h, punto

en el cual la mezcla se enfría y se apaga con ácido clorhídrico acuoso 1N después se remueve THF por evaporación rotatoria. La mezcla se diluye con agua (10 ml) y el pH se ajusta a 10 con hidróxido de sodio 1 N, extraído con acetato de etilo y la fase orgánica se seca sobre sulfato de sodio, se filtra, y se concentra para proporcionar (221 mg, 75%) de [3-fluoro-4-(4-metilpiperazin-1-il)fenil]bencilamina. ^{1}H NMR (400 MHz, CD_3OD): 7.23-7.11 (m, 3H), 4.05 (s, 2H), 3.49-3.40 (m, 2H), 3.26-3.20 (m, 2H), 3.17-3.08 (m, 2H), 2.99-2.91 (m, 2H), 2.68 (s, 3H). MS (EI) para $C_{12}H_{18}FN_3$: 224 (MH^+).

PREPARACIÓN DEL REACTIVO 6: 3-fluoro-4-metoxibencilamina:



[00877] ETAPA 1: Una mezcla de ácido 3-fluoro-4-hidroxibenzoico (500 mg, 3.2 mmol), carbonato de cesio (3.1 g, 9.6 mmol) y yodometano (440 µl, 7.0 mmol) en dimetilformamida (7 mL) se agita a temperatura ambiente por 4 horas. La mezcla se diluye con acetato de etilo y se lava con 5% de cloruro de litio acuoso, hidróxido de sodio acuoso 1N, salmuera, después se seca sobre sulfato de sodio anhidro. La filtración y concentración proporciona 534 mg, 2.9 mmol (92%) de 3-fluoro-4-(metiloxi)benzoato de metilo. MS (EI) para $C_9H_9FO_3$: 185 (MH^+).

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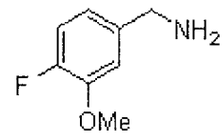
[00878] ETAPA 2: Una solución de 3-fluoro-4-(metiloxi)benzoato de metilo (534 mg, 2.9 mmol) en 35% de hidróxido de potasio acuoso:metanol (1:4, 10 mL) se agita a reflujo por 1 hora. La solución se enfría a temperatura ambiente y se evapora el metanol. El pH de la porción acuosa se lleva a 2 usando ácido clorhídrico concentrado. Lo precipitado el cual se forma, se recolecta por filtración y se lava con agua para proporcionar 400 mg, 2.4 mmol (83%) de ácido 3-fluoro-4-metoxibenzoico. MS (EI) para $C_8H_7FO_3$: 169 (M-H).

[00879] ETAPA 3: A una solución de ácido 3-fluoro-4-metoxibenzoico (400 mg, 2.4 mmol) y trietilamina (560 µl, 3.5 mmol) en tetrahidrofurano (10 mL) se enfría a 0°C, se agrega isobutilcloroformiato (320 µl, 2.4 mmol), y la mezcla se agita a 0°C por 1 hora. La solución se calienta a temperatura ambiente y se satura con gas amoníaco, después se agita por 15 horas a temperatura ambiente. La mezcla se diluye con acetato de etilo, después se lava con 20% de ácido cítrico acuoso, bicarbonato de sodio acuoso saturado, y salmuera, después se seca sobre sulfato de sodio anhidro. La filtración y concentración proporciona 280mg, 1.7 mmol (70%) de 3-fluoro-4-(metiloxi)benzamida. MS (EI) para $C_8H_8FNO_2$: 170 (MH^+).

[00880] ETAPA 4: A una solución de 3-fluoro-4-(metiloxi)benzamida (100 mg, 0.60 mmol) en tetrahidrofurano (5 mL) se agrega borohidruro de sodio (115 mg, 3.0 mmol) seguido por la adición por goteo de una solución de trifluoruro eterato de boro (48% BF_3 ca., 475 µl, 3.8 mmol) en tetrahidrofurano (3 mL). La mezcla se agita a reflujo por 15 horas, después se enfría a temperatura ambiente y se diluye con acetato de etilo. La porción orgánica se extrae con 20% de ácido cítrico acuoso. La porción acuosa se lleva a pH 8 usando bicarbonato de sodio sólido, después se extrae varias veces usando acetato de etilo. La porción orgánica combinada se lava con salmuera después se seca sobre sulfato de sodio anhidro. La filtración y concentración proporciona un residuo amarillo, el cual se purifica por cromatografía en columna de gel de sílice usando 10% de metanol en diclorometano como eluyente. Las fracciones purificadas se combinan y se concentran para proporcionar 56 mg, 0.36 mmol (61%) de 3-fluoro-4-metoxibencilamina como un residuo incoloro. MS (EI) para $C_8H_{10}FNO$: 156 (MH^+).

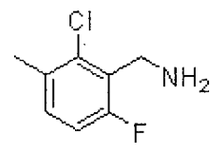
[00881] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes reactivos intermediarios. Se obtienen comercialmente reactivos de partida alternativos.

[00882] 4-fluoro-3-metoxibencilamina:



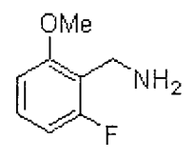
Preparado de conformidad con el método del reactivo de la preparación 6 por omisión de etapa 1 y 2, y usando ácido 2-fluoro-6-metoxibenzoico en la etapa 3. MS (EI) para $C_8H_{10}FNO$: 156 (MH^+).

[00883] 2-cloro-6-fluoro-3-metilbencilamina:



Preparado de conformidad con el método del reactivo de la preparación 6 por omisión de etapa 1 y 2, y usando ácido 2-cloro-6-fluoro-3-metilbenzoico en la etapa 3. MS (EI) para C_8H_9ClFN: 178 (MH^+).

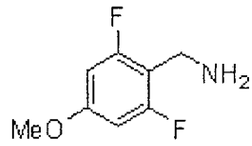
[00884] 2-fluoro-6-metoxibencilamina:



Preparado de conformidad con el método del reactivo de la preparación 6 por omisión de etapa 1 y 2, y usando ácido 2-fluoro-6-metoxibenzoico en la etapa 3. MS (EI) para

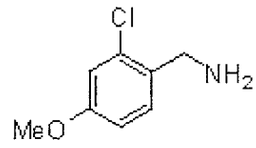
$C_8H_{10}FNO$: 156 (MH^+).

[00885] 2,6-difluoro-4-metoxibencilamina:



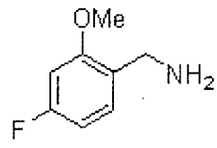
Preparado de conformidad con el método del reactivo de la preparación 6 por omisión de etapa 1 y 2, y usando ácido 2,6-difluoro-4-metoxibenzoico en la etapa 3. MS (EI) para $C_8H_9F_2NO$: 174 (MH^+).

[00886] 2-cloro-4-metoxibencilamina:



Preparado de conformidad con el método del reactivo de la preparación 6 usando ácido 2-cloro-4-hidroxibenzoico en la etapa 1. MS (EI) para $C_8H_{10}ClNO$: 173 (MH^+).

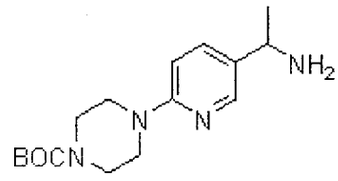
[00887] 4-fluoro-2-metoxibencilamina:



Preparado de conformidad con el método del reactivo de la preparación 6 usando ácido 4-fluoro-2-hidroxibenzoico

en la etapa 1. MS (EI) para $C_8H_{10}FNO$: 156 (MH^+).

PREPARACIÓN DEL REACTIVO 7: 4-(5-(1-aminoetil)piridin-2-il)piperazin-1-carboxilato de terc-butilo:



[00888] ETAPA 1: Una mezcla de 6-cloronicotinato de etilo (2.67 g, 14.4 mmol), piperazin-1-carboxilato de terc-butilo (2.5 g, 13.4 mmol) y N,N-diisopropiletilamina (3.5 mL, 20 mmol) en DME (15 mL) se calienta a 120°C por 12 horas. La mezcla después se enfría a temperatura ambiente y se divide con acetato de etilo y 10% de ácido cítrico acuoso. La capa orgánica se lava dos veces con 10% de ácido cítrico acuoso después salmuera y se seca sobre sulfato de sodio anhidro. La filtración y la concentración seguido por cromatografía instantánea en gel de sílice del residuo usando 3:1 hexanos:acetato de etilo a 100% de acetato de etilo proporciona 4-(5-(etoxicarbonil)piridin-2-il)piperazin-1-carboxilato de terc-butilo (3.65 g). ^{1}H NMR (400 MHz, $CDCl_3$): 8.81 (s, 1H), 8.04 (d, 1H), 6.58 (d, 1H), 4.33 (q, 2H), 3.70-3.67 (m, 4H), 3.56-3.53 (m, 4H), 1.49 (s, 9H), 1.37 (tr, 3H).

[00889] ETAPA 2: 4-(5-(etoxicarbonil)piridin-2-il)piperazin-1-carboxilato de terc-butilo (3.65 g, 10.9 mmol)

se recupera en metanol (40 mL) seguido por adición de hidróxido de sodio acuoso 1M (15 mL) y THF (15 mL), y la mezcla se calienta a 50°C por una hora. Una porción adicional de hidróxido de sodio acuoso 1M (10 mL) después se agrega y el calentamiento se continúa dos horas adicionales. La mezcla después se enfría a temperatura ambiente y se concentra para remover solventes orgánicos. El residuo acuoso se divide con éter de etilo y se desecha la capa orgánica. La fase acuosa cuidadosamente se lleva a pH 5-6 por adición de ácido clorhídrico acuoso 1M para dar una suspensión blanca espesa. Lo sólido se recolecta por filtración y se seca para dar ácido 6-(4-(terc-butoxicarbonil)piperazin-1-il)nicotínico (2.0 g). ^{1}H NMR (400 MHz, DMSO-d_6): 12.57 (br s, 1H), 8.64 (s, 1H), 7.95 (d, 1H), 6.86 (d, 1H), 3.67-3.62 (m, 4H), 3.45-3.40 (m, 4H), 1.43 (s, 9H).

[00890] ETAPA 3: ácido 6-(4-(terc-butoxicarbonil)piperazin-1-il)nicotínico (2.0 g, 6.5 mmol) se recupera en DMF (10 mL) seguido por adición de HATU (2.48 g, 6.5 mmol), N,N-diisopropiletilamina (2.5 mL, 14.1 mmol) y clorhidrato de N,O-dimetilhidroxilamina (652 mg, 6.7 mmol), y la mezcla se agita a temperatura ambiente durante 12 horas. La solución resultante se divide con acetato de etilo y agua, después la fase orgánica se lava con agua (3x), 10% de ácido cítrico acuoso (2x) después hidróxido de sodio acuoso 0.5M y

salmuera. La solución orgánica se seca sobre sulfato de sodio anhidro, se filtra y se concentra, después se purifica por cromatografía instantánea en gel de sílice con éter de etilo como eluyente para proporcionar 4-(5-(metoxi(metil)carbamoil)piridin-2-il)piperazin-1-carboxilato de terc-butilo (1.45 g). MS (EI) para $C_{17}H_{26}N_4O_4$: 351 (MH^+).

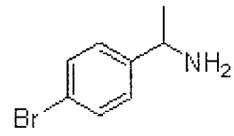
[00891] ETAPA 4: 4-(5-(metoxi(metil)carbamoil)piridin-2-il)piperazin-1-carboxilato de terc-butilo (1.45 g, 4.1 mmol) se recupera en THF (20 mL) y la solución se enfría a 0°C bajo una atmósfera de nitrógeno. Se agrega bromuro de metilo magnesio (3.0M en éter de etilo, 3.5 mL) en porciones y la mezcla se deja agitar 10 minutos seguido por adición de otro 1.5 mL de alícuota, después la mezcla se calienta a temperatura ambiente. La solución después se divide con éter de etilo y agua, y la fase orgánica se lava con salmuera después se seca sobre sulfato de sodio anhidro, se filtra y se concentra. El residuo se recupera en metanol (25 mL) seguido por adición en porciones de borohidruro de sodio sólido (250 mg) durante 10 minutos. La mezcla se deja agitar a temperatura ambiente otros 10 minutos, después se concentra. El residuo se divide con éter de etilo y agua, y la fase acuosa se extrae de éter de etilo (2x). Las capas orgánicas combinadas se secan sobre sulfato de sodio anhidro, se filtra y se concentra para dar 4-(5-(1-

hidroxietil)piridin-2-il)piperazin-1-carboxilato de terc-butilo (1.48 g) el cual se lleva hacia adelante sin purificación adicional.

[00892] ETAPA 5: 4-(5-(1-hidroxietil)piridin-2-il)piperazin-1-carboxilato de terc-butilo (1.48 g) como se obtiene en la etapa 4 se recupera en DMF (10 mL) seguido por adición de azida de sodio (580 mg, 8.9 mmol), DPPA (1.6g, 5.7 mmol) y N,N-diisopropiletilamina (0.72 mL, 4.2 mmol) y la mezcla se calienta a 60°C por 12 horas. Después se agregan Alícuotas adicionales de azida de sodio y DPPA a la mezcla de reacción y la temperatura se eleva a 75°C por 12 horas adicionales. La mezcla después se enfría a temperatura ambiente y se divide con éter de etilo y agua. La capa orgánica se lava con agua (2x), hidróxido de sodio acuoso 0.5M (2x) después con 10% de ácido cítrico acuoso, se lleva a pH 1 con ácido clorhídrico acuoso 1M. La fase orgánica se desecha y la fase acuosa acídica rápidamente se basifica a pH 7 por adición en porciones de bicarbonato de sodio sólido y 50% de hidróxido de sodio acuoso. La fase acuosa neutralizada se extrae una vez con éter de etilo y la capa orgánica se seca sobre sulfato de sodio anhidro, se filtra, y se concentra para proporcionar 4-(5-(1-azidoetil)piridin-2-il)piperazin-1-carboxilato de terc-butilo (1.21 g).

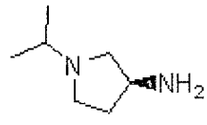
[00893] ETAPA 6: 4-(5-(1-azidoetil)piridin-2-il)piperazin-1-carboxilato de terc-butilo (1.21 g), como se obtiene en la etapa 5, se hidrogena en metanol (50 mL) en la presencia de 10% de paladio en carbono (390 mg) a una atmósfera de hidrógeno por 6 horas. La mezcla después se filtra y se concentra para proporcionar 4-(5-(1-aminoetil)piridin-2-il)piperazin-1-carboxilato de terc-butilo (1.1 g).

PREPARACIÓN DEL REACTIVO 8: 1-(4-bromofenil)etilamina:



[00894] Sintetizado de conformidad con el método de ejemplo 12 etapa 1 usando 1-(4-bromo-2-fluorofenil)etanona. MS (EI) para C_8H_9BrFN: 219 (MH^+).

PREPARACIÓN DEL REACTIVO 9: (3S)-1-(1-metiletil)pirrolidin-3il-amina:



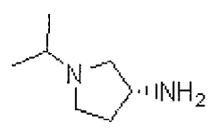
[00895] A una solución de (3S)-pirrolidin-3il carbamato de 1,1-dimetiletilo (500 mg, 2.68 mmol) en acetona (0.5 mL, 6.80 mmol) se agrega triacetoxiborohidruro de sodio (1.50 g, 7.07 mmol). Después de 15 minutos de agitación, se agrega triacetoxiborohidruro de sodio adicional (750 mg, 3.53 mmol)

1428

y la mezcla se agita durante la noche a temperatura ambiente. Se agrega acetato de etilo (15 mL) a la mezcla de reacción y la capa orgánica se lava con solución acuosa de hidróxido de sodio 0.5 M (10 mL) y salmuera, se seca con sulfato de sodio anhidro, después se filtra y se concentra. El residuo se diluye con acetonitrilo (15 mL) y se agrega cloruro de hidrógeno 4 M en dioxano (5 mL). La mezcla se agita por 2 hr a 40 °C, después se concentra y se seca in vacuo para dar sal de clorhidrato del compuesto del título (384 mg, 72.0%). ^{1}H NMR (400 MHz, d_4-metanol): 4.00-4.30 (m, 1H), 3.50-3.90 (m, 4H), 3.30 (m, 1H), 2.50-2.70 (m, 1H), 2.15 (m, 1H), 1.45 (d, 6H).

[00896] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes reactivos. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

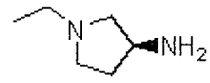
[00897] (3R)-1-(1-metiletil)pirrolidin-3-amina:



Sintetizado de conformidad con el método del reactivo de la preparación 9 usando (3R)-pirrolidin-3il carbamato de 1,1-dimetiletilo. MS (EI) para $C_7H_{16}N_2$: 129 (MH^+).

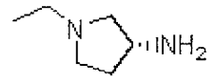
1129

[00898] (3S)-1-etilpirrolidin-3-amina:



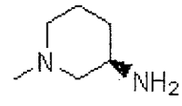
Sintetizado de conformidad con el método del reactivo de la preparación 9 usando acetaldehído. MS (EI) para $C_6H_{14}N_2$: 115 (MH^+).

[00899] (3R)-1-etilpirrolidin-3-amina:



Sintetizado de conformidad con el método del reactivo de la preparación 9 usando acetaldehído y (3R)-pirrolidin-3il carbamato de 1,1-dimetiletilo. MS (EI) para $C_6H_{14}N_2$: 115 (MH^+).

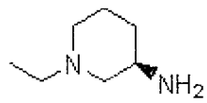
[00900] (3R)-1-metilpiperidin-3-amina:



Sintetizado de conformidad con el método del reactivo de la preparación 9 usando formaldehído acuoso y (3R)-piperidin-3-il carbamato de 1,1-dimetiletilo. MS (EI) para $C_6H_{14}N_2$: 115 (MH^+).

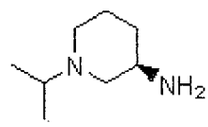
1130

[00901] (3R)-1-etilpiperidin-3-amina:



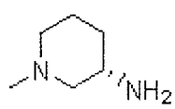
Sintetizado de conformidad con el método del reactivo de la preparación 9 usando acetaldehído y (3R)-piperidin-3-il carbamato de 1,1-dimetiletilo. MS (EI) para $C_7H_{16}N_2$: 129 (MH^+).

[00902] (3R)-1-(1-metiletil)piperidin-3-amina:



Sintetizado de conformidad con el método del reactivo de la preparación 9 usando (3R)-piperidin-3-il carbamato de 1,1-dimetiletilo. MS (EI) para $C_8H_{18}N_2$: 143 (MH^+).

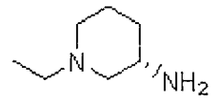
[00903] (3S)-1-metilpiperidin-3-amina:



Sintetizado de conformidad con el método del reactivo de la preparación 9 usando formaldehído acuoso y (3S)-piperidin-3-il carbamato de 1,1-dimetiletilo. MS (EI) para $C_6H_{14}N_2$: 113 (M-H).

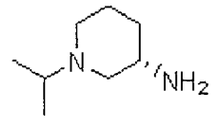
1131

[00904] (3S)-1-etilpiperidin-3-amina:



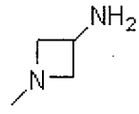
Sintetizado de conformidad con el método del reactivo de la preparación 9 usando acetaldehído y (3S)-piperidin-3-il carbamato de 1,1-dimetiletilo. MS (EI) para $C_7H_{16}N_2$: 131 (MH^+).

[00905] (3S)-1-(1-metiletil)piperidin-3-amina:



Sintetizado de conformidad con el método del reactivo de la preparación 9 usando (3S)-piperidin-3-il carbamato de 1,1-dimetiletilo. MS (EI) para $C_8H_{18}N_2$: 143 (MH^+).

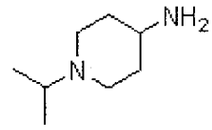
[00906] 1-metilazetidin-3-amina:



Sintetizado de conformidad con el método del reactivo de la preparación 9 usando formaldehído y azetidin-3-ilcarbamato de 1,1-dimetiletilo.

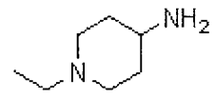
1132

[00907] 1-(1-metiletil)piperidin-4-amina:



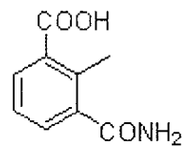
Sintetizado de conformidad con el método del reactivo de la preparación 9 usando acetona y piperidin-4-ilcarbamato de 1,1-dimetiletilo. MS (EI) para $C_8H_{18}N_2$: 143 (MH^+).

[00908] 1-etilpiperidin-4-amina:



Sintetizado de conformidad con el método del reactivo de la preparación 9 usando acetaldehído y piperidin-4-ilcarbamato de 1,1-dimetiletilo. MS (EI) para $C_7H_{16}N_2$: 131 (MH^+).

PREPARACIÓN DEL REACTIVO 10: Ácido 3-(aminocarbonil)-2-metilbenzoico:



[00909] ETAPA 1: A una solución de 3-bromo-2-metilbenzoato de metilo (0.646 g, 2.8 mmol) en 4 ml de dimetilamina se agrega $Pd(OAc)_2$ (0.5mol%), carbonato de sodio (0.3 g, 2.8 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.262 g, 0.62 mmol). La mezcla se

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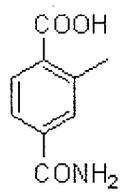
calienta a 120°C y se agita a esta temperatura por 4 horas después a RT por 18 horas. La mezcla de reacción se diluye con 30 ml de acetato de etilo y la suspensión resultante se filtra a través de Celite. Lo filtrado se lava con agua (2x15 ml) después 5% de hidróxido de amonio acuoso (1x15 ml). La capa orgánica se seca sobre sulfato de sodio anhidro después se filtra y se concentra para proporcionar 3-ciano-2-metilbenzoato de metilo (0.248 g, 50% de rendimiento) (*S.Weissman, D. Zewge, C. Chen; J. Org. Chem. 2005, 70, 1508-1510*). ^{1}H-NMR(400 MHz, DMSO-d_6): 8.09(d, 1H), 8.04(d, 1H), 7.53(t, 1H), 3.87 (s, 3H), 2.66 (s, 3H).

[00910] ETAPA 2: A una solución de 3-ciano-2-metilbenzoato de metilo (0.111 g, 0.63 mmol) en 3 ml de t-butanol se agrega hidróxido de potasio (0.29 g, 5.1 mmol). La mezcla se somete a reflujo por 6 horas y se agita a temperatura ambiente por 48 horas. La mezcla se evapora por rotación a sequedad y el residuo se disuelve en agua, después se extrae con acetato de etilo (2x20 ml). La capa acuosa se acidifica con ácido clorhídrico acuoso concentrado a pH 1-2 y se extrae con acetato de etilo (3x20 ml). La capa de acetato de etilo se seca sobre sulfato de sodio anhidro, después se filtra y se concentra para proporcionar ácido 3-(aminocarbonil)-2-metilbenzoico (86 mg).

PREPARACIÓN DEL REACTIVO 11: Ácido 4-(aminocarbonil)-2-metilbenzoico:

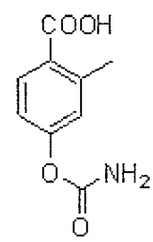


[00911] ETAPA 1: A una solución de 4-bromo-3-metilbenzonitrilo (0.48 g, 2.43 mmol) en 1 ml de tolueno a -78°C, se agrega 1 ml de 2.6M n-BuLi en tolueno seguido por apagado con hielo seco (0.5g, 12.5 mmol). La mezcla de reacción se calienta a temperatura ambiente, después se recupera en agua y se extrae con acetato de etilo (2x 15 ml). La capa acuosa se acidifica a pH 1-2 por adición de ácido clorhídrico acuoso concentrado y se extrae con acetato de etilo (3x 15 ml). La capa orgánica se seca sobre sulfato de sodio anhidro, después se filtra y se concentra para dar ácido 4-ciano-2-metilbenzoico (0.08g, 20% de rendimiento). ^{1}H-NMR (400 MHz, DMSO-d_6): 13.10 (br s, 1H), 7.92 (d, 1H), 7.84 (m, 1H), 7.76 (d, 1H), 2.53 (s, 3H).

[00912] ETAPA 2: A ácido 4-ciano-2-metilbenzoico (0.071 g, 0.44 mmol) en 2 ml de t-butanol se agrega hidróxido de potasio (0.13 g, 2.15 mmol). La mezcla de reacción se somete a reflujo por 30 min y se enfría a temperatura ambiente. A la mezcla de reacción se agrega 10 ml de salmuera y la mezcla de

reacción se extrae con acetato de etilo (2x 15 ml). La capa acuosa se acidifica a pH 1-2 con ácido clorhídrico acuoso concentrado para dar un precipitado blanco. Lo sólido se recolecta por filtración, se lava varias veces con agua (3x 15 ml) y se seca in vacuo para proporcionar ácido 4-(aminocarbonil)-2-metilbenzoico (0.038 g, 49% de rendimiento). ^{1}H-NMR (400 MHz, DMSO-d_6): 13.10 (br s, 1H), 8.07(s, 1H), 7.87 (d, 1H), 7.78-7.72 (m, 2H), 7.50 (s, 1H), 2.54 (s, 3H).

PREPARACIÓN DEL REACTIVO 12: Ácido 4-[(aminocarbonil)oxi]-2-metilbenzoico:



[00913] ETAPA 1: Una solución de ácido 4-hidroxi-2-metilbenzoico (550 mg, 3.60 mmol), cloruro de bencilo (458 mg, 3.60 mmol) y N,N-diisopropiletilamina (465 mg, 3.6 mmol) se agita a 70° C por 22 h. Una solución de bicarbonato de sodio saturado se agrega y la mezcla se extrae con acetato de etilo. La capa orgánica se separa, se seca sobre sulfato de sodio anhidro, se filtra y se concentra in vacuo. El residuo se purifica por cromatografía en columna (SiO_2, hexanos/acetato de etilo) para proporcionar 4-hidroxi-2-

metilbenzoato de fenilmetilo (687 mg, 79%). ^{1}H NMR (400 MHz, DMSO): 10.21-10.18 (br. s, 1H), 7.84-7.77 (d, 1H), 7.48-7.31 (m, 5H), 6.71-6.64 (br. s, 2H), 5.26 (s, 2H), 2.47 (s, 3H). MS (EI) para $C_{15}H_{14}O_3$: 243 (MH^+).

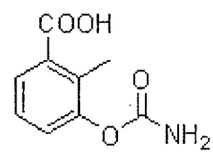
[00914] ETAPA 2: A una solución de 4-hidroxi-2-metilbenzoato de fenilmetilo (687 mg, 2.82 mmol) en diclorometano (8 ml) a 0° C, se agrega isocianato de clorosulfonilo (1.20 g, 8.50 mmol). La reacción se deja calentar a 25° C y se agita por 20 h. La mezcla de reacción se concentra después se recupera en acetato de etilo y se lava con agua. La capa orgánica se separa, se seca sobre sulfato de sodio anhidro, se filtra y se concentra in vacuo. El residuo se purifica por cromatografía en columna (SiO_2, hexanos/acetato de etilo) para proporcionar 4-[(aminocarbonil)oxi]-2-metilbenzoato de fenilmetilo (356 mg, 89%). ^{1}H NMR (400 MHz, DMSO): 7.91-7.87 (d, 1H), 7.49-7.29 (m, 5H), 7.11-7.00 (m, 4H), 5.31 (s, 2H), 2.52 (s, 3H). MS (EI) para $C_{16}H_{15}NO_4$: 286 (MH^+).

[00915] ETAPA 3: Una mezcla de 4-[(aminocarbonil)oxi]-2-metilbenzoato de fenilmetilo (356 mg, 1.25 mmol), 5% de paladio en carbono (50 mg) y etanol (10 ml) se hidrogena a 10 psi usando un aparato Parr. Después de la terminación de hidrogenación, la mezcla se filtra y lo filtrado se concentra

in vacuo. El ácido 4-[(aminocarbonil)oxi]-2-metilbenzoico crudo resultante (14 mg, 6%) se usa sin purificación adicional. ^{1}H NMR (400 MHz, DMSO): 12.86-12.69 (br. s, 1H), 7.87-7.81 (d, 1H), 7.34-7.27 (br. s, 1H), 7.07-6.98 (m, 3H), 2.52 (s, 3H). MS (EI) para $C_9H_9NO_4$: 196 (MH^+).

[00916] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes reactivos. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00917] Ácido 3-[(aminocarbonil)oxi]-2-metilbenzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 12 partiendo con ácido 3-hidroxi-2-metilbenzoico. ^{1}H NMR (400 MHz, DMSO): 12.87-12.70 (br. s, 1H), 7.65-7.60 (d, 1H), 7.35-7.19 (m, 3H), 7.00-6.93 (br. s, 1H), 2.30 (s, 3H). MS (EI) para $C_9H_9NO_4$: 196 (MH^+).

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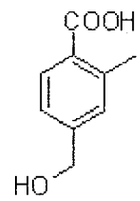
PREPARACIÓN DEL REACTIVO 13: Ácido 4-(hidroximetil)-2-metilbenzoico:



[00918] ETAPA 1: A ácido 4-bromo-2-metilo benzoico (2.50 g, 11.6 mmol) suspendido en THF anhidro (90 ml) a -78° C se agrega n-butil litio (9.8 ml, 2.5 M en hexano) y dimetilformamida (2.0 ml). La reacción se agita a -78° C por 1 h y después se calienta a 25° C y se le permite reaccionar por una hora adicional. La reacción se apaga con ácido clorhídrico acuoso 1 N y se extrae con acetato de etilo. La capa orgánica se extrae con hidróxido de sodio acuoso 1 N y la capa acuosa se separa y el pH se ajusta con ácido clorhídrico acuoso 1 N. La fase acuosa se extrae con acetato de etilo, después se lava con salmuera, se seca sobre sulfato de sodio, se filtra y se concentra. El ácido 4-formil-2-metilbenzoico crudo resultante (900 mg, 47%) se obtiene y se usa sin purificación adicional. ^{1}H NMR (400 MHz, CD_3OD): 10.02-10.00 (s, 1H), 8.04-8.01 (d, 1H), 7.81-7.76 (m, 2H), 2.66-2.63 (s, 3H). MS (EI) para $C_9H_8O_3$: 163 (M^-).

[00919] ETAPA 2: A ácido 4-formil-2-metilbenzoico (75 mg, 0.46 mmol), en metanol (5 ml), se agrega borohidruro de sodio

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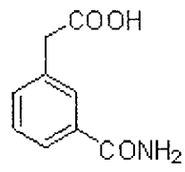
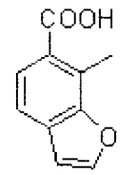
(26 mg, 0.69 mmol). La solución se agita a 25° C por 1 h. La reacción se apaga con cloruro de amonio acuoso saturado y el pH se ajusta a 2 con ácido clorhídrico acuoso 2 N, después se extrae con diclorometano. La capa orgánica se separa, se seca sobre sulfato de sodio anhidro, se filtra y se concentra. El ácido 4-(hidroximetil)-2-metilbenzoico crudo resultante (37 mg, 76%) se obtiene y se usa sin purificación adicional. ^{1}H NMR (400 MHz, DMSO): 12.73-12.68 (s, 1H), 7.82-7.77 (d, 1H), 7.24-7.19 (m, 2H), 5.32-5.27 (m, 1H), 4.53-4.48 (d, 2H), 2.53-2.49 (s, 3H). MS (EI) para $C_9H_{10}O_3$: 167 (MH^+).

PREPARACIÓN DEL REACTIVO 14: ácido 2-[3-(aminocarbonil)fenil]acético:



[00920] Una solución de ácido 3-cianofenilacético (0.2g, 1.24 mmol) en una mezcla de ácido trifluoroacético (1 ml) y ácido sulfúrico concentrado (0.5 ml) se agita a temperatura ambiente por 16h. La mezcla de reacción después se vierte en agua enfriada con hielo y lo sólido resultante se filtra, se lava con agua y se seca bajo vacío para dar ácido 2-[3-(aminocarbonil)fenil]acético (0.167g, 75% de rendimiento). MS (EI) para $C_9H_9NO_3$: 178 (M-H).

PREPARACIÓN DEL REACTIVO 15: ácido 7-metil-1-benzofuran-6-carboxílico:



[00921] ETAPA 1: Una solución de ácido 3-hidroxi-2-metilbenzoico (5 g, 33 mmol) y ácido sulfúrico (500 µl) en metanol (20 mL) se agita a reflujo por 15 horas. La mezcla de reacción se deja enfriar a temperatura ambiente y se divide entre agua y acetato de etilo. La porción acuosa se extrae con acetato de etilo y la porción orgánica combinada se lava con bicarbonato de sodio saturado, salmuera, y después se seca sobre sulfato de sodio, se filtra y se concentra bajo presión reducida para proporcionar (5.46 g, 100%) 3-hidroxi-2-metilbenzoato de metilo. ^{1}H NMR (400 MHz, DMSO-d_6): 9.71 (s, 1H), 7.20-7.17 (m, 1H), 7.11-7.07 (m, 1H), 7.01-6.97 (m, 1H), 3.79 (s, 3H), 2.28 (s, 3H). MS (EI) para $C_9H_{10}O_3$: 166 (MH^+).

[00922] ETAPA 2: Una mezcla de 3-hidroxi-2-metilbenzoato (5.46 g, 33 mmol), bromuro de alilo (4.33 mL, 50 mmol) y carbonato de cesio (21.5 g, 66 mmol) en dimetilformamida (60 mL) se agita a 60°C por 2.5 horas. La mezcla de reacción se deja enfriar a temperatura ambiente y después se divide entre agua y acetato de etilo. La porción acuosa se extrae dos veces usando acetato de etilo, y la porción orgánica

combinada se lava con 5% de cloruro de litio acuoso, hidróxido de sodio acuoso 1N, salmuera, y después se seca sobre sulfato de sodio, se filtra y se concentra in vacuo para proporcionar (6.85 g, 100%) 2-metil-3-(prop-2-en-1-iloxi)benzoato de metilo como un aceite incoloro. ^{1}H NMR (400 MHz, DMSO-d_6): 7.33-7.30 (m, 1H), 7.27-7.23 (m, 1H), 7.18-7.15 (m, 1H), 6.13-6.02 (m, 1H), 5.35 (dd, 2H), 4.61 (d, 2H), 3.82 (s, 3H), 2.35 (s, 3H). MS (EI) para $C_{12}H_{14}O_3$: 207 (MH^+).

[00923] ETAPA 3: El 2-metil-3-(prop-2-en-1-iloxi)benzoato de metilo anterior se calienta a 180°C por 1 hora. La mezcla de reacción se deja enfriar a temperatura ambiente después se purifica por cromatografía en columna usando 10-20% de acetato de etilo en hexanos como eluyente. Las fracciones puras combinadas se concentran y se secan in vacuo para proporcionar (1.64 g, 24%) 3-hidroxi-2-metil-4-prop-2-en-1-ilbenzoato de metilo. ^{1}H NMR (400 MHz, DMSO-d_6): 8.62 (br s, 1H), 7.22 (d, 1H), 6.99 (d, 1H), 6.00-5.89 (m, 1H), 5.07-5.02 (m, 2H), 3.79 (s, 3H), 3.40-3.35 (m, 2H), 2.35 (3H). MS (EI) para $C_{12}H_{14}O_3$: 207 (MH^+).

[00924] ETAPA 4: Una solución de 3-hidroxi-2-metil-4-prop-2-en-1-ilbenzoato de metilo (1.64 g, 8.0 mmol) en metanol (20 mL) se enfría a -78°C. Mientras se mantiene la temperatura de reacción a -78°C, se burbujea ozono en la mezcla de reacción por 30 minutos, seguido por la adición de sulfuro de dimetilo

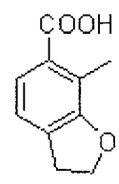
(5 mL). La mezcla de reacción se deja calentar a temperatura ambiente y después se agita por 15 horas adicionales. La mezcla de reacción se concentra in vacuo y se diluye con éter de dietilo. La porción orgánica se lava con agua, salmuera, se seca sobre sulfato de sodio y se concentra para proporcionar (1.59 g, 90%) 7-metil-2-(metiloxi)-2,3-dihidro-1-benzofuran-6-carboxilato de metilo como un aceite amarillo. MS (EI) para $C_{12}H_{14}O_4$: 223 (MH^+).

[00925] ETAPA 5: Una solución de 7-metil-2-(metiloxi)-2,3-dihidro-1-benzofuran-6-carboxilato de metilo en ácido fosfórico (3 mL) se agita a temperatura ambiente por 10 minutos y después se agita a 100°C por 15 minutos. La mezcla de reacción se enfría a temperatura ambiente y después se divide entre agua y éter de dietilo. La porción acuosa se extrae tres veces con éter de dietilo. La porción orgánica combinada se lava tres veces con agua y dos veces con 10% de carbonato de potasio acuoso. La porción básica se extrae tres veces con éter de dietilo y las porciones orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio, se filtran y se concentran in vacuo para proporcionar un residuo marrón el cual se purifica por cromatografía en columna eluyendo con 5% de acetato de etilo en hexanos. Las fracciones puras se concentran in vacuo para proporcionar (371 mg, 54%) 7-metil-1-benzofuran-6-carboxilato de metilo

como un aceite incoloro. ^{1}H NMR (400 MHz, DMSO-d_6): 8.21-8.18 (m, 1H), 7.80-7.77 (m, 1H), 7.60-7.56 (m, 1H), 7.07-7.04 (m, 1H), 3.86 (s, 3H), 2.72 (s, 3H). MS (EI) para $C_{11}H_{10}O_3$: 191 (MH^+).

[00926] ETAPA 6: Una solución de 7-metil-1-benzofuran-6-carboxilato de metilo (370 mg, 1.95 mmol) en 35% de hidróxido de potasio acuoso/metanol (1:3, 4mL) se agita a reflujo por 30 minutos. El metanol se remueve bajo presión reducida y la porción acuosa resultante se lleva a pH 2 usando ácido clorhídrico acuoso 6N. Lo precipitado el cual se forma, se recolecta por filtración y se seca in vacuo para proporcionar (258 mg, 75%) de ácido 7-metil-1-benzofuran-6-carboxílico. ^{1}H NMR (400 MHz, DMSO-d_6): 8.17 (d, 1H), 7.78 (d, 1H), 7.54 (d, 1H), 7.03 (d, 1H), 2.72 (s, 3H). MS (EI) para $C_{10}H_8O_3$: 177 (MH^+).

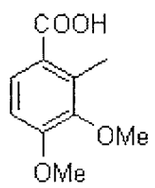
PREPARACIÓN DEL REACTIVO 16: ácido 7-metil-2,3-dihidrobenzofuran-6-carboxílico:



[00927] Se solubiliza ácido 7-Metil-1-benzofuran-6-carboxílico (sintetizado en la preparación del reactivo 15)

(0.050 g, 0.28 mmol) en etanol anhidro (2.0 mL) y se agrega 0.050 g de hidróxido de paladio (II) (20%). Esta mezcla se agita por 3 horas bajo 35 psi de gas hidrógeno usando un aparato hidrogenador Parr. La mezcla se filtra a través de celite y se concentra in vacuo para dar ácido 7-metil-2,3-dihidro-1-benzofuran-6-carboxílico crudo (0.049 g, 97% de rendimiento) el cual se usa sin purificación adicional. ^{1}H NMR (400 MHz, d_6-DMSO): 12.67 (amplio s, 1H), 7.33 (d, 1H), 7.11 (d, 1H), 4.55 (t, 2H), 3.23 (t, 2H), 2.32 (s, 3H).

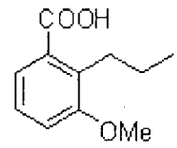
PREPARACIÓN DEL REACTIVO 17: ácido 3,4-dimetoxi-2-metilbenzoico:



[00928] A una mezcla de virutas de magnesio (0.059 g, 2.40 mmol) en tetrahidrofurano (1 ml) se agrega una solución de tolueno 6-bromo-2,3-dimetoxi (0.660 g, 2.3 mmol) en tetrahidrofurano (1 ml). La reacción se inicia por adición de bromuro de metilmagnesio y la solución se agita a temperatura ambiente durante la noche bajo nitrógeno. A la mezcla después se agrega un exceso de hielo seco. Cuando la adición se completa, se agrega agua (2 ml) seguido por ácido clorhídrico 1.5 M a pH 2. La fase acuosa se extrae con acetato de etilo (2x 5 ml) y las capas orgánicas combinadas se secan sobre

sulfato de sodio, se filtran y se concentran para dar ácido 3,4-dimetoxi-2-metilbenzoico (0.315 g, 70% de rendimiento). MS (EI) para $C_{10}H_{12}O_4$: 195 (M-H).

PREPARACIÓN DEL REACTIVO 18: ácido 3-(metiloxi)-2-propilbenzoico:



[00929] ETAPA 1: A 3-hidroxi-2-prop-2-en-1-ilbenzoato de metilo (10.3 g, 53.6 mmol, M.A. Eissenstat et al., *J. Med. Chem.* 1995, *38*, 3094-3105) y carbonato de cesio (26.2 g, 80.4 mmol) en DMF (100 ml) se agrega yoduro de metilo (15.2 g, 102.2 mmol). La mezcla de reacción se agita a temperatura ambiente por 18 h, después se filtra y se concentra. El residuo se divide entre acetato de etilo (250 mL) y agua (100 mL). Las capas se separan, la capa orgánica se lava con 5% de cloruro de litio (2 x 100 mL) y salmuera (100 mL), se seca sobre sulfato de sodio, y se concentra para proporcionar 3-(metiloxi)-2-prop-2-en-1-ilbenzoato de metilo (10.3 g, 93% de rendimiento) como un aceite amarillo pálido. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (m, 1H), 7.24 (m, 1H), 7.02 (m, 1H), 6.97 (m, 1H), 4.97 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.73 (m, 2H).

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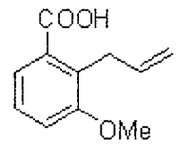
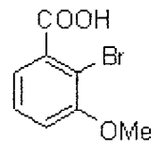
[00930] ETAPA 2: Se hidrogena 3-(metiloxi)-2-prop-2-en-1-ilbenzoato de metilo (100 mg, 0.48 mmol) en metanol (2 mL) sobre 5% de paladio en carbono por 15 h bajo presión atmosférica. La mezcla de reacción se filtra y se agrega 35% de hidróxido de potasio acuoso (1 mL). La mezcla se somete a reflujo por 1 h y después se concentra. El pH se ajusta a 2 con HCl 6N. Lo precipitado se filtra, se lava con agua y se seca para dar ácido 3-(metiloxi)-2-propilbenzoico (35 mg, 38% de rendimiento). MS (EI) para $C_{11}H_{14}O_3$: 193 (M-H)

PREPARACIÓN DEL REACTIVO 19: ácido 3-(metiloxi)-2-prop-2-en-1-ilbenzoico:



[00931] Procediendo como en la preparación del reactivo 18 y omitiendo la etapa de hidrogenación se prepara ácido 2,3-(metiloxi)-2- prop-2-en-1-ilbenzoico.

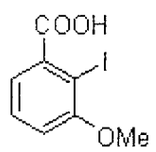
PREPARACIÓN DEL REACTIVO 20: ácido 2-bromo-3-(metiloxi)benzoico:



[00932] A ácido 2-amino-3-(metiloxi)benzoico (4.00 g, 23.9

mmol) en 10% de ácido bromhídrico acuoso (54 ml) a 0°C se agrega nitrito de sodio (1.65 g, 23.9 mmol) en agua (17 ml). A esta solución se agrega por goteo una solución de bromuro de cobre (I) (3.78 g, 26.3 mmol) en 48% ácido bromhídrico (22 ml) y se calienta a 60°C por 2 h. La mezcla se enfría a 0°C, y lo precipitado resultante se recolecta por filtración, se lava con agua fría y se recristaliza a partir de agua para dar ácido 2-bromo-3-(metiloxi)benzoico puro (4.07g, 74%). MS (EI) para $C_8H_7BrO_3$: 232 (MH^+).

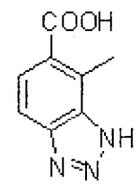
PREPARACIÓN DEL REACTIVO 21: ácido 2-yodo-3-(metiloxi)benzoico:



[00933] A ácido 2-amino-3-metoxibenzoico (1.00 g, 5.98 mmol) en 25% de ácido clorhídrico acuoso (8 ml) a 0°C se agrega nitrito de sodio (0.45 g, 6.50 mmol) en agua (3 ml). Esta solución se agrega por goteo a una solución de yoduro de potasio (15.8 g, 59.3 mmol) en agua (60 ml) y se deja calentar a 25°C después se agita por 16 h. La mezcla de reacción se apaga con bicarbonato de sodio acuoso 1 N hasta que el pH llega a ser básico. La solución se extrae con cloruro de metileno y lo orgánico se seca sobre sulfato de sodio, se filtra, y se concentra para dar un aceite púrpura.

El residuo se purifica por cromatografía en columna, eluyendo con 10% de metanol en diclorometano. Las fracciones puras se concentran para proporcionar (0.623 g, 38%) de ácido 2-yodo-3-metoxibenzoico. MS (EI) para $C_8H_7IO_3$: 279 (MH^+).

PREPARACIÓN DEL REACTIVO 22: ácido 7-metil-1H-benzotriazol-6-carboxílico:



[00934] Etapa 1: ácido 4-(Acetilamino)-2-metilbenzoico (3.93 g, 20.3 mmol) se recupera en ácido sulfúrico concentrado (20 mL) y se calienta para solubilizar. La solución después se enfría con un baño helado. Se agrega ácido nítrico humeante (0.86 mL) en ácido sulfúrico (2.0 mL) por goteo y la solución resultante se agita una hora. La solución después se diluye con agua y se recolecta un sólido amarillo por filtración y se desecha. En reposo, se forma un sólido anaranjado en lo filtrado, el cual se recolecta por filtración para dar (0.61 g) de ácido 4-amino-2-metil-3-nitrobenzoico. Lo filtrado acuoso después se extrae (3 x 100 mL de 10% de metanol en acetato de etilo), y las capas orgánicas combinadas se secan (sulfato de magnesio), se filtran y se concentran para proporcionar ácido 4-amino-2-metil-3-nitrobenzoico adicional (0.90 g). ^1H NMR (400 MHz, d_6-

DMSO): 7.75 (d, 1H), 6.75 (d, 1H), 2.41 (s, 3H). MS (EI) para $C_8H_8N_2O_4$: 195 (MH^+).

[00935] Etapa 2: Se solubiliza ácido 4-Amino-2-metil-3-nitrobenzoico (1.87 g, 9.54 mmol) en metanol (100 mL) y tetrahidrofurano (100 mL) y se trata con solución de (trimetilsilil)diazometano (5.3 mL, 10.5 mmol, 2.0M en éter de dietilo). Después de que la reacción muestra estar completa, la mezcla se concentra y el residuo se purifica vía cromatografía en columna (gel de sílice, 5:1 hexanos/acetato de etilo) para dar 1.10 g (55% de rendimiento) de 4-amino-2-metil-3-nitrobenzoato de metilo. ^{1}H NMR (400 MHz, d_6-DMSO): 7.73 (d, 1H), 6.75 (d, 1H), 6.51 (amplio s, 2H), 3.75 (s, 3H), 2.37 (s, 3H). MS (EI) para $C_9H_{10}N_2O_4$: 210 (MH^+).

Etapa 3: A una solución de 4-amino-2-metil-3-nitrobenzoato de metilo (1.10 g, 5.22 mmol) en tetrahidrofurano (75 mL) y agua (25 mL) se agrega formiato de amonio (6.6 g, 104 mmol) y polvo de hierro (2.92 g, 52.2 mmol). Esta mezcla se somete a reflujo por 12 horas, después se filtra y la torta filtrada se enjuaga con acetato de etilo. Las capas filtradas se separan y la capa orgánica se seca (sulfato de magnesio), se filtra y se concentra para dar 0.92 g (98% de rendimiento) de 3,4-diamino-2-metilbenzoato de metilo crudo, el cual se usa sin purificación adicional. ^{1}H NMR (400 MHz, d_6-DMSO): 7.05 (d, 1H), 6.40 (d, 1H), 3.69 (s,

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3H), 2.29 (s, 3H). MS (EI) para $C_9H_{12}N_2O_2$: 181 (MH^+).

[00936] Etapa 4: Se recupera 3,4-diamino-2-metilbenzoato de metilo (0.27 g, 1.5 mmol) en ácido sulfúrico concentrado (30 mL) y se calienta para solubilizar, después se enfría con un baño helado. Al mismo tiempo, se solubiliza nitrito de sodio (0.14 g, 2.1 mmol) en ácido sulfúrico concentrado (8.4 mL) usando el calentamiento. Esta solución de nitrito de sodio después se enfría y se agrega por goteo a la solución de adiamina enfriada. La mezcla se agita a 0°C por 30 minutos, después se calienta a 60°C por 15 minutos. La solución después se vierte en hielo y se extrae con 10% de metanol en acetato de etilo (2 x 100 mL). Las capas orgánicas combinadas se secan (sulfato de magnesio), se filtran y se concentran para dar 0.3 g de 7-metil-1*H*-benzotriazol-6-carboxilato de metilo crudo, el cual se recupera en metanol (5 mL) y tetrahidrofurano (10 mL), y se trata con hidróxido de litio acuoso 2M (5 mL), después se calienta a 70°C por una hora. Esta solución se hace acídica usando ácido clorhídrico acuoso concentrado, después se extrae con 10% de metanol en acetato de etilo (2 x 50 mL). Las capas orgánicas combinadas se secan (sulfato de magnesio), se filtran y se concentran para dar 0.26 g de ácido 7-metil-1H-benzotriazol-6-carboxílico. ^{1}H NMR (400 MHz, d_6-DMSO): 7.94 (d, 1H), 7.72 (m, 1H), 2.95 (s, 3H). MS (EI) para $C_8H_7N_3O_2$: 178 (MH^+).

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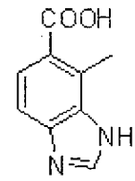
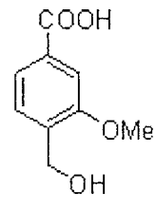
PREPARACIÓN DEL REACTIVO 23: ácido 7-metil-1H-bencimidazol-6-carboxílico:



[00937] Se recupera 3,4-diamino-2-metilbenzoato de metilo (sintetizado en la preparación del reactivo 22) (0.18 g, 1.0 mmol) en ácido fórmico (8.0 mL) y se somete a reflujo por 4 horas. La solución después se concentra in vacuo. El material se recupera en metanol (2.5 mL) y tetrahidrofurano (5.0 mL), y se trata con hidróxido de litio acuoso 2M (2.5 mL) y se calienta a 70°C por 12 horas. Esta solución se hace acídica usando ácido clorhídrico acuoso concentrado, después se extrae con 10% de metanol en acetato de etilo (2 x 50 mL). Las capas orgánicas combinadas se secan (sulfato de magnesio), se filtran y se concentran para dar 0.055 g de ácido 7-metil-1H-bencimidazol-6-carboxílico. ^{1}H NMR (400 MHz, d_6-DMSO): 9.34 (s, 1H), 7.94 (d, 1H), 7.64 (d, 1H), 2.85 (s, 3H). MS (EI) para $C_9H_8N_2O_2$: 177 (MH^+).

PREPARACIÓN DEL REACTIVO 24: ácido 4-(hidroximetil)-3-(metiloxi)benzoico:



[00938] ETAPA 1: Una mezcla de 4-metil-3-(metiloxi)benzoato de metilo (1.00 g, 5.55 mmol), N-bromosuccinimida (1.09 g, 6.10 mmol) y una cantidad catalítica de 2,2'-azobis(isobutironitrilo) (AIBN) se somete a reflujo en tetracloruro de carbono (40 ml) por 16h. La mezcla de reacción se filtra y la solución se lava con salmuera (25 ml), se seca sobre sulfato de sodio y se concentra para dar 4-(bromometil)-3-(metiloxi)benzoato de metilo (1.4g, 97% de rendimiento).

[00939] ETAPA 2: Se suspende 4-(bromometil)-3-(metiloxi)benzoato de metilo (300 mg, 1.15 mmol) en agua (3 ml) y se agrega ácido clorhídrico acuoso concentrado (380 µl). La mezcla de reacción se somete a reflujo por 16 h, después se enfría a temperatura ambiente y se divide con acetato de etilo (10 ml). La fase orgánica se separa, se lava con salmuera, se seca sobre sulfato de sodio y se concentra. El residuo se purifica por cromatografía instantánea en gel de sílice (diclorometano:metanol 95:5) para proporcionar

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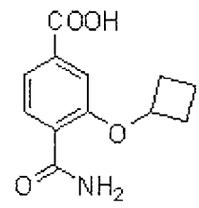
ácido 4-(hidroximetil)-3-(metiloxi)benzoico (74 mg, 35% de rendimiento). MS (EI) por $C_9H_{10}O_4$: 181(M-H).

PREPARACIÓN DEL REACTIVO 25: ácido 4-(aminocarbonil)-3-(ciclobutiloxi)benzoico:



[00940] ETAPA 1: A una solución de 4-bromo-3-hidroxibenzoato de metilo (1.01g, 4.4 mmol) en 7 ml de dimetilamina se agrega $Pd(OAc)_2$ (15 mg, 0.5 mol%), carbonato de sodio (0.47 g, 4.4 mmol) y ferricianuro de potasio (0.41 g, 0.97 mmol). La mezcla se calienta a 120°C y se agita a esta temperatura por 4 horas y a RT por 18 horas. La mezcla de reacción se diluye con 30 ml de acetato de etilo y la suspensión resultante se filtra a través de Celite. Lo filtrado se lava con agua (2x15 ml) y 5% de hidróxido de amonio acuoso (1x15 ml). La capa orgánica se seca sobre sulfato de sodio, se filtra y se concentra para proporcionar 4-ciano-3-hidroxibenzoato de metilo (0.26g, 33.5% de rendimiento) (S.Weissman, D. Zewge, C. Chen; *J.Org. Chem.* 2005, *70*, 1508-1510). ^{1}H NMR(400 MHz, CD_3OD): 7.65 (d, 1H), 7.56-7.54 (m, 2H), 3.91(s, 3H). MS (EI) para $C_9H_7NO_3$: 178 (MH^+).

[00941] ETAPA 2: A una solución de 4-ciano-3-hidroxibenzoato de metilo (0.067 g, 0.38 mmol) en 2 ml de DMF se agrega carbonato de cesio (0.2 g, 0.62 mmol), bromociclobutano (0.051 g, 0.38 mmol), y la mezcla de reacción se calienta a 60°C y se agita a esta temperatura por 3 hrs. La mezcla de reacción se enfría a RT, se vierte en agua helada, y se extrae varias veces con acetato de etilo (3x 20 ml). La solución orgánica se seca sobre Na_2SO_4, se filtra, se evapora rotatoriamente a sequedad, después se seca in vacuo para proporcionar 4-ciano-3-(ciclobutiloxi)benzoato de metilo (0.055 g, 63%). ^{1}H NMR (400 MHz, CD_3OD): 7.74 (d, 1H), 7.67 (d, 1H), 7.54 (s, 1H), 3.93 (s, 3H), 2.57-2.52 (m, 2H), 2.26-2.21 (m, 2H), 1.94-1.90 (m, 1H), 1.94-1.78 (m, 2H). MS (EI) para $C_{13}H_{13}NO_3$: 232 (MH^+).

[00942] ETAPA 3: A una solución de 4-ciano-3-(ciclobutiloxi)benzoato de metilo (0.051 g, 0.23 mmol) en 2 ml de etanol se agrega 0.5 ml de DMSO, 1ml de hidróxido de sodio acuoso 1N, 1 ml de peróxido de hidrógeno acuoso al 30%, y la mezcla de reacción se agita a RT por 18 hrs. La mezcla de reacción se diluye con 10 ml de agua y la solución acuosa extraída tres veces con acetato de etilo (20 ml). La capa acuosa se acidifica a pH 3-4 por adición en porciones de ácido clorhídrico acuoso, después se extrae con acetato de etilo (3x 20 mL). La solución orgánica se evapora por

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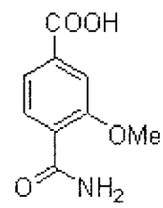
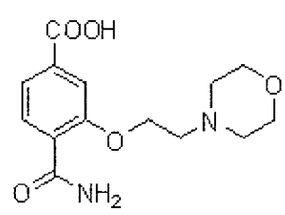
rotación a sequedad y se seca in vacuo para proporcionar ácido 4-(aminocarbonil)-3-(ciclobutiloxi)benzoico (0.026 g, 50%). ^{1}H NMR(400 MHz, DMSO-d_6): 13.25 (s, 1H), 7.80 (d, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.55 (d, 1H), 7.41 (s, 1H), 4.88-4.85 (m, 1H), 2.44-2.43 (m, 2H), 2.18-2.14 (m, 2H), 1.99-1.73 (m, 2H). MS (EI) para $C_{12}H_{13}NO_4$: 236 (MH^+).

PREPARACIÓN DEL REACTIVO 26: ácido 4-(aminocarbonil)-3-(metoxi)benzoico:



[00943] Sintetizado de conformidad con el método del reactivo de la preparación 25 usando yodometano en la etapa 2. ^{1}HNMR (400 MHz, CD_3OD): 13.21 (s, 1H), 7.81 (d, 1H), 7.67 (d, 1H), 7.59 (d, 1H), 2.49 (s, 3H). MS(EI) para $C_9H_9NO_4$: 196(MH^+).

PREPARACIÓN DEL REACTIVO 27: ácido 4-(aminocarbonil)-3-[(2-morfolin-4-iletil)oxi]benzoico:



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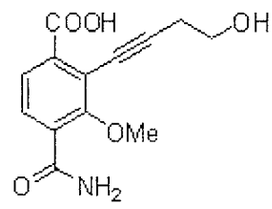
[00944] Sintetizado de conformidad con el método del reactivo de la preparación 25 usando clorhidrato de 4-(2-cloroetil)morfolina en la etapa 2. MS(EI) para $C_{14}H_{18}N_2O_5$: 295(MH^+).

PREPARACIÓN DEL REACTIVO 28: ácido 4-(aminocarbonil)-2-(4-hidroxibut-1-inil)-3-metoxibenzoico:



[00945] ETAPA 1: A una solución de ácido 2-bromo-3-metoxibenzoico (718 mg, 3.11 mmol) en metanol (20 mL) se agrega una cantidad catalítica de ácido sulfúrico concentrado y la mezcla se lleva a reflujo por 20 h. En enfriamiento a temperatura ambiente, la solución se concentra y el residuo se recupera en acetato de etilo y se lava con agua, bicarbonato de sodio acuoso saturado (2x) y salmuera, después se seca sobre sulfato de sodio. La solución después se filtra y se concentra para dar 2-bromo-3-metoxibenzoato de metilo (610 mg, 80%). MS (EI) para $C_9H_9BrO_3$: 245 (MH^+).

[00946] ETAPA 2: Una mezcla de 2-bromo-3-metoxibenzoato de metilo (0.4 g, 1.63 mmol), $Pd(PPh_3)_2Cl_2$ (0.057 g, 0.082 mmol), yoduro de cobre (I) (0.031 g, 0.16 mmol) y 3-butin-1-ol

(0.173 ml, 2.28 mmol) se agitan en trietilamina (5 ml) a 80 °C por 20h. El solvente se concentra bajo vacío, y el residuo se divide entre acetato de etilo (15 ml) y agua (5 ml). La capa orgánica se seca sobre sulfato de sodio, se filtra y se concentra. El residuo se purifica por cromatografía en columna de gel de sílice usando hexanos:acetato de etilo 2:1 como eluyente para proporcionar 2-(4-hidroxibut-1-in-1-il)-3-(metiloxi)benzoato de metilo (0.056 g; 15 % de rendimiento). MS (EI) para $C_{13}H_{14}O_4$: 235 (MH^+).

[00947] ETAPA 3: Se disuelve 2-(4-hidroxibut-1-in-1-il)-3-(metiloxi)benzoato de metilo (0.056 g, 0.24 mmol) en metanol (2 ml), y se agrega una solución de hidróxido de potasio (0.027 g, 0.48 mmol) en agua (0.5 ml). La mezcla de reacción se agita a 60 °C por 1h, se enfría a temperatura ambiente, y se agrega ácido clorhídrico 1.5M a pH 4. La mezcla acuosa se extrae con acetato de etilo, y la capa orgánica se lava con salmuera, después se seca sobre sulfato de sodio. La mezcla después se filtra y se concentra para dar ácido 2-(4-hidroxibut-1-in-1-il)-3-(metiloxi)benzoico (0.052 g, 99% de rendimiento). MS (EI) para $C_{12}H_{12}O_4$: 219 (M-H).

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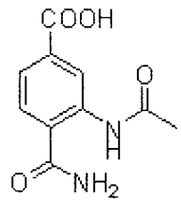
PREPARACIÓN DEL REACTIVO 29: ácido 3-(acetilamino)-4-(aminocarbonil)benzoico:



[00948] ETAPA 1: Se agrega N,N-Diisopropiletilamina (0.41 mL, 2.30 mmol) a una mezcla de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (321 mg, 0.84 mmol) y ácido 4-{[(1,1-dimetiletil)oxi]carbonil}-2-nitrobenzoico (preparado de conformidad con Gao, Y. et. Al WO2001070737) (205 mg, 0.77 mmol) en N,N-dimetilformamida (2 mL), y la mezcla de reacción se agita a temperatura ambiente por 30 minutos. Se burbujea amoníaco en la mezcla de reacción y la agitación se continúa por 45 minutos. La mezcla de reacción se apaga con solución acuosa de ácido clorhídrico 0.5M (20 mL) y se extrae con acetato de etilo (3 x 20 mL), y el extracto combinado se lava con agua (20 mL), después salmuera (20 mL), se seca sobre sulfato de sodio, se filtra y se concentra. El residuo se purifica por cromatografía instantánea en gel de sílice (25 a 75% de acetato de etilo en hexanos) para dar 4-(aminocarbonil)-3-nitrobenzoato de 1,1-dimetiletilo (160 mg, 78% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 8.55 (s, 1H), 8.25 (d, 1H), 7.64 (d, 1H), 6.51 (br, 1H), 6.26 (br, 1H), 1.61 (s 9H); MS (EI) para $C_{12}H_{14}N_2O_5$: 267

(MH^+).

[00949] ETAPA 2: Una mezcla de 4-(aminocarbonil)-3-nitrobenzoato de 1,1-dimetiletilo (213 mg, 0.80 mmol), 10% de paladio en carbón vegetal (Tipo Degussa, 200 mg) en acetato de etilo (20 mL) se agita en un aparato de hidrogenación Parr a 35 psi por 4 horas. La mezcla de reacción se filtra y se concentra para dar 3-amino-4-(aminocarbonil)benzoato de 1,1-dimetiletilo (180 mg, 95% de rendimiento). MS (EI) para $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[00950] ETAPA 3: Se agrega cloruro de acetilo (50 uL, 0.32 mmol) a una solución de 3-amino-4-(aminocarbonil)benzoato de 1,1-dimetiletilo (126 mg, 0.53 mmol) y piridina (52 uL, 0.64 mmol) en tetrahidrofurano (3 mL) a 0°C, y la mezcla resultante se agita a 0°C por una hora. La mezcla se apaga con agua helada (10 mL) y se extrae acetato de etilo (3x 10 mL). El extracto combinado se lava con 15 mL, cada solución de 5% de ácido cítrico acuoso, bicarbonato de sodio acuoso saturado, y salmuera después se seca sobre sulfato de sodio, se filtra y se concentra para dar 3-(acetilamino)-4-(aminocarbonil)benzoato de 1,1-dimetiletilo (140 mg, 94% de rendimiento). MS (EI) para $C_{14}H_{18}N_2O_4$: 279 (MH^+).

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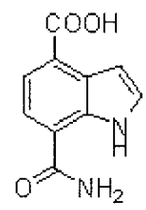
[00951] ETAPA 4: Una solución de 3-(acetilamino)-4-(aminocarbonil)benzoato de 1,1-dimetiletilo (110 mg, 0.47 mmol) en ácido trifluoroacético (2 mL) se agita a temperatura ambiente por 15 minutos, se concentra, y el residuo se enjuaga con hexano (3 x 3 mL) y se seca in vacuo para dar ácido 3-(acetilamino)-4-(aminocarbonil)benzoico (100 mg, 97% de rendimiento), MS (EI) para $C_{10}H_{10}N_2O_4$: 223 (MH^+).

PREPARACIÓN DEL REACTIVO 30: ácido 7-(aminocarbonil)-1H-indol-4-carboxílico:



[00952] ETAPA 1: A una solución de 2-nitrotereftalato de 4-terc-butil 1-metilo (preparado de conformidad con Gao, Y. et. Al WO2001070737) (2.15 g, 7.64 mmol) en tetrahidrofurano (30 mL) se agrega una solución 1M de bromuro de vinilmagnesio en tetrahidrofurano (23.0 mL) a -40 °C, seguido por la agitación a temperatura ambiente por 18 horas. La mezcla de reacción se apaga por la adición de una solución 1M de cloruro de amonio acuoso, y la porción orgánica del solvente se evapora. El material resultante se divide con acetato de etilo (300 mL), y la capa orgánica se separa, después se lava con 10% de ácido cítrico acuoso (100 mL) y salmuera, se seca sobre

sulfato de sodio, se filtra y el solvente se concentra. El material resultante crudo se purifica por cromatografía en columna (hexano:acetato de etilo 9:1 a 7:3 eluyente) para dar 1H-indol-4,7-dicarboxilato de 4-terc-butil 7-metilo (0.58 g, 27%). ^{1}H NMR (400 MHz, $CDCl_3$): 10.00 (bs, 1H), 7.88 (dd, 2H), 7.43 (m, 1H), 7.19 (m, 1H), 4.00 (s, 3H), 1.66 (s, 9H). MS (EI) para $C_{15}H_{17}NO_4$: 274 (M-H).

[00953] ETAPA 2: A una solución de 1H-indol-4,7-dicarboxilato de 4-terc-butil 7-metilo (0.58 g, 2.10 mmol) en una mezcla de metanol (20 mL), tetrahidrofurano (10 mL) y agua (10 mL) se agrega una solución 2M de hidróxido de litio acuoso (2.1 mL, 4.20 mmol), y la mezcla de reacción se agita a 40 °C hasta que se consume completamente el material de partida. La porción orgánica del solvente se evapora y el pH de la solución acuosa se ajusta a 3-4 por la adición de ácido clorhídrico acuoso 1M. La fase acuosa acídica se divide con acetato de etilo (150 mL), y la capa orgánica se separa y se lava con salmuera, se seca sobre sulfato de sodio, se filtra y se concentra para dar ácido 4-(terc-butoxicarbonil)-1H-indol-7-carboxílico (0.36 g, 67%). MS (EI) para $C_{14}H_{15}NO_4$: 260 (M-H).

[00954] ETAPA 3: Una solución de ácido 4-(terc-butoxicarbonil)-1H-indol-7-carboxílico (0.36 g, 1.38 mmol),

HATU (0.30 g, 1.60 mmol), 4-metilmorfolina (0.75 mL, 6.89 mmol) y una solución 2M de amoníaco en metanol (1.80 mL, 3.45 mmol) en dimetilformamida (5 mL) se agita a temperatura ambiente por 18 horas. La mezcla de reacción se diluye con acetato de etilo (150 mL) y la capa orgánica se lava con salmuera, se seca sobre sulfato de sodio, se filtra y se concentra. La purificación por cromatografía en columna cloroformo:(10% hidróxido de amonio en metanol) 9:1 como eluyente proporciona 7-carbamoil-1H-indol-4-carboxilato de terc-butilo (0.18 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): 10.50 (bs, 1H), 7.83 (d, 1H), 7.43 (m, 2H), 7.15 (m, 1H), 6.30 (bd, 2H), 1.62 (s, 9H). MS (EI) para $C_{14}H_{16}N_2O_3$: 259 (M-H).

[00955] ETAPA: 4: A una solución de 7-carbamoil-1H-indol-4-carboxilato de terc-butilo (0.15 g, 0.58 mmol) en diclorometano (10 mL) se agrega ácido trifluoroacético (10 mL), y la mezcla se calienta a reflujo hasta que el material de partida se consume completamente. El solvente se evapora seguido por evaporación rotatoria del residuo a partir de una mezcla de acetato de etilo (50 mL) y tolueno (50 mL). El procedimiento se repite tres veces y el residuo se seca in vacuo para obtener ácido 7-(aminocarbonil)-1H-indol-4-carboxílico (0.16 g, 89%). MS (EI) para $C_{10}H_8N_2O_3$: 205 (MH^+).

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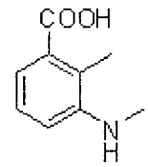
PREPARACIÓN DEL REACTIVO 31: ácido 2-metil-3-(metilamino)benzoico:



[00956] ETAPA 1: A ácido 3-amino-2-metilbenzoico (500 mg, 3.3 mmol) en metanol (20 ml) se agrega ácido sulfúrico (500 µl) y se calienta a 70°C por 22 h, punto en el cual el volumen se reduce por evaporación rotatoria. El residuo se diluye con bicarbonato de sodio saturado y se extrae con acetato de etilo. La capa orgánica resultante se seca sobre sulfato de sodio, se filtra, y después se concentra para proporcionar un aceite bronceado (125 mg, 23%) de 3-amino-2-metilbenzoato de metilo, el cual se usa sin purificación adicional. ^{1}H NMR (400 MHz, DMSO-d_6): 6.99-6.93 (m, 1H), 6.89-6.86 (d, 1H), 6.81-6.78 (d, 1H), 5.12-5.07 (br. s, 2H), 3.78 (s, 3H), 2.16 (s, 3H). MS (EI) para $C_9H_{11}NO_2$: 166 (MH^+).

[00957] ETAPA 2: A 3-amino-2-metilbenzoato de metilo (125 mg, 0.758 mmol) en DMF (2 ml) se agrega DIPEA (291 µl, 1.67 mmol) y yoduro de metilo (104 µl, 1.67 mmol), y se calienta a 70°C por 6 h en un recipiente sellado. La mezcla se diluye con hidróxido de potasio acuoso 1N (3 ml) e inmediatamente se extrae con acetato de etilo. La capa orgánica resultante se seca sobre sulfato de sodio, se filtra y se concentra para

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proporcionar un residuo marrón el cual se purifica por cromatografía en columna eluyendo con 15% de acetato de etilo en hexanos. Las fracciones puras se concentran para proporcionar (30 mg) de una fracción eluyente más rápida que consiste de 3-(dimetilamino)-2-metilbenzoato de metilo y (125 mg) de una fracción eluyente más lenta que consiste de 2-metil-3-(metilamino)benzoato de metilo. ^{1}H NMR 2-metil-3-(metilamino)benzoato de metilo (400 MHz, DMSO-d_6): 7.14-7.08 (m, 1H), 6.91-6.87 (d, 1H), 6.67-6.62 (d, 1H), 5.34-5.27 (br. s, 1H), 3.78 (s, 3H), 2.76-2.71 (d, 3H), 2.17 (s, 3H). MS (EI) para $C_{10}H_{13}NO_2$: 180 (MH^+). ^{1}H NMR 3-(dimetilamino)-2-metilbenzoato de metilo (400 MHz, DMSO-d_6): 7.40-7.36 (d, 1H), 7.28-7.22 (m, 2H), 3.81 (s, 3H), 2.63 (s, 6H), 2.39 (s, 3H). MS (EI) para $C_{11}H_{15}NO_2$: 194 (MH^+).

[00958] ETAPA 3: A 2-metil-3-(metilamino)benzoato de metilo (125 mg, 0.698 mmol) en metanol (7 ml) se agrega hidróxido de litio acuoso 2M (1.8 ml, 3.63 mmol), y la solución se agita a 25°C por 3 h, punto en el cual el volumen se reduce por evaporación rotatoria. La mezcla acuosa se diluye con agua (3 ml) y el pH se ajusta a 5 con ácido clorhídrico 1 N. Lo precipitado resultante se recolecta por filtración y se seca in vacuo para proporcionar (50 mg, 42%) de ácido 2-metil-3-(metilamino)benzoico. MS (EI) para $C_9H_{11}NO_2$: 166 (MH^+).

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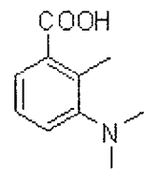
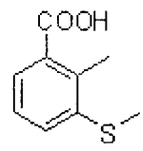
PREPARACIÓN DEL REACTIVO 32: ácido 3-(dimetilamino)-2-metilbenzoico:



[00959] Sintetizado de conformidad con el método del reactivo de la preparación 31 usando 3-(dimetilamino)-2-metilbenzoato de metilo (preparación del reactivo 31 etapa 2) en la etapa 3. MS (EI) para $C_{10}H_{13}NO_2$: 180 (MH^+).

[00960] PREPARACIÓN DEL REACTIVO 33: ácido 2-metil-3-(metiltio)benzoico:



[00961] ETAPA 1: A una solución de ácido 3-amino-2-metilbenzoico (500 mg, 3.3 mmol) en metanol (5 mL) se enfría a 0°C, se agrega ácido clorhídrico concentrado (1 mL), seguido por una solución de nitrito de sodio (275 mg, 4.0 mmol) en agua (2 mL). La mezcla se agita a 0 °C por 30 minutos, después se calienta a temperatura ambiente y se agita por 30 minutos adicionales. La solución se diluye con éter de dietilo para proporcionar un residuo sólido que se recolecta por filtración, después se lava con éter de dietilo adicional para proporcionar 700 mg de la sal de diazonio

intermediario. La sal de diazonio después se transfiere a una solución caliente (55 °C) de etilxantogenato de potasio (635 mg, 4.0 mmol) en agua (5 mL) mientras se mantiene el pH a 8 por adición en porciones de carbonato de sodio sólido. La solución se agita a 55 °C por 30 minutos, después se enfría a temperatura ambiente y se vierte en solución acuosa de ácido clorhídrico 6N (30 mL). Lo precipitado el cual se forma, se recolecta por filtración, se lava con agua, después éter de dietilo para proporcionar 270 mg, 1.05 mmol (32%) de ácido 3-{[(etiloxi)carbonotioil]tio}-2-metilbenzoico. MS (EI) para $C_{11}H_{12}S_2O_3$: 257 (MH^+).

[00962] ETAPA 2: ácido 3-{[(etiloxi)carbonotioil]tio}-2-metilbenzoico (270 mg, 1.05 mmol) en una solución acuosa de hidróxido de sodio 1N (3 mL) se agita a reflujo por 15 horas. La mezcla se enfría a temperatura ambiente y el pH se ajusta a 2 usando ácido clorhídrico acuoso concentrado. La mezcla acuosa se extrae dos veces usando diclorometano y las soluciones orgánicas combinadas se lavan con salmuera, después se seca sobre sulfato de sodio anhidro. La filtración y concentración proporciona 180 mg, 1.05 mmol (99%) de ácido 3-mercapto-2-metilbenzoico. ^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (d, 1H), 7.47 (d, 1H), 7.16-7.11 (m, 1H), 3.43 (s, 1H), 2.62 (s, 3H).

[00963] ETAPA 3: Una mezcla de ácido 3-mercapto-2-metilbenzoico (180 mg, 1.05 mmol), carbonato de cesio (690 mg, 2.1 mmol) y yodometano (132 µl, 2.10 mmol) en dimetilformamida (3 mL) se agita a temperatura ambiente por 2 horas. La mezcla se diluye con acetato de etilo, después se lava con 5% de cloruro de litio acuoso, hidróxido de sodio acuoso 1N, y salmuera después se seca sobre sulfato de sodio anhidro. La filtración y concentración proporciona 138 mg, 0.62 mmol (58%) de 2-metil-3-(metiltio)benzoato de metilo. ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (d, 1H), 7.41 (d, 1H), 7.21-7.16 (m, 1H), 4.09 (s, 3H), 2.83 (s, 3H), 2.58 (s, 3H). MS (EI) para $C_{10}H_{12}SO_2$: 197 (MH^+).

[00964] ETAPA 4: Una solución de 2-metil-3-(metiltio)benzoato de metilo (138 mg, 0.62 mmol) en 35% hidróxido de potasio acuoso:metanol (1:3, 4 mL) se agita a 80°C por 1 hora. Después del enfriamiento a temperatura ambiente se evapora el metanol. Se agrega agua (4 mL) y el pH de la mezcla resultante se ajusta a 2 usando ácido clorhídrico acuoso concentrado. Lo precipitado el cual se forma, se recolecta por filtración, se lava con agua, después éter de dietilo para proporcionar, 85 mg, 0.43 mmol (70%) de ácido 2-metil-3-(metiltio)benzoico. ^{1}H NMR (400 MHz, $CDCl_3$): 7.76 (d, 1H), 7.37 (d, 1H), 7.29-7.25 (m, 1H), 2.65 (s, 3H), 2.49 (s, 3H). MS (EI) para $C_9H_{10}SO_2$: 181 (M-H).

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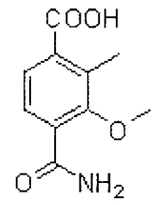
[00965] PREPARACIÓN DEL REACTIVO 34: ácido 4-(aminocarbonil)-2-metil-3-(metiloxi)benzoico:



[00966] ETAPA 1: Una solución de ácido 3-hidroxi-2-metilbenzoico (5 g, 33 mmol) y ácido sulfúrico concentrado (3 mL) en metanol (300 mL) se agita a reflujo por 48 horas. La mezcla se enfría a temperatura ambiente y el pH se ajusta a 7 usando bicarbonato de sodio sólido. Algo de metanol se evapora y el residuo se divide entre bicarbonato de sodio acuoso saturado y acetato de etilo. La porción orgánica se lava con salmuera después se seca sobre sulfato de sodio anhidro. La filtración y concentración proporciona 5.3 g, 32 mmol (97%) de 3-hidroxi-2-metilbenzoato de metilo. ^{1}H NMR (400 MHz, $CDCl_3$): 7.41 (d, 1H), 7.13-7.09 (m, 1H), 6.94 (d, 1H), 3.89 (s, 3H), 2.46 (s, 3H). MS (EI) para $C_9H_{10}O_3$: 167 (MH^+).

[00967] ETAPA 2: A una solución de terc-butilamina (1.6 mL, 15 mmol) en diclorometano (100 mL) a -78°C se agrega por goteo durante 30 minutos una solución de bromo (773 µl, 15 mmol en 15 mL de diclorometano). La solución se agita a -78°C por 30 minutos. Mientras se mantiene la temperatura a -78°C,

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se agrega una solución de 3-hidroxi-2-metilbenzoato de metilo (2.5 g, 15 mmol en 15 mL de diclorometano) a la mezcla de reacción por goteo durante 30 minutos. La mezcla se deja calentar a temperatura ambiente y se agita por 15 horas. La mezcla se lava con 20% de ácido cítrico acuoso después salmuera y se seca sobre sulfato de sodio anhidro. La filtración y concentración proporciona un residuo marrón que se purifica por cromatografía en columna de gel de sílice. Eluyendo con 10% éter de dietilo en hexano, las fracciones purificadas se combinan y se concentran para proporcionar 612 mg, 2.5 mmol (17%) de 4-bromo-3-hidroxi-2-metilbenzoato de metilo como un aceite incoloro. ^{1}H NMR (400 MHz, $CDCl_3$): 7.37-7.29 (m, 2H), 5.71 (s, 1H), 3.81 (s, 3H), 2.53 (s, 3H). MS (EI) para $C_9H_9BrO_3$: 245 (MH^+).

[00968] ETAPA 3: Una solución de 4-bromo-3-hidroxi-2-metilbenzoato de metilo (610 mg, 2.5 mmol), carbonato de cesio (1.22 g, 3.7 mmol) y yodometano (162 µl, 2.6 mmol) en dimetilformamida (5 mL) se agita a temperatura ambiente por 15 horas. La mezcla se diluye con acetato de etilo, después se lava con 5% de cloruro de litio acuoso, después salmuera y se seca sobre sulfato de sodio anhidro. La filtración y la concentración proporcionan un residuo anaranjado, el cual se purifica por cromatografía en columna de gel de sílice. Eluyendo con 15% de éter de dietilo en hexano, las fracciones

purificadas se combinan y se concentran para proporcionar 455 mg, 1.76 mmol (71%) de 4-bromo-2-metil-3-(metiloxi)benzoato de metilo como un residuo incoloro. ^{1}H NMR (400 MHz, $CDCl_3$): 7.52 (d, 1H), 7.43 (d, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 2.55 (s, 3H). MS (EI) para $C_{10}H_{11}BrO_3$: 260 (MH^+).

[00969] ETAPA 4: A un recipiente de tubo sellado se agrega 4-bromo-2-metil-3-(metiloxi)benzoato de metilo (280 mg, 1.08 mmol), cianuro de cobre (I) (97 mg, 1.08 mmol) y dimetilformamida (2 mL). La mezcla se calienta a 150°C por 24 horas, después se enfría a temperatura ambiente y se filtra a través de una almohadilla de Celite. Después de lavar el Celite con acetato de etilo, lo filtrado combinado se lava con 5% de cloruro de litio acuoso, y salmuera, después se seca sobre sulfato de sodio anhidro. La filtración y concentración proporciona un residuo marrón que se purifica por cromatografía en columna de gel de sílice. Eluyendo con 10% de acetato de etilo en hexano, las fracciones purificadas se combinan y se concentran para proporcionar 150 mg, 0.73 mmol (68%) de 4-ciano-2-metil-3-(metiloxi)benzoato de metilo. ^{1}H NMR (400 MHz, $CDCl_3$): 7.61 (d, 1H), 7.47 (d, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 2.49 (s, 3H). MS (EI) para $C_{11}H_{11}NO_3$: 206 (MH^+).

[00970] ETAPA 5: 4-ciano-2-metil-3-(metiloxi)benzoato de metilo (150 mg, 0.73 mmol) en una solución de 35% de hidróxido de potasio acuoso:metanol (1:3, 4 mL) se agita a 60°C por 1 hora. La mezcla se enfría a temperatura ambiente, y el metanol se remueve por evaporación rotatoria. Se agrega agua (4 mL) a la mezcla y el pH se ajusta a 2 usando ácido clorhídrico acuoso concentrado. Lo precipitado el cual se forma, se recolecta por filtración y se lava con agua, después hexanos para proporcionar 86 mg, 0.45 mmol (62%) de ácido 4-ciano-2-metil-3-(metiloxi)benzoico. ^{1}H NMR (400 MHz, d_6-DMSO): 7.72 (d, 1H), 7.60 (d, 1H), 3.90 (s, 3H), 2.40 (s, 3H). MS (EI) para $C_{10}H_9NO_3$: 190 (M-H).

[00971] ETAPA 6: A una solución de ácido 4-ciano-2-metil-3-(metiloxi)benzoico (80 mg, 0.42 mmol) en DMSO:etanol (1:4, 1 mL) se agrega hidróxido de sodio acuoso 1N (1 mL), y peróxido de hidrógeno (30% en peso de agua, 1 mL). La mezcla se agita a temperatura ambiente por 72 horas, después se divide entre hidróxido de sodio acuoso 1N y acetato de etilo, y la capa orgánica se desecha. El pH de la porción acuosa se ajusta a 7 usando ácido clorhídrico acuoso 1N. La porción acuosa se extrae varias veces usando acetato de etilo, y la porción orgánica combinada se lava con salmuera después se seca sobre sulfato de sodio anhidro. La filtración y concentración proporciona 55 mg, 0.26 mmol (63%) de ácido 4-

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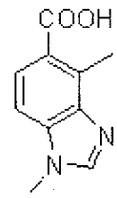
(aminocarbonil)-2-metil-3-(metiloxi)benzoico. ^1H NMR (400 MHz, d_6-DMSO): 7.77 (br s, 1H), 7.60 (br s, 1H), 7.54 (d, 1H), 7.41 (d, 1H), 3.72 (s, 3H), 2.41 (s, 3H). MS (EI) para $C_{10}H_9NO_3$: 190 (M-H).

PREPARACIÓN DEL REACTIVO 35: ácido 1,4-dimetil-1H-benzoimidazol-5-carboxílico:



[00972] ETAPA 1: Una mezcla de ácido 4-amino-2-metil-3-nitrobenzoico (sintetizado en la preparación del reactivo 22, etapa 1) (500 mg, 2.6 mmol) metanol (25 mL) y ácido sulfúrico concentrado (1.25 mL) se agita a 60°C por 18 horas. La mezcla de reacción enfría se concentra, se diluye con acetato de etilo (50 mL), se lava con agua (50 mL), solución bicarbonato de sodio acuoso saturado (2x 30 mL), salmuera (30 mL), se seca sobre sulfato de sodio, se filtra y se concentra para dar 4-amino-2-metil-3-nitrobenzoato de metilo (400 mg, 75% de rendimiento), MS (EI) para $C_9H_{10}N_2O_4$: 211 (MH^+).

[00973] ETAPA 2: Se agrega yodometano (125 uL, 2.0 mmol) a una mezcla de 4-amino-2-metil-3-nitrobenzoato de metilo (400 mg, 1.9 mmol) y hidruro de sodio (60% de dispersión aceitosa,

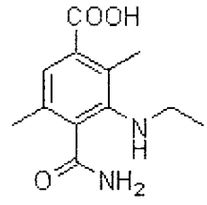
84 mg, 2.1 mmol) en tetrahidrofurano (10 mL) a 0°C. La mezcla de reacción lentamente se calienta a temperatura ambiente y se agita por 18 horas. La mezcla de reacción se apaga con solución de cloruro de amonio acuoso saturado y se extrae con acetato de etilo. El extracto combinado se lava con agua (2x 30 mL), salmuera (30 mL), se seca sobre sulfato de sodio, se filtra y se concentra, después se purifica por cromatografía instantánea (25% de acetato de etilo en hexanos) para dar 2-metil-4-(metilamino)-3-nitrobenzoato de metilo (308 mg, 72% de rendimiento). ^{1}H NMR (400MHz, $CDCl_3$): 7.94 (d, 1H), 6.63 (d, 1H), 5.68 (br, 1H), 3.86 (d, 2H), 2.58 (s, 3H); MS (EI) para $C_{10}H_{12}N_2O_4$: 225 (MH^+).

[00974] ETAPA 3: Una mezcla de 2-metil-4-(metilamino)-3-nitrobenzoato de metilo (90 mg, 0.4 mmol), 10% de paladio en carbón vegetal (Tipo Degussa, 90 mg), ácido acético (124 uL, 1.5 mmol), y acetato de etilo (20 mL) se agita en un aparato de hidrogenación Parr a 40 psi por 18 horas. La mezcla de reacción después se filtra y se concentra. El residuo se disuelve en ácido fórmico se agita a 100 °C por 1.5 hora. La mezcla de reacción se concentra, se apaga con agua helada (15 mL) y el pH se ajusta a básico por adición en porciones de bicarbonato de sodio después se extrae con acetato de etilo. El extracto combinado se lava con agua (2x 30 mL), salmuera (30 mL), se seca sobre sulfato de sodio, se filtra y se

concentra para dar 1,4-dimetil-1H-bencimidazol-5-carboxilato de metilo (78 mg, 95% de rendimiento). MS (EI) para $C_{11}H_{12}N_2O_2$: 205 (MH^+).

[00975] ETAPA 4: Una mezcla de 1,4-dimetil-1H-bencimidazol-5-carboxilato de metilo (78 mg, 0.38 mmol) en metanol (2 mL) y 5% de solución acuosa de hidróxido de sodio (2 mL) se agita a 60°C por una hora. La mezcla de reacción se concentra, se diluye con agua (10 mL) y el pH se ajusta a 4, después se satura con cloruro de sodio sólido. La mezcla acuosa se extrae con acetato de etilo (3x 10 mL) y el extracto combinado se lava con agua (15 mL), salmuera (15 mL), se seca sobre sulfato de sodio, se filtra y se concentra para dar ácido 1,4-dimetil-1H-bencimidazol-5-carboxílico (46 mg, 63% de rendimiento), MS (EI) para $C_{10}H_{10}N_2O_2$: 191 (MH^+).

PREPARACIÓN DEL REACTIVO 36: ácido 4-(aminocarbonil)-3-(etilamino)-2,5-dimetilbenzoico:



[00976] ETAPA 1: Se suspende ácido 2,5-Dimetiltereftálico (3 g, 15.5 mmol) en éter (30 mL) y metanol (10 mL), y se enfría en un baño helado. Se agrega por goteo

(trimetilsilil)diazometano (solución 2 M en hexanos; 16 mL). La mezcla se agita a temperatura ambiente por 0.5 h y después se apaga con ácido acético (2 mL) y se concentra. El residuo se divide entre acetato de etilo y bicarbonato de sodio acuoso saturado. La porción orgánica se lava con salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar 2,5-dimetiltereftalato de dimetilo (3.18 g, 14.3 mmol, 93% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 2H), 3.91 (s, 6H), 2.57 (s, 6H); MS (EI) para $C_{12}H_{14}O_4$: 223 (MH^+).

[00977] ETAPA 2: Se disuelve 2,5-dimetiltereftalato de dimetilo (3.14 g, 14.1 mmol) en diclorometano (30 mL) y se enfría en un baño helado. Se agregan ácido nítrico humeante (7.6 mL) y ácido sulfúrico concentrado (0.92 mL) cuidadosamente, y la mezcla se agita por 1.75 h. La mezcla después se apaga con agua y se diluye con diclorometano. La porción acuosa se extrae con diclorometano. La porción orgánica combinada se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar un aceite amarillo el cual se purifica por cromatografía en columna (gel de sílice, 10-20% de acetato de etilo en hexanos) para proporcionar 2,5-dimetil-3-nitrotereftalato de dimetilo (2.78 g, 10.4 mmol, 74% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 2.49 (s, 3H), 2.46 (s, 3H); GCMS

por $C_{12}H_{13}NO_6$: 267 (M^+).

[00978] ETAPA 3: Se disuelve 2,5-dimetil-3-nitrotereftalato de dimetilo (2.27 g, 8.50 mmol) en 1,4-dioxano (20 mL) y se enfría en un baño helado. Se agrega por goteo hidróxido de sodio 1N (8.5 mL), y la mezcla se agita a temperatura ambiente por 2.25 h. Se agrega por goteo hidróxido de sodio 1N adicional (0.5 mL) y la mezcla se agita a temperatura ambiente por 1 h adicional, punto en el cual se agrega otra alícuota 0.5 mL de hidróxido de sodio acuoso 1N y la agitación se continúa por 1 h adicional. La mezcla de reacción se diluye con agua y se lava con éter. La porción acuosa se acidifica con ácido clorhídrico 1N a pH ~2 y después se extrae con acetato de etilo (2x). La porción de acetato de etilo combinada se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar ácido 4-(metoxicarbonil)-2,5-dimetil-3-nitrobenzoico (rendimiento cuantitativo). ^{1}H NMR (400 MHz, d_6-DMSO): δ 13.8 (br s, 1H), 7.93 (d, 1H), 3.81 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H); MS (EI) para $C_{11}H_{11}NO_6$: 252 (M-H).

[00979] ETAPA 4: Se suspende ácido 4-(metoxicarbonil)-2,5-dimetil-3-nitrobenzoico (9.5 mmol) en diclorometano (30 mL) y se agregan clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (1.82 g, 9.5 mmol) y 4-dimetilaminopiridina

(1.16 g, 9.5 mmol). La mezcla se agita a temperatura ambiente por 0.5 h. Se agrega terc-butanol (6 mL, 64 mmol) y la mezcla se agita por 15.5 h. Se agrega terc-butanol (20 mL, 213 mmol) y la mezcla se agita a reflujo por 1 h. El diclorometano se remueve y la mezcla se agita a 75 °C por 21 h. Se agregan trietilamina (1.3 mL, 9.3 mmol) y cloruro de difenilfosforilo (1.96 mL, 9.5 mmol), y la mezcla se agita a 75 °C por 6 h. La mezcla se enfría a temperatura ambiente y después se concentra. El residuo se divide entre acetato de etilo y ácido clorhídrico 1N. La porción orgánica se lava con hidróxido de sodio 1N, salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar un semi-sólido anaranjado, el cual se purifica por cromatografía en columna (gel de sílice, 5-15% de acetato de etilo en hexanos) para proporcionar 2,5-dimetil-3-nitrotereftalato de 1-terc-butil 4-metilo crudo (1.98 g, 6.4 mmol, 68% de rendimiento) como un aceite incoloro. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 3.88 (s, 3H), 2.45 (s, 3H), 2.44 (s, 3H), 1.60 (s, 9H); GCMS por $C_{15}H_{19}NO_6$: 309 (M^+).

[00980] ETAPA 5: Se disuelve 2,5-dimetil-3-nitrotereftalato de 1-terc-butil 4-metilo (0.5 g, 1.62 mmol) en tetrahidrofurano (4 mL). Se agrega 10% en peso de paladio en carbono (Tipo Degussa, 50 mg) a la solución y la mezcla se trata con hidrógeno a temperatura ambiente por 3 h. Se agrega

10% en peso de paladio en carbono (Tipo Degussa, 50 mg) a la solución, y la mezcla se trata con hidrógeno a temperatura ambiente por 2 h adicionales. Se agrega 10% en peso de paladio en carbono (Tipo Degussa, 100 mg) a la solución, y la mezcla se trata con hidrógeno a temperatura ambiente por 5 h adicionales. La mezcla se filtra y lo filtrado se concentra para proporcionar 3-amino-2,5-dimetiltereftalato de 1-terc-butil 4-metilo (0.444 g, 1.59 mmol, 98% de rendimiento) como un aceite marrón. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (s, 1H), 5.20 (br s, 2H), 3.90 (s, 3H), 2.40 (s, 3H), 2.24 (s, 3H), 1.59 (s, 9H); MS (EI) para $C_{15}H_{21}NO_4$: 280 (MH^+).

[00981] ETAPA 6: Se disuelve 3-amino-2,5-dimetiltereftalato 1-terc-butil 4-metilo (0.444 g, 1.59 mmol) en THF (10 mL), y la mezcla se rocía con nitrógeno por 10 minutos. Se agregan yoduro de cobre (I) (302 mg, 1.59 mmol) y diyodometano (0.64 mL, 7.93 mmol) seguido por nitrito de isoamilo (0.63 mL, 4.74 mmol), y la mezcla se agita a reflujo por 20 h. La mezcla se enfría a temperatura ambiente y después se divide entre acetato de etilo y ácido clorhídrico 1N. La porción acuosa se extrae con acetato de etilo (2x). La porción orgánica combinada se lava con salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar un aceite el cual se purifica por cromatografía en columna (gel de sílice, 2-10% de acetato de etilo en hexanos). Las

fracciones limpias se combinan y se concentran, y el residuo se divide entre acetato de etilo y 1:1 solución saturada de bicarbonato de sodio: tiosulfato de sodio 1M. La porción acuosa se extrae con acetato de etilo. La porción orgánica combinada se lava con salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar 3-yodo-2,5-dimetiltereftalato de 1-terc-butil 4-metilo (300 mg, 0.769 mmol, 48% de rendimiento) como un aceite amarillo. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 1H), 3.96 (s, 3H), 2.60 (s, 3H), 2.31 (s, 3H), 1.59 (s, 9H); GCMS por $C_{15}H_{19}IO_4$: 359 ($[M-OCH_3]^+$).

[00982] ETAPA 7: 3-yodo-2,5-dimetiltereftalato de 1-terc-butil 4-metilo (300 mg, 0.769 mmol) se disuelve en dioxano (3 mL) y se rocía con nitrógeno por 15 minutos. Se agregan XANTPHOS (18 mg, 0.031 mmol), carbonato de cesio (326 mg, 1.00 mmol), etilamina (0.1 mL) y tris(dibencilidenacetona)dipaladio (14 mg, 0.015 mmol), y la mezcla se agita en un tubo sellado a 95°C por 19 h. Se agregan XANTPHOS (36 mg, 0.062 mmol), etilamina (0.1 mL) y tris(dibencilidenacetona)dipaladio (28 mg, 0.030 mmol) y la mezcla se agita en un tubo sellado a 95 °C por 20 h adicionales. La mezcla de reacción se enfría a temperatura ambiente y se filtra a través de celite. La torta filtrada se lava con acetato de etilo, y lo filtrado se concentra para

proporcionar un aceite anaranjado el cual se purifica por cromatografía en columna (gel de sílice, 2-10% de acetato de etilo en hexanos) para proporcionar 3-(etilamino)-2,5-dimetiltereftalato de 1-terc-butil 4-metilo (158 mg, 0.515 mmol, 67% de rendimiento) como un aceite amarillo. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 3.91 (s, 3H), 3.83 (br s, 1H), 3.00 (q, 2H), 2.36 (s, 3H), 2.29 (s, 3H), 1.59 (s, 9H), 1.14 (t, 3H); MS (EI) para $C_{17}H_{25}NO_4$: 308 (MH^+).

[00983] ETAPA 8: Se disuelve 3-(etilamino)-2,5-dimetiltereftalato de 1-terc-butil 4-metilo (142 mg, 0.463 mmol) en dioxano (2 mL) y se enfría en un baño helado. Se agrega hidróxido de litio 2N (0.25 mL) y la mezcla se agita por 16 h y se agregan después metanol (0.5 mL) e hidróxido de litio 2N (0.25 mL), y la mezcla se agita a temperatura ambiente por 1.5 h. La mezcla se enfría en un baño helado y se agrega hidróxido de sodio 1N (0.5 mL), y la mezcla se agita por 1 h y después se calienta a temperatura ambiente y se agita por 1 h adicional. La mezcla se agita a 50-55 °C por 16 h adicionales y después se enfría a temperatura ambiente y se acidifica con ácido clorhídrico 1N a pH ~4.5. La mezcla se diluye con agua y se extrae con acetato de etilo (2x). La porción orgánica se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar ácido 4-(terc-butoxicarbonil)-2-(etilamino)-3,6-dimetilbenzoico (115 mg,

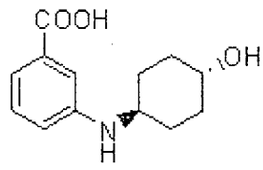
0.392 mmol, 85% de rendimiento) como un aceite marrón. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 2.97 (q, 2H), 2.67 (s, 3H), 2.46 (s, 3H), 1.61 (s, 9H), 1.34 (t, 3H); MS (EI) para $C_{16}H_{23}NO_4$: 294 (MH^+).

[00984] ETAPA 9: Se disuelve ácido 4-(terc-Butoxicarbonil)-2-(etilamino)-3,6-dimetilbenzoico (115 mg, 0.392 mmol) en tetrahidrofurano (1 mL) y después se enfría en un baño helado. Se agregan N,N-Diisopropiletilamina (0.07 mL, 0.403 mmol) y trifósgeno (40 mg, 0.135 mmol), y la mezcla se agita a temperatura ambiente por 0.5 h. La mezcla se apaga con agua y se extrae con diclorometano (2x). La porción orgánica combinada se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar 1-etil-5,8-dimetil-2,4-dioxo-2,4-dihidro-1H-benzo[d][1,3]oxazin-7-carboxilato de terc-butilo (109 mg, 0.342 mmol, 87% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 1H), 4.06 (q, 2H), 2.70 (s, 3H), 2.46 (s, 3H), 1.62 (s, 9H), 1.28 (t, 3H); MS (EI) para $C_{17}H_{21}NO_5$: 320 (MH^+).

[00985] ETAPA 10: Se disuelve 1-etil-5,8-dimetil-2,4-dioxo-2,4-dihidro-1H-benzo[d][1,3]oxazin-7-carboxilato de terc-butilo (90 mg, 0.282 mmol) en tetrahidrofurano (6 mL), se trata con amoníaco por 15 min y después se agita a temperatura ambiente por 1 h. La mezcla se concentra, y el

residuo se agita por 15 min como una suspensión en 20% de ácido cítrico (3 mL) y tetrahidrofurano (1 mL). La mezcla se extrae con acetato de etilo. La porción acuosa se basifica con bicarbonato de sodio y después se extrae con acetato de etilo. La porción orgánica combinada se lava con agua, salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar una película anaranjada, la cual se trata con ácido trifluoroacético (1 mL) a temperatura ambiente por 2 h. La mezcla se concentra y el residuo se trata con ácido clorhídrico 1N y se concentra. El residuo se disuelve en una mezcla de ácido clorhídrico 1N y acetonitrilo y después se liofiliza para proporcionar sal de clorhidrato del ácido 4-aminocarbonil-3-(etilamino)-2,5-dimetilbenzoico (rendimiento cuantitativo). MS (EI) para $C_{12}H_{16}N_2O_3$: 237 (MH^+).

PREPARACIÓN DEL REACTIVO 37: ácido 3-[(trans-4-hidroxiciclohexil)-amino]benzoico:



[00986] ETAPA 1: Una suspensión de 3-bromobenzoato de metilo (0.43 g, 2.00 mmol), trans-4-aminociclohexanol (0.35 g, 3.00 mmol), carbonato de cesio (1.63 g, 5.00 mmol), Xantphos (0.024 g, 0.02 mmol) y tris(dibencilidenacetona)dipaladio(0) (0.010 g, 0.01 mmol) en

1,4-dioxano (25 mL) se agita a 80 °C bajo atmósfera N_2 por 18 horas. Después del enfriamiento a temperatura ambiente la mezcla de reacción se filtra a través de una almohadilla de Celite y se lava con acetato de etilo (200 mL), y lo filtrado combinado se divide con agua. La capa orgánica se separa y se lava con ácido clorhídrico acuoso 1M y salmuera, se seca sobre sulfato de sodio, se filtra, y la solución se concentra. El residuo se purifica por cromatografía en columna (hexano:acetato de etilo 4:1 a 3:2) para dar 3-[(trans-4-hidroxiciclohexil)amino]benzoato de metilo. (0.28 g, 56%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.18 (m, 2H), 7.08 (m, 1H), 6.82 (m, 1H), 5.82 (d, 1H), 3.84 (s, 3H), 3.34 (m, 1H), 2.57 (m, 1H), 1.85 (m, 2H), 1.71 (m, 2H), 1.58 (m, 2H), 1.46 (m, 2H). MS (EI) para $C_{14}H_{19}NO_3$: 250 (MH^+).

[00987] ETAPA 2: A una solución de 3-[(trans-4-hidroxiciclohexil)amino]benzoato de metilo (0.25 g, 1.00 mmol) en una mezcla de metanol (20 mL), tetrahidrofurano (10 mL) y agua (10 mL) se agrega una solución acuosa de hidróxido de potasio 4M (0.5 mL, 2.00 mmol), y la mezcla de reacción se calienta a reflujo por cinco minutos. La porción orgánica del solvente se evapora, y el pH de la solución acuosa se ajusta a 2 por la adición de ácido clorhídrico acuoso 2M. La mezcla acuosa se divide con acetato de etilo, la capa orgánica se separa y se lava con salmuera, se seca sobre sulfato de

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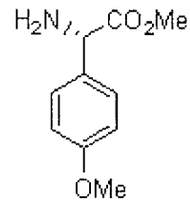
sodio, se filtra, y la solución se concentra para dar ácido 3-[(trans-4-hidroxiciclohexil)amino]benzoico (40 mg, 17%). MS (EI) para $C_{13}H_{17}NO_3$: 234 (M-H).

PREPARACIÓN DEL REACTIVO 38: 2-amino-2-(4-metoxifenil)-acetato de (S)-metilo:



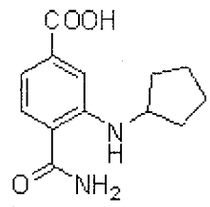
[00988] ETAPA 1: A una solución de L-4-hidroxifenilglicina (1.00 g, 5.98 mmol) y hidrogencarbonato de sodio (2.50 g, 29.11 mmol) en una mezcla de 1,4-dioxano (20 mL) y agua (20 mL) se agrega di-terc-butilo dicarbonato (1.40 g, 6.58 mmol) a 0 °C, seguido por agitación a temperatura ambiente durante 18 horas. La porción orgánica del solvente se evapora, y la mezcla de reacción se divide entre acetato de etilo (300 mL) y ácido clorhídrico acuoso 0.5M (50 mL). La capa orgánica se separa y se lava con ácido clorhídrico acuoso 0.5M, agua y salmuera, se seca sobre sulfato de sodio, se filtra y el solvente se concentra para dar ácido (S)-2-(terc-butoxicarbonilamino)-2-(4-hidroxifenil)acético (1.6 g, cuantitativo). ^{1}H NMR (400 MHz, $CDCl_3$): 8.80 (bs, 1H), 7.12 (d, 2H), 6.62 (d, 2H), 5.80 (d, 1H), 5.00 (d, 1H), 1.22 (s, 9H). MS (EI) para $C_{13}H_{17}NO_5$: 266 (M-H).

[00989] ETAPA 2: A una solución de ácido (S)-2-(terc-butoxicarbonilamino)-2-(4-hidroxifenil)acético (1.60 g, 5.98 mmol) en dimetilformamida (20 mL) se agrega carbonato de potasio (1.85 g, 13.42 mmol), y la mezcla se agita a temperatura ambiente por treinta minutos, seguido por la adición de yoduro de metilo (0.76 mL, 12.20 mmol). La mezcla de reacción después se agita a temperatura ambiente por 18 horas. El solvente se evapora y el residuo se divide entre acetato de etilo (250 mL) y agua (50 mL). La capa orgánica se separa y se lava con hidrogencarbonato de sodio acuoso saturado, agua y salmuera, se seca sobre sulfato de sodio, se filtra y el solvente se concentra para dar 2-(terc-butoxicarbonilamino)-2-(4-metoxifenil)acetato de (S)-metilo (1.8 g, cuantitativo). ^{1}H NMR (400 MHz, $CDCl_3$): 7.16 (d, 2H), 6.72 (d, 2H), 5.68 (d, 1H), 5.14 (d, 1H), 3.62 (s, 3H), 3.56 (s, 3H), 1.24 (s, 9H). MS (EI) para $C_{15}H_{21}NO_5$: 294 (MH^-).

[00990] ETAPA 3: A una solución de 2-(terc-butoxicarbonilamino)-2-(4-metoxifenil)acetato de (S)-metilo (0.30 g, 1.00 mmol) en diclorometano (10 mL) se agrega ácido trifluoroacético (2 mL) y la mezcla se calienta a 40 °C por treinta minutos. El solvente se evapora seguido por evaporación rotatoria del residuo a partir de tolueno y secado in vacuo para obtener 2-amino-2-(4-metoxifenil)acetato de (S)-metilo como la sal de

trifluoroacetato (0.30 g, cuantitativo). ^{1}H NMR (400 MHz, DMSO-d_6): 7.18 (d, 2H), 6.82 (d, 2H), 5.68 (d, 1H), 4.82 (d, 1H), 3.78 (s, 3H), 3.64 (s, 3H). MS (EI) para $C_{10}H_{13}NO_3$: 196 (MH^+).

PREPARACIÓN DEL REACTIVO 39: ácido 4-(aminocarbonil)-3-(ciclopentilamino)-benzoico:



[00991] ETAPA 1: Una mezcla de 3-bromo-4-cianobenzoato de etilo (500 mg, 1.97 mmol), XANTPHOS (228 mg, 0.39 mmol), carbonato de cesio (1.282 g, 3.94 mmol), ciclopentilamina (233 mg, 2.75 mmol), y tris(dibencilidenacetona)dipaladio (180 mg, 0.20 mmol) en dioxano (5 mL) se agita a 100 °C por 17 h. La mezcla de reacción se divide entre acetato de etilo (100 mL) y agua (50 mL), la capa orgánica se lava con salmuera (50 mL), se seca sobre sulfato de sodio, se filtra y se concentra. La cromatografía en columna en sílice (hexanos:acetato de etilo 9:1) proporciona 4-ciano-3-(ciclopentilamino)benzoato de etilo (366 mg, 72% de rendimiento) como un aceite marrón. ^{1}H NMR (400 MHz, $CDCl_3$): 7.43 (m, 2H), 7.35 (m, 1H), 7.27 (m, 1H), 4.62 (d, 1H), 4.38 (q, 2H), 3.93 (m, 1H), 2.10 (m, 2H), 1.78 (m, 2H), 1.67 (m,

2H), 1.53 (m, 2H), 1.39 (t, 3H). MS (EI) para $C_{15}H_{18}N_2O_2$: 259 (MH^+).

[00992] ETAPA 2: Una solución de 4-ciano-3-(ciclopentilamino)benzoato de etilo (363 mg, 1.41 mmol), carbonato de potasio (50 mg, 0.36 mmol), y 30% peróxido de hidrógeno acuoso (0.25 mL) en DMSO (1.5 mL) se agita a 60 °C por 1 h. Después del enfriamiento a temperatura ambiente, se agrega agua y la mezcla resultante se extrae con acetato de etilo (50 mL). La capa orgánica se lava con agua (10 mL) y salmuera (10 mL), se seca sobre sulfato de sodio, se filtra y se concentra para dar 4-(aminocarbonil)-3-(ciclopentilamino)-benzoato de etilo (333 mg, 86% de rendimiento). MS (EI) para $C_{15}H_{20}N_2O_3$: 277 (MH^+).

[00993] ETAPA 3: Una suspensión de 4-(aminocarbonil)-3-(ciclopentilamino)benzoato de etilo (333 mg, 1.21 mmol) e hidróxido de potasio (135 mg, 2.41 mmol) en metanol (6 mL) y agua (2 mL) se agita a 55 °C por 1 h. Después del enfriamiento a temperatura ambiente, se agrega agua y el pH se ajusta a 4 con ácido clorhídrico acuoso 1N. Lo precipitado resultante se recolecta por filtración, se lava con agua y se seca para proporcionar ácido 4-(aminocarbonil)-3-(ciclopentilamino) benzoico (260 mg, 87% de rendimiento). ^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (br s, 1H), 8.17 (d, 1H), 7.97 (br s, 1H), 7.66

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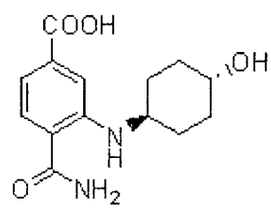
(d, 1H), 7.34 (br s, 1H), 7.21 (d, 1H), 7.04 (dd, 1H), 3.81 (m, 1H), 1.99 (m, 2H), 1.64 (m, 4H), 1.42 (m, 2H). MS (EI) para $C_{13}H_{16}N_2O_3$: 249 (MH^+).

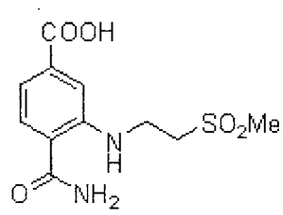
[00994] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes compuestos. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[00995] Ácido 4-(Aminocarbonil)-3-[(trans-4-hidroxiciclohexil)amino]benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando trans 4-aminociclohexanol en la etapa 1. MS (EI) para $C_{14}H_{18}N_2O_4$: 279 (MH^+).

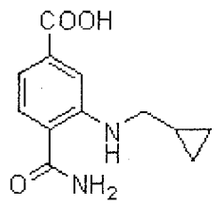
[00996] Ácido 4-(Aminocarbonil)-3-{[2-(metilsulfonil)etil]-amino}benzoico:



Preparado de conformidad con el método del reactivo

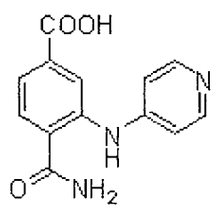
de la preparación 39 usando clorhidrato de 2-aminoetilmetilsulfona en la etapa 1. MS (EI) para $C_{11}H_{14}N_2O_5S$: 287 (MH^+).

[00997] Ácido 4-(Aminocarbonil)-3-[(ciclopropilmetil)amino]benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando aminometilciclopropano en la etapa 1. MS (EI) para $C_{12}H_{14}N_2O_3$: 235 (MH^+).

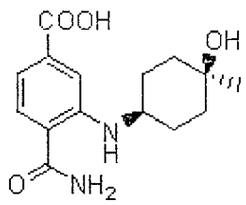
[00998] Ácido 4-(Aminocarbonil)-3-(piridin-4-il-amino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 4-aminopiridina en la etapa 1. ^1H NMR (400 MHz, DMSO-d_6): 9.82 (s, 1H), 8.30 (d, 2H), 8.23 (s, 1H), 7.97 (d, 1H), 7.79 (d, 1H), 7.76 (s, 1H), 7.57 (dd, 1H), 7.03 (d, 2H). MS (EI) para $C_{13}H_{11}N_3O_3$: 258 (MH^+).

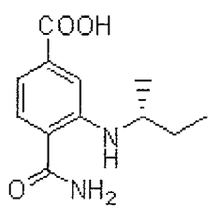
1194

[00999] Ácido 4-(Aminocarbonil)-3-[(cis-4-hidroxi-4-metil-ciclohexil)amino]benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando cis-4-hidroxi-4-metilciclohexil-amina (sintetizado de conformidad con WO2005009966) en la etapa 1. MS (EI) para $C_{15}H_{20}N_2O_4$: 293 (MH^+).

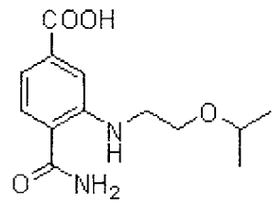
[001000] Ácido 4-(Aminocarbonil)-3-{[(1R)-1-metilpropil]-amino}benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando (R)-(-)-3-metil-2-butilamina en la etapa 1. ^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (br s, 1H), 8.26 (d, 1H), 7.97 (br s, 1H), 7.67 (d, 1H), 7.33 (br s, 1H), 7.20 (d, 1H), 7.00 (dd, 1H), 3.42 (m, 1H), 1.79 (m, 1H), 1.07 (d, 3H), 0.94 (d, 3H), 0.88 (d, 3H). MS (EI) para $C_{13}H_{18}N_2O_3$: 249 (M-H).

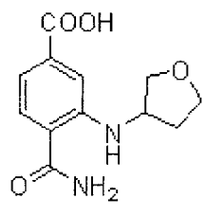
1195

[001001] Ácido 4-(Aminocarbonil)-3-({2-[(1-metiletil)oxi]etil}amino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 2-{(1-metiletil)oxi}etanamina en la etapa 1. MS (EI) para $C_{13}H_{18}N_2O_4$: 267 (MH^+).

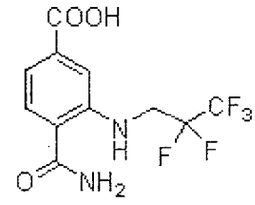
[001002] Ácido 4-(Aminocarbonil)-3-(tetrahidrofuran-3-ilamino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando clorhidrato de (±)-tetrahidrofuran-3-amina en la etapa 1. MS (EI) para $C_{12}H_{14}N_2O_4$: 251 (MH^+).

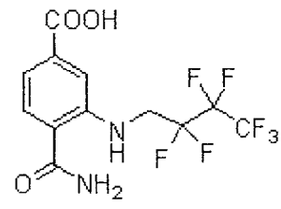
1296

[001003] Ácido 4-(Aminocarbonil)-3-(2,2,3,3,3-pentafluoropropilamino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 2,2,3,3,3-pentafluoropropilamina en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.1 (br s, 1H), 8.54 (t, 1H), 8.11 (br s, 1H), 7.73 (d, 1H), 7.54 (br s, 1H), 7.42 (s, 1H), 7.19 (dd, 1H), 4.23 (td, 2H). MS (EI) para $C_{11}H_9F_5N_2O_3$: 311 (M-H).

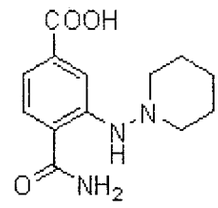
[001004] Ácido 4-(Aminocarbonil)-3-(2,2,3,3,4,4,4-heptafluorobutilamino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 2,2,3,3,4,4,4-heptafluorobutilamina en la etapa 1. MS (EI) para $C_{12}H_9F_7N_2O_3$: 363 (MH^+).

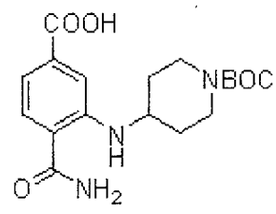
1197

[001005] Ácido 4-(Aminocarbonil)-3-(piperidin-1-ilamino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando piperidin-1-amina en la etapa 1. ^{1}H NMR (400 MHz, CD_3OD): 8.00 (d, 1H), 7.58 (d, 1H), 724 (dd, 1H), 2.71 (br s, 4H), 1.75-1.69 (m, 4H), 1.47 (br s, 2H). MS (EI) para $C_{13}H_{17}N_3O_3$: 264 (MH^+).

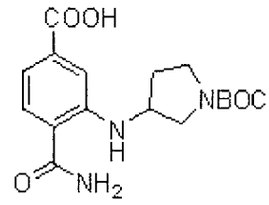
[001006] Ácido 4-(Aminocarbonil)-3-[(1-{[(1,1-dimetiletil)oxi]carbonil}piperidin-4-il)amino]benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 1-terc-butoxicarbonil-4-aminopipiperidina en la etapa 1. ^{1}HNMR (400 MHz, metanol-d_4): 7.63 (d, J = 8.0Hz, 1H), 7.40 (s, 1H), 7.20 (d, J = 8.0Hz, 1H), 3.93 (m, 2H), 3.67 (m, 1H), 3.05 (m, 2H), 2.03 (m, 2H), 1.46 (s, 9H), 1.40 (m, 2H). MS (EI) para $C_{18}H_{25}N_3O_5$: 364 (MH^+).

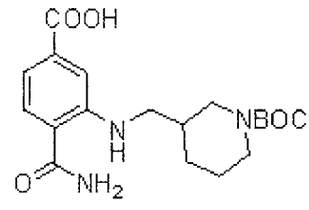
1198

[001007] Ácido 4-(Aminocarbonil)-3-[(1-{[(1,1-dimetiletil)oxi]carbonil}pirrolidin-3-il)amino]benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 1-terc-butoxicarbonil-3-aminopirrolidina en la etapa 1. ^{1}HNMR (400 MHz, metanol-d_4): 7.65 (d, J = 8.0Hz, 1H), 7.38 (s, 1H), 7.25 (d, J = 8.0Hz, 1H), 4.20 (m, 1H), 3.70 (m, 1H), 3.50 (m, 2H), 2.26 (m, 1H), 2.28 (m, 1H), 1.95 (m, 1H), 1.44 (s, 9H). MS (EI) para $C_{17}H_{23}N_3O_5$ 250 (MH^+-Boc).

[001008] Ácido 4-(Aminocarbonil)-3-{(1-{[(1,1-dimetiletil)oxi]carbonil}piperidin-3-il)metil]amino}benzoico:

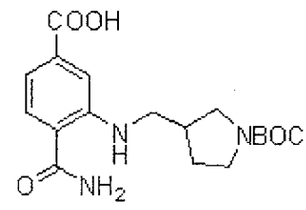


Preparado de conformidad con el método del reactivo de la preparación 39 usando 4-aminometil-1-N-(terc-butoxicarbonil)pipiperidina en la etapa 1. ^{1}HNMR (400 MHz, metanol-d_4): 7.63 (d, J = 8.0Hz, 1H), 7.34 (s, 1H), 7.20 (d, J = 8.0Hz, 1H), 3.80 (br, s, 1H), 3.14 (m, 2H), 2.95 (m, 2H),

1199

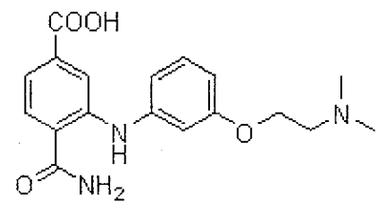
1.95-1.60 (m, 3H), 1.44 (m, 3H), 1.40 (s, 9H). MS(EI) para $C_{19}H_{27}N_3O_5$ 378 (MH^+).

[001009] 4-(Aminocarbonil)-3-{(1-{[(1,1-dimetiletil)oxi]carbonil}pirrolidin-3-il)metil]amino}benzoico ácido:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 3-(aminometil)pirrolidin-1-carboxilato de terc-butilo en la etapa 1. ^{1}HNMR (400 MHz, metanol-d_4): 7.63 (d, J = 8.0Hz, 1H), 7.36 (s, 1H), 7.21 (d, J = 8.0Hz, 1H), 3.56 (m, 1H), 3.47 (m, 1H), 3.30 (m, 1H), 3.12 (m, 1H), 3.09 (m,1H), 2.56 (m,1H), 2.11 (m,1H), 1.74 (m, 1H), 1.45 (s, 9H). MS(EI) para $C_{18}H_{25}N_3O_5$ 364 (MH^+).

[001010] Ácido 4-(Aminocarbonil)-3-[(3-{[(2-dimetilamino)etil]oxi}fenil)-amino]benzoico:

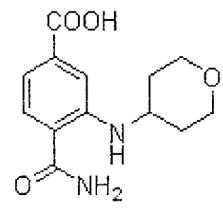


Preparado de conformidad con el método del reactivo

1200

de la preparación 39 usando 3-[2-(dimetilamino)etoxi]anilina (*Bioorg. & Med. Chem. Lett. 2005, 15(22)*, 4989-4993) en la etapa 1. ^{1}HNMR (400 MHz, DMSO-d_6): 13.18 (br, s, 1H), 9.96 (s, 1H), 8.23 (s,1H), 7.83 (s, 1H), 7.79 (d, J = 8.0Hz, 1H), 7.69 (s, 1H), 7.31 (m, 2H), 6.82 (m, 2H), 6.69 (d, J = 8.0Hz, 1H), 4.34 (m, 2H), 3.50 (m, 2H), 2.84 (s, 6H). MS(EI) para $C_{18}H_{21}N_3O_4$ 344 (MH^+).

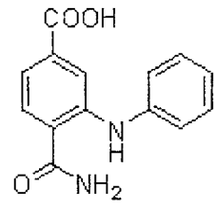
[001011] Ácido 4-(Aminocarbonil)-3-(tetrahidro-2H-piran-4-ilamino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 4-aminotetrahidropirano en la etapa 1. ^{1}H NMR (400 MHz, metanol-d_4): 7.64 (d, 1H), 7.41 (d, 1H), 7.21 (dd, 1H), 3.96 (dt, 2H), 3.73-3.65 (m, 1H), 3.60 (td, 2H), 2.08-2.00 (m, 2H), 1.58-1.48 (m, 2H). MS (EI) para $C_{13}H_{16}N_2O_4$: 265 (MH^+).

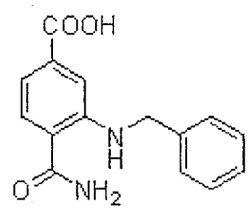
1201

[001012] Ácido 4-(Aminocarbonil)-3-(fenilamino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando anilina en la etapa 1. ^{1}H NMR (400 MHz, metanol-d_4): 7.91 (d, 1H), 7.71 (d, 1H), 7.39-7.32 (m, 3H), 3.19 (d, 2H), 7.04 (t, 1H). MS (EI) para $C_{14}H_{12}N_2O_3$: 257 (MH^+).

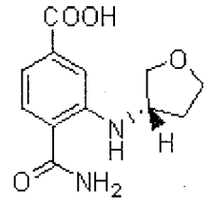
[001013] Ácido 4-(Aminocarbonil)-3-(bencilamino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando bencilamina en la etapa 1. ^{1}H NMR (400 MHz, metanol-d_4): 7.63 (d, 1H), 7.40-7.36 (m, 2H), 7.34-7.30 (m, 3H), 7.24 (d, 1H), 7.21 (dd, 1H), 4.43 (s, 2H). MS (EI) para $C_{15}H_{14}N_2O_3$: 271 (MH^+).

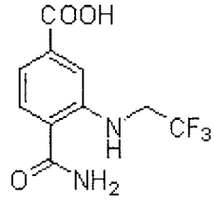
1202

[001014] Ácido (S)-4-(Aminocarbonil)-3-(tetrahidrofuran-3-ilamino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando (S)-tetrahidrofuran-3-amina en la etapa 1. ^{1}H NMR (400 MHz, metanol-d_4): 7.69-7.63 (m, 1H), 7.40-7.36 (m, 1H), 7.30-7.25 (m, 1H), 7.30-7.25 (m, 1H), 4.24-4.18 (m, 1H), 4.04-3.91 (m, 2H), 3.90-3.83 (m, 1H), 3.73-3.67 (m, 1H), 2.38-2.27 (m, 1H), 1.94-1.85 (m, 1H). MS (EI) para $C_{12}H_{14}N_2O_4$: 251 (MH^+).

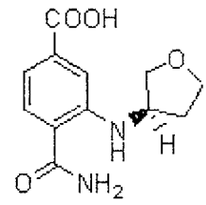
[001015] Ácido 4-(Aminocarbonil)-3-(2,2,2-trifluoroetilamino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 2,2,2-trifluoroetilamina en la etapa 1. MS (EI) para $C_{10}H_9F_3N_2O_3$: 261 (M-H).

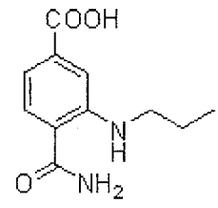
1203

[001016] Ácido (R)-4-(Aminocarbonil)-3-(tetrahidrofuran-3-ilamino)benzoico:



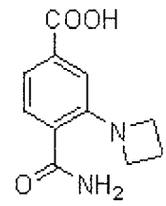
Preparado de conformidad con el método del reactivo de la preparación 39 usando (R)-tetrahidrofuran-3-amina en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.04 (br s, 1H), 8.27 (br s, 1H), 8.02 (s, 1H), 7.69 (d, 1H), 7.41 (s, 1H), 7.19 (s, 1H), 7.09 (d, 1H), 4.16-4.09 (br s, 1H), 3.92-3.86 (m, 1H), 3.84-3.72 (m, 2H), 3.56-3.49 (m, 1H), 2.32-2.20 (m, 1H), 1.77-1.68 (m, 1H). MS (EI) para $C_{12}H_{14}N_2O_4$: 251 (MH^+).

[001017] Ácido 4-(Aminocarbonil)-3-(propilamino)benzoico:



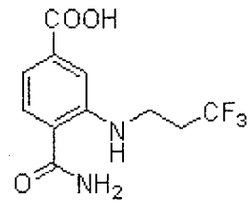
Preparado de conformidad con el método del reactivo de la preparación 39 usando n-propilamina en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.01 (br s, 1H), 8.12 (t, 1H), 7.98 (br s, 1H), 7.67 (d, 1H), 7.36 (br s, 1H), 7.17 (s, 1H), 7.05 (dd, 1H), 3.12-3.07 (m, 2H), 1.64-1.56 (m, 2H), 0.96 (t, 3H). MS (EI) para $C_{11}H_{14}N_2O_3$: 221 (M-H).

[001018] Ácido 4-(Aminocarbonil)-3-(azetidin-1-il)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando azetidina en la etapa 1. MS (EI) para $C_{11}H_{12}N_2O_3$: 221 (MH+).

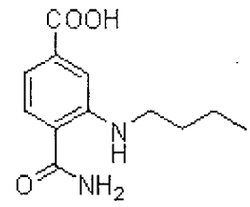
[001019] Ácido 4-(Aminocarbonil)-3-(3,3,3-trifluoropropilamino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 3,3,3-trifluoropropilamina en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.06 (br s, 1H), 8.23 (t, 1H), 8.01 (br s, 1H), 7.69 (d, 1H), 7.41 (br s, 1H), 7.20 (dd, 1H), 3.46-3.41 (m, 2H), 2.66-2.54 (m, 3H). MS (EI) para $C_{11}H_{11}F_3N_2O_3$: 277 (MH^+).

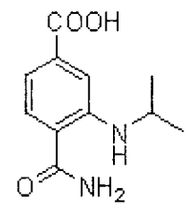
1203

[001020] 4-(Aminocarbonil)-3-(butilamino)benzoico:



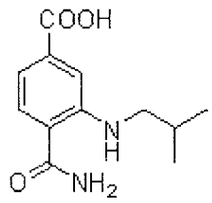
Preparado de conformidad con el método del reactivo de la preparación 39 usando n-butilamina en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.02 (br s, 1H), 8.09 (t, 1H), 7.98 (br s, 1H), 7.67 (d, 1H), 7.35 (br s, 1H), 7.17 (d, 1H), 7.05 (dd, 1H), 3.15-3.10 (m, 2H), 1.059-1.54 (m, 2H), 1.42-1.37 (m, 2H), 0.95-0.91 (m, 3H). MS (EI) para $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[001021] Ácido 4-(aminocarbonil)-3-[(1-metiletil)amino]benzoico:



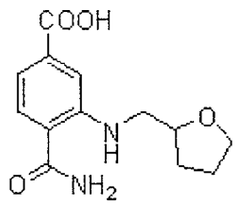
Preparado de conformidad con el método del reactivo de la preparación 39 usando isopropilamina en la etapa 1. MS (EI) para $C_{11}H_{14}N_2O_3$: 223 (MH^+).

[001022] Ácido 4-(aminocarbonil)-3-[(2-metilpropil)amino]benzoico:



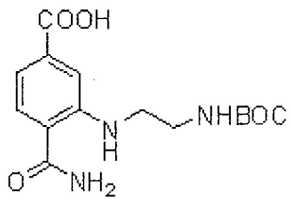
Preparado de conformidad con el método del reactivo de la preparación 39 usando isobutilamina en la etapa 1. MS (EI) para $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[001023] Ácido 4-(aminocarbonil)-3-[(tetrahidrofuran-2-ilmetil)amino]benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 2-tetrahidrofurfurilamina en la etapa 1. MS (EI) para $C_{13}H_{16}N_2O_4$: 265 (MH^+)

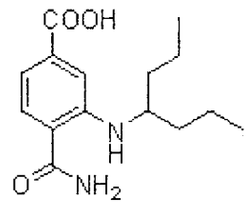
[001024] Ácido 4-(aminocarbonil)-3-{[2-({[(1,1-dimetiletil)oxi]carbonil}amino)etil]amino}benzoico:



1507.

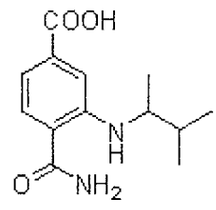
Preparado de conformidad con el método del reactivo de la preparación 39 usando N-Boc-etilendiamina en la etapa 1. MS (EI) para $C_{15}H_{21}N_3O_5$: 324 (MH^+).

[001025] Ácido 4-(aminocarbonil)-3-[(1-propilbutil)amino]benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 4-heptilamina en la etapa 1. MS (EI) para $C_{15}H_{22}N_2O_3$: 279 (MH^+).

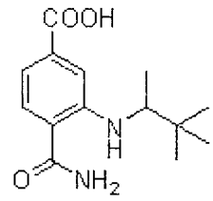
[001026] Ácido 4-(aminocarbonil)-3-[(1,2-dimetilpropil)amino]benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 1,2-dimetilpropilamina en la etapa 1. MS (EI) para $C_{13}H_{18}N_2O_3$: 251 (MH^+).

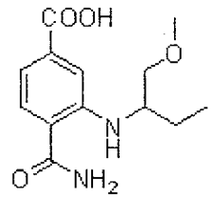
1208

[001027] Ácido 4-(aminocarbonil)-3-[(1,2,2-trimetilpropil)amino]benzoico:



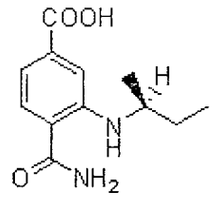
Preparado de conformidad con el método del reactivo de la preparación 39 usando 1,2,2-trimetilpropilamina en la etapa 1. MS (EI) para $C_{14}H_{20}N_2O_3$: 265 (MH^+).

[001028] Ácido 4-(aminocarbonil)-3-({1-[(metiloxi)metil]propil}amino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando 2-amino-1-metioxibutano en la etapa 1. MS (EI) para $C_{13}H_{18}N_2O_4$: 267 (MH^+).

[001029] Ácido 4-(aminocarbonil)-3-{[(1*S*)-1-metilpropil]amino}benzoico:

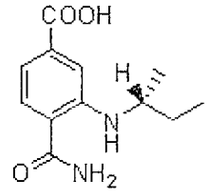


Preparado de conformidad con el método del reactivo de la preparación 39 usando (*S*)-(+)-2-butilamina en la etapa

1209

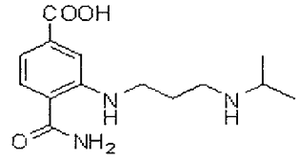
1. MS (EI) para $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[001030] Ácido 4-(aminocarbonil)-3-{[(1*R*)-1-metilpropil]amino}benzoico:



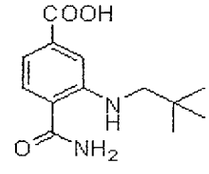
Preparado de conformidad con el método del reactivo de la preparación 39 usando (*R*)-(-)-2-butilamina en la etapa 1. MS (EI) para $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[001031] Ácido 4-(aminocarbonil)-3-({3-[(1-metiletil)amino]propil}amino)benzoico:



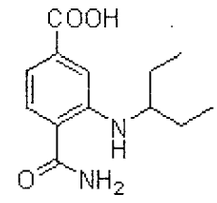
Preparado de conformidad con el método del reactivo de la preparación 39 usando N-isopropil-1,3-propandiamina en la etapa 1. MS (EI) para $C_{14}H_{21}N_3O_3$: 507.2 (MH^+).

[001032] Ácido 4-(aminocarbonil)-3-[(2,2-dimetilpropil)amino]benzoico:



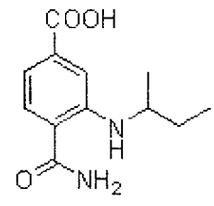
Preparado de conformidad con el método del reactivo de la preparación 39 usando neopentilamina en la etapa 1. MS (EI) para $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001033] Ácido 4-(aminocarbonil)-3-[(1-etilpropil)amino]benzoico:



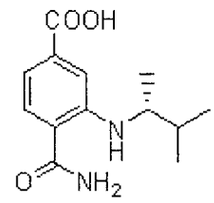
Preparado de conformidad con el método del reactivo de la preparación 39 usando 3-aminopentano en la etapa 1. MS (EI) para $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001034] Ácido 4-(aminocarbonil)-3-[(1-metilpropil)amino]benzoico:



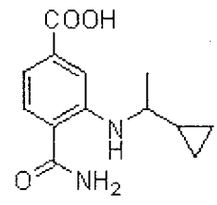
Preparado de conformidad con el método del reactivo de la preparación 39 usando 2-aminobutano en la etapa 1. MS (EI) para $C_{12}H_{16}N_2O_3$: 251 (MH^+).

[001035] Ácido 4-(aminocarbonil)-3-{[(1R)-1,2-dimetilpropil]amino}benzoico:



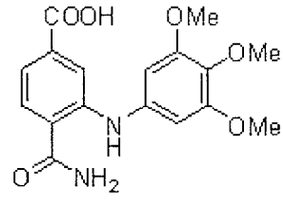
Preparado de conformidad con el método del reactivo de la preparación 39 usando (2R)-3-metilbutan-2-amina en la etapa 1. ^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (s, 1H), 8.30-8.24 (d, 1H), 7.98 (s, 1H), 7.69-7.64 (d, 1H), 7.33 (s, 1H), 7.20 (s, 1H), 7.03-6.98 (d, 1H), 3.46-3.39 (m, 1H), 1.85-1.75 (m, 1H), 1.09-1.04 (d, 3H), 0.97-0.93 (d, 3H), 0.91-0.87 (d, 3H). MS (EI) para $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001036] Ácido 4-(aminocarbonil)-3-[(1-ciclopropiletil)amino]benzoico:



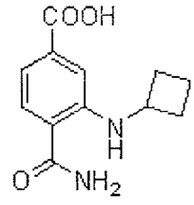
Preparado de conformidad con el método del reactivo de la preparación 39 usando 1-ciclopropiletanamina en la etapa 1. ^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (br s, 1H), 8.14 (d, 1H), 7.96 (s, 1H), 7.65 (d, 1H), 7.33 (s, 1H), 7.18 (d, 1H), 7.01 (dd, 1H), 3.14 (m, 1H), 1.18 (d, 3H), 0.95 (m, 1H), 0.44 (m, 2H), 0.24 (m, 2H). MS (EI) para $C_{13}H_{16}N_2O_3$: 247 (M-H).

[001037] Ácido 4-(aminocarbonil)-3-{[3,4,5-tris(metiloxi)fenil]amino}benzoico:



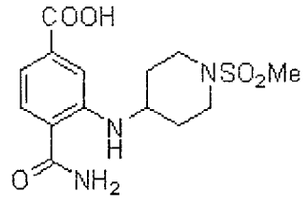
Preparado de conformidad con el método del reactivo de la preparación 39 usando 3,4,5-trimetoxianilina en la etapa 1. MS (EI) para $C_{17}H_{18}N_2O_6$: 345 (M-H).

[001038] Ácido 4-(aminocarbonil)-3-(ciclobutilamino) benzoico:



Preparado de conformidad con el método del reactivo de la preparación 39 usando ciclobutilamina en la etapa 1. MS (EI) para $C_{12}H_{14}N_2O_3$: 233 (M-H).

[001039] Ácido 4-(aminocarbonil)-3-{[1-(metilsulfonil)piperidin-4-il]amino}benzoico:



Preparado de conformidad con el método del reactivo

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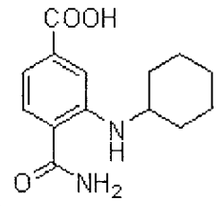
de la preparación 39 usando clorhidrato de metilsulfonil-piperidin-4-ilamina en la etapa 1. MS (EI) para $C_{14}H_{19}N_3O_5S$: 340 (M-H).

PREPARACIÓN DEL REACTIVO 40: ácido 4-(aminocarbonil)-3-(ciclohexilamino)benzoico:



[001040] ETAPA 1: A un recipiente de presión se agregan 3-bromo-4-cianobenzoato de bencilo (150 mg, 0.47 mmol) preparado como se describe en el Ejemplo 11 (etapas 1, 2), carbonato de cesio (310 mg, 0.95 mmol), ciclohexilamina (108 uL, 0.95 mmol), XANTPHOS (27 mg, 0.047 mmol), tris(dibencilidenacetona)dipaladio(0) (21 mg, 0.023 mmol), y dioxano (3 mL). El recipiente se sella y se calienta a 95°C por 4 h. Después del enfriamiento a temperatura ambiente, la mezcla se diluye con acetato de etilo y se lava con agua. La fase acuosa se extrae con acetato de etilo. Los extractos orgánicos combinados se secan sobre sulfato de magnesio, se filtran, y se concentran. El residuo se purifica por cromatografía en columna (10% de acetato de etilo en hexanos) para proporcionar 4-ciano-3-(ciclohexilamino)benzoato de bencilo (118 mg, 0.35 mmol, 75% de rendimiento) como un jarabe amarillo. ^{1}H NMR (400 MHz, $CDCl_3$): 7.45-7.30 (m, 7H),

7.27 (dd, 1H), 5.36 (s, 2H), 4.56 (d, 1H), 3.48-3.38 (m, 1H), 2.08-2.01 (m, 2H), 1.83-1.75 (m, 2H), 1.71-1.64 (m, 1H), 1.46-1.35 (m, 2H), 1.31-1.20 (m, 3H); MS (EI) para $C_{21}H_{22}N_2O_2$: 333 (M-H).

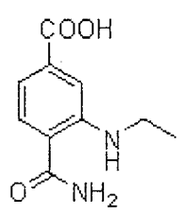
[001041] ETAPA 2: A una solución de 4-ciano-3-(ciclohexilamino)benzoato de bencilo (66.2 mg, 0.198 mmol) en DMSO (2 mL) se agrega carbonato de potasio (27.4 mg, 0.198 mmol) seguido por 30% peróxido de hidrógeno acuoso (5 gotas). La mezcla se agita a temperatura ambiente por 45 min, y después se diluye con acetato de etilo. Se agrega agua y después las capas se separan. La fase acuosa después se extrae con acetato de etilo. Los extractos orgánicos combinados se secan sobre sulfato de magnesio, se filtran, y se concentran. El residuo se purifica por cromatografía en columna (40% de acetato de etilo en hexanos) para proporcionar 4-(aminocarbonil)-3-(ciclohexilamino)benzoato de bencilo (45.0 mg, 0.128 mmol, 64% de rendimiento) como una película amarilla. ^{1}H NMR (400 MHz, $CDCl_3$): 7.81 (d, 1H), 7.46-7.32 (m, 7H), 7.16 (dd, 1H), 5.77 (br s, 2H), 5.36 (s, 2H), 3.48-3.38 (m, 1H), 2.05-1.98 (m, 2H), 1.80-1.72(m, 2H), 1.66-1.59 (m, 1H), 1.45-1.23 (m, 4H); MS (EI) para $C_{21}H_{24}N_2O_3$: 353 (MH^+).

[001042] ETAPA 3: A una solución de 4-(aminocarbonil)-3-

(ciclohexilamino)benzoato de bencilo (45 mg, 0.128 mmol) en metanol (2 mL) se agrega paladio en carbono (10% en peso, Tipo Degussa, 45 mg). La mezcla vigorosamente se agita bajo 1 atm de hidrógeno por 50 minutos. El catalizador se remueve por filtración a través de celite, y lo filtrado se concentra para proporcionar ácido 4-(aminocarbonil)-3-(ciclohexilamino)benzoico (25 mg, 0.095 mmol, 74% de rendimiento) como un polvo amarillo. ^{1}H NMR (400 MHz, CD_3OD): 7.59 (d, 1H), 7.35 (s, 1H), 7.14 (dd, 1H), 3.47-3.39 (m, 1H), 2.05-1.98 (m, 2H), 1.81-1.73 (m, 2H), 1.68-1.60 (m, 1H), 1.52-1.41 (m, 2H), 1.38-1.25 (m, 3H).

[001043] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes reactivos. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

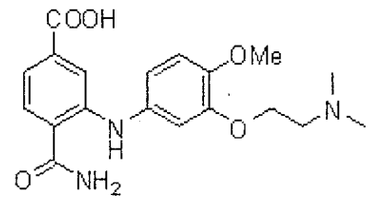
[001044] Ácido 4-(aminocarbonil)-3-(etilamino)benzoico:



Preparado de conformidad con el método de preparación del reactivo 40 usando etilamina en la etapa 1. ^{1}H NMR (400 MHz, DMSO-d_6): 7.99-7.95 (m, 2H), 7.66 (d, 1H), 7.34 (br s, 1H), 7.17 (d, 1H), 7.06 (dd, 1H), 3.19-3.12 (m,

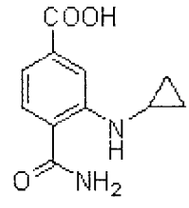
2H), 1.20 (t, 3H); MS (EI) para $C_{10}H_{12}N_2O_3$: 209 (MH^+).

[001045] Ácido 4-(aminocarbonil)-3-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino}benzoico:



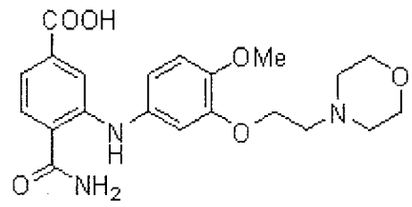
Preparado de conformidad con el método del reactivo de la preparación 40 usando 3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenilamina (Gaster et al. *J. Med. Chem.* 1998, *41(8)*, 1218-1235) en la etapa 1. ^{1}H NMR (400 MHz, CD_3OD): 7.74 (s, 1H), 7.66 (d, 1H), 7.29 (d, 1H), 7.02-6.97 (m, 2H), 6.87 (dd, 1H), 4.34-4.30 (m, 2H), 3.86 (s, 3H), 3.55-3.51 (m, 2H), 2.99 (s, 6H).

[001046] Ácido 4-(aminocarbonil)-3-(ciclopropilamino)benzoico:



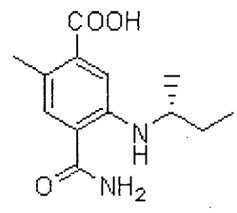
Preparado de conformidad con el método del reactivo de la preparación 40 usando ciclopropilamina en la etapa 1. MS (EI) para $C_{11}H_{12}N_2O_3$: 221 (MH^+).

[001047] Ácido 4-(aminocarbonil-3-[4-metoxi-3-(2-morfolinoetoxi)fenilamino]-benzoico:



Preparado de conformidad con el método del reactivo de la preparación 40 usando 4-metoxi-3-(2-morfolinoetoxi)anilina (Witty et al. *Bioorg. Med. Chem. Lett.* 2006, *16*, 4865-4871) en la etapa 1. MS (EI) para $C_{21}H_{25}N_3O_6$: 414 (M-H).

PREPARACIÓN DEL REACTIVO 41: Ácido (R)-5-(sec-butilamino)-4-(aminocarbonil)-2-metilbenzoico:



[001048] ETAPA 1: A una solución enfriada (0°C) de ácido 4-bromo-2-metilbenzoico (15.1 g, 0.070 mol) en tetrahidrofurano (180 mL) y metanol (45 mL) se agrega lentamente (trimetilsilil)diazometano (2.0M en hexanos, 42 mL, 0.084 mol). La mezcla de reacción se deja calentar a temperatura ambiente y se agita por 1h, tiempo en el cual se concentra in vacuo para proporcionar 4-bromo-2-metilbenzoato de metilo (16

g, 100%) como un aceite amarillo. El residuo se toma en la siguiente etapa sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$): 7.78 (d, 1H), 7.42 (s, 1H), 7.38 (d, 1H), 3.88 (s, 3H), 2.58 (s, 3H). MS (EI) para $C_9H_9BrO_2$: 230 (MH^+).

[001049] ETAPA 2: A una solución de 4-bromo-2-metilbenzoato de metilo (26.6 g, 0.116 mol) en DMF (300 mL) se agrega cianuro de zinc (8.1 g, 0.07 mol) seguido por tetraquis(trifenilfosfina)paladio(0) (6.7 g, 0.0058 mol). La mezcla de reacción se coloca en un baño de aceite a 100°C y se agita por 2 h, tiempo en el cual se filtra a través de un lecho de celite y la torta filtrada se enjuaga con acetato de etilo. Lo filtrado se concentra in vacuo y el residuo se purifica por cromatografía instantánea (10% de acetato de etilo en hexanos) para proporcionar 4-ciano-2-metilbenzoato de metilo (18.1 g, 89%) como un polvo blanco. ^{1}H NMR (400 MHz, $CDCl_3$): 7.97 (d, 1H), 7.55 (s, 1H), 7.53 (br m, 1H), 3.93 (s, 3H), 2.62 (s, 3H).

[001050] ETAPA 3: Una solución de 4-ciano-2-metilbenzoato de metilo (18.1 g, 0.103 mol) en ácido sulfúrico concentrado (130 mL) se enfría a -10°C. Mientras se mantiene esta temperatura interna, se agrega lentamente ácido nítrico humeante (15.6 mL) durante un periodo de 30 min. La mezcla de reacción se agita 2.5 h adicionales a 0°C, tiempo en el cual

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se vierte sobre 1.0 L de hielo y después se divide con acetato de etilo. La capa orgánica se lava con bicarbonato de sodio saturado, salmuera, se seca sobre sulfato de magnesio anhidro, y después se concentra in vacuo. El residuo se tritura con 10% de acetato de etilo/hexanos para proporcionar 4-ciano-2-metil-5-nitrobenzoato de metilo (14.8 g, 65%) como un polvo blanco. El producto del título se aísla como el isómero principal en una mezcla regioisomérica 9:1. ^{1}H NMR (400 MHz, $CDCl_3$), Mayor: 8.85 (s, 1H), 7.81 (s, 1H), 4.00 (s, 3H), 2.77 (s, 3H); Menor: 8.07 (d, 1H), 7.72 (d, 1H), 3.98 (s, 3H), 2.57 (s, 3H). MS (EI) para $C_{10}H_8N_2O_4$: 238 ($M+H_2O$).

[001051] ETAPA 4: A una solución de 4-ciano-2-metil-5-nitrobenzoato de metilo (14.8 g, 0.0672 mol) en ácido acético (250 mL) se agrega polvo de hierro (22.5 g, 0.40 mol). La mezcla de reacción se calienta a 45°C y se agita por 1 h, tiempo en el cual se enfría a temperatura ambiente. La mezcla de reacción se filtra a través de un lecho de celite, y la torta filtrada se enjuaga con acetato de etilo. El volumen de lo filtrado se reduce a la mitad y después se divide entre agua y acetato de etilo. La capa orgánica se lava con 10% de cloruro de litio seguido por bicarbonato de sodio acuoso saturado. La capa orgánica se lava adicionalmente con salmuera, se seca sobre sulfato de magnesio anhidro, se filtra y se concentra. El residuo se tritura con hexanos para

proporcionar 5-amino-4-ciano-2-metilbenzoato de metilo (11.7 g, 91%) como un polvo amarillo brillante. ^{1}H NMR (400 MHz, $CDCl_3$): 7.28 (s, 1H), 7.26 (s, 1H), 4.35 (br s, 2H), 3.89 (s, 3H), 2.43 (s, 3H). MS (EI) para $C_{10}H_{10}N_2O_2$: 191 (MH^+).

[001052] ETAPA 5: A una solución de 5-amino-4-ciano-2-metilbenzoato de metilo (5.0 g, 0.0262 mol) en THF (100 mL) se agrega yoduro de cobre (5.0 g, 0.0262 mol), diyodometano (10.5 mL, 0.131 mol) y nitrito de isoamilo (10.5 mL, 0.0786 mol). La mezcla de reacción se calienta a 85°C y se agita por 3 h, tiempo en el cual se enfría a temperatura ambiente. La mezcla heterogénea se filtra a través de un lecho de celite, y la torta filtrada se enjuaga con acetato de etilo. Lo filtrado se concentra y el residuo se purifica por cromatografía instantánea (100% hexanos a 2% éter de dietilo en hexanos), después se tritura con hexanos para proporcionar 4-ciano-5-yodo-2-metilbenzoato de metilo (3.7 g, 76%) como un polvo blanco. ^{1}H NMR (400 MHz, $CDCl_3$): 8.39 (s, 1H), 7.50 (s, 1H), 3.94 (s, 3H), 2.56 (s, 3H).

[001053] ETAPA 6: A una solución de 4-ciano-5-yodo-2-metilbenzoato de metilo (500 mg, 1.66 mmol) en 1,4-dioxano (25 mL) se agrega 9,9-dimetil-4,5-(bis(difenilfosfino)xanteno (96 mg, 0.166 mmol), tris(dibencilidenacetona)-dipaladio (76 mg, 0.083 mmol), carbonato de cesio (1.08 g, 3.32 mmol) y

(R)-butan-2-amina (506 µL, 4.98 mmol). La mezcla de reacción se calienta a 95°C y se agita por 16 h, tiempo en el cual se enfría a temperatura ambiente. La mezcla heterogénea se filtra a través de un lecho de celite, y la torta filtrada se enjuaga con acetato de etilo. Lo filtrado se concentra, y el residuo se purifica por cromatografía instantánea (100% hexanos a 5% de acetato de etilo en hexanos) para proporcionar 5-(sec-butilamino)-4-ciano-2-metilbenzoato de (R)-metilo (300 mg, 73%) como un aceite amarillo brillante. MS (EI) para $C_{14}H_{18}N_2O_2$: 247 (MH^+).

[001054] ETAPA 7: A una solución enfriada (0°C) de 5-(sec-butilamino)-4-ciano-2-metilbenzoato de (R)-metilo (300 mg, 1.22 mmol) en DMSO (1.5 mL) se agrega 30% solución de peróxido de hidrógeno (258 µL, 8.96 mmol) y carbonato de potasio (56 mg, 0.402 mmol). La mezcla de reacción se deja calentar a temperatura ambiente y se agita por 4 h, tiempo en el cual se concentra in vacuo. El residuo se purifica por cromatografía instantánea (100% hexanos a 10% de acetato de etilo en hexanos) para proporcionar 5-(sec-butilamino)-4-(aminocarbonil)-2-metilbenzoato de (R)-metilo (300 mg, 93%) como cristales amarillos. MS (EI) para $C_{14}H_{20}N_2O_3$: 265 (MH^+).

[001055] ETAPA 8: A una solución de 5-(sec-butilamino)-4-(aminocarbonil)-2-metilbenzoato de (R)-metilo (300 mg, 1.13

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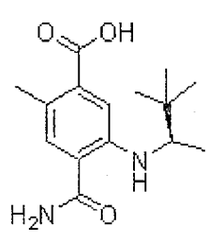
mmol) en metanol (2.0 mL) y diclorometano (1.0 mL) se agrega solución acuosa de hidróxido de sodio 2.0M (2.0 mL, 4.0 mmol). La mezcla de reacción se calienta a 45°C y se agita por 2 h, tiempo en el cual se enfría a temperatura ambiente y todos los volátiles se remueven por evaporación rotatoria. A la solución residual lentamente se agrega ácido clorhídrico acuoso 1.0M hasta pH < 2. Lo precipitado amarillo se recolecta por filtración y se lava con agua para proporcionar ácido (R)-5-(sec-butilamino)-4-(aminocarbonil)-2-metilbenzoico (210 mg, 65%). MS (EI) para $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001056] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes reactivos. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[001057] Ácido (R)-4-(aminocarbonil)-5-(3,3-dimetilbutan-2-ilamino)-2-metilbenzoico:

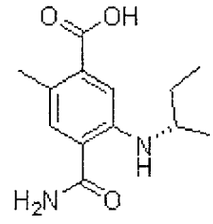


Sintetizado de conformidad con el método del reactivo de la preparación 41 usando (R)-3,3-dimetilbutan-2-

1123

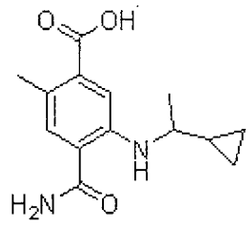
amina en la etapa 6. MS (EI) para $C_{15}H_{22}N_2O_3$: 279 (MH^+).

[001058] Ácido (S)-5-(sec-butilamino)-4-(aminocarbonil)-2-metilbenzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 usando (S)-butan-2-amina en la etapa 6. MS (EI) para $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001059] Ácido 4-(aminocarbonil)-5-(1-ciclopropiletilamino)-2-metilbenzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 usando 1-ciclopropiletanamina en la etapa 6. MS (EI) para $C_{14}H_{18}N_2O_3$: 263 (MH^+).

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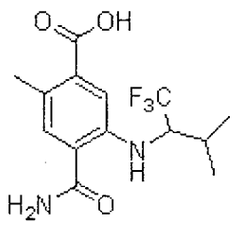
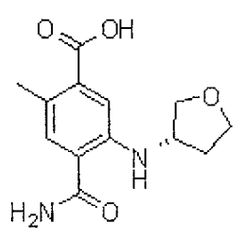
[001060] Ácido 4-(aminocarbonil)-2-metil-5-(1,1,1-trifluoro-3-metilbutan-2-ilamino)benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 usando 1,1,1-trifluoro-3-metilbutan-2-amina en la etapa 6. ^{1}H NMR (400 MHz, CD_3OD): 7.53 (s, 1H), 7.37 (s, 1H), 4.12-4.05 (m, 1H), 2.45 (s, 3H), 2.30-2.22 (m, 1H), 1.07 (d, 3H), 1.02 (d, 3H); MS (EI) para $C_{14}H_{17}F_3N_2O_3$: 319 (MH^+).

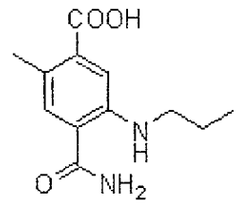
[001061] Ácido (S)-4-(aminocarbonil)-2-metil-5-(tetrahidrofuran-3-ilamino)benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 usando (S)-tetrahidrofuran-3-amina en la etapa 6. ^{1}H NMR (400 MHz, d_6-DMSO): 12.95 (br s, 1H), 7.99 (d, 1H), 7.94 (br s, 1H), 7.53 (s, 1H), 7.36 (br s, 1H), 7.06 (br s, 1H), 4.11-4.04 (m, 1H), 3.90-3.70 (m, 1H), 3.50 (dd, 1H), 2.35 (s, 3H), 2.27-2.17 (m, 1H), 1.75-1.66 (m,

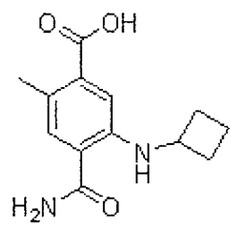
1H); MS (EI) para $C_{13}H_{16}N_2O_4$: 265 (MH^+).

[001062] Ácido 4-(aminocarbonil)-2-metil-5-(propilamino)benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 usando propan-1-amina en la etapa 6. ^{1}HNMR (400 MHz, CD_3OD): 7.45 (s, 1H), 7.21 (s, 1H), 3.12 (t, 2H), 2.42 (s, 3H), 1.69 (q, 2H), 1.03 (t, 3H). MS (EI) para $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[001063] Ácido 4-(aminocarbonil)-5-(ciclobutilamino)-2-metilbenzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 usando ciclobutanamina en la etapa 6. ^{1}HNMR (400 MHz, CD_3OD): 7.43 (s, 1H), 7.04 (s, 1H), 3.95 (m, 1H), 2.46 (m, 2H), 2.40 (s, 3H), 1.85 (m, 4H). MS (EI) para $C_{13}H_{16}N_2O_3$: 249 (MH^+).

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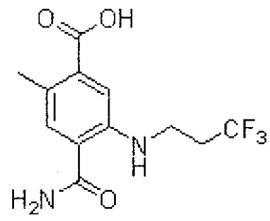
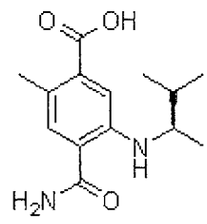
[001064] Ácido 4-(aminocarbonil)-2-metil-5-(3,3,3-trifluoropropilamino)benzoico:



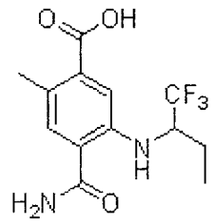
Sintetizado de conformidad con el método del reactivo de la preparación 41 usando 3,3,3-trifluoropropan-1-amina en la etapa 6. MS (EI) para $C_{12}H_{13}F_3N_2O_3$: 291 (MH^+).

[001065] Ácido (R)-4-(aminocarbonil)-2-metil-5-(3-metilbutan-2-ilamino)benzoico:



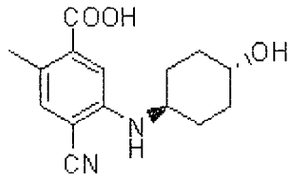
Sintetizado de conformidad con el método del reactivo de la preparación 41 usando (R)-3-metilbutan-2-amina en la etapa 6. MS (EI) para $C_{14}H_{20}N_2O_3$: 265 (MH^+).

[001066] Ácido 4-(aminocarbonil)-2-metil-5-(1,1,1-trifluorobutan-2-ilamino)benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 usando sal clorhidrato de 1,1,1 trifluorobutano-2-amina (sintetizado en la preparación del reactivo 53) en la etapa 6. MS (EI) para $C_{13}H_{15}F_3N_2O_3$: 305 (MH^+).

[001067] Ácido 4-ciano-5-(trans-4-hidroxiciclohexilamino)-2-metilbenzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 usando trans-4-(terc-butilodimetilsililoxi)ciclohexanamina en la etapa 6 seguido por desprotección del grupo protector sililo como se describe por Greene, T.W. y Wuts, P.G.M, *Protective Groups en Organic Synthesis* 1999, John Wiley y Sons, Inc., New York, NY, después de la omisión de la etapa 7. MS (EI) para $C_{15}H_{18}N_2O_3$: 273 (M-H).

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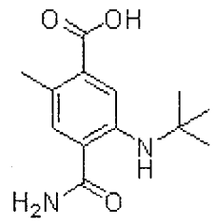
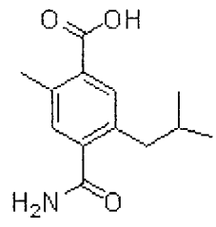
[001068] Ácido 4-(aminocarbonil)-5-[(1,1-dimetiletil)amino]-2-metilbenzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 usando 1,1-dimetiletilamina en la etapa 6. MS (EI) para $C_{13}H_{18}N_2O_3$: 251 (MH^+).

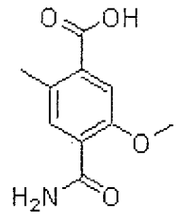
[001069] Ácido 4-(aminocarbonil)-2-metil-5-(2-metilpropil)benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 usando ácido isobutilborónico en la etapa 6. ^1H NMR (400 MHz, CD_3OD): 7.84 (s,1H), 7.39 (s,1H), 2.80-2.78 (d, 2H), 2.66 (s, 3H), 2.03-1.99 (m, 1H), 1.00-0.99 (d, 6H). MS (EI) para $C_{13}H_{17}NO_3$: 236 (M-H).

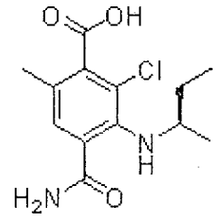
1229

[001070] Ácido 4-(aminocarbonil)-2-metil-5-(metiloxi)benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 reemplazando la etapa 6 con la conversión de 4-ciano-5-yodo-2-metilbenzoato de metilo a 4-ciano-5-hidroxi-2-metilbenzoato de metilo de conformidad con el método descrito en Chemical & Pharmaceutical Bulletin (2007), 55(9), 1361-1364 seguido por alquilación de fenol con yodometano después de proceder con las etapas 7 y 8. ^{1}H NMR (400 MHz, DMSO-d_6): 7.69 (b, 1H), 7.63 (b, 2H), 7.45 (s, 1H), 3.88 (s, 3H), 2.44 (s, 3H); MS (EI) para $C_{10}H_{11}NO_4$: 210 (MH^+).

[001071] Ácido 4-(aminocarbonil)-2-cloro-6-metil-3-{[(1R)-1-metilpropil]amino}benzoico:

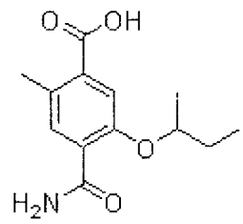


Sintetizado de conformidad con el método del reactivo de la preparación 41 usando (R)-1-metilpropilamina en la etapa 6 seguido por cloración de la anilina resultante

1230

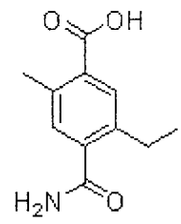
usando N-clorosuccinimida después de proceder con las etapas 7 y 8. MS (EI) para $C_{13}H_{17}N_2O_3Cl$: 285 (MH^+).

[001072] Ácido 4-(aminocarbonil)-2-metil-5-[(1-metilpropil)oxi]benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 reemplazando la etapa 6 con la conversión de 4-ciano-5-yodo-2-metilbenzoato de metilo a 4-ciano-5-hidroxi-2-metilbenzoato de metilo de conformidad con el método descrito en Chemical & Pharmaceutical Bulletin (2007), 55(9), 1361-1364 seguido por alquilación de fenol con 2-bromobutano después de proceder con las etapas 7 y 8. MS (EI) para $C_{13}H_{17}NO_4$: 252 (MH^+).

[001073] Ácido 4-(aminocarbonil)-5-etil-2-metilbenzoico:

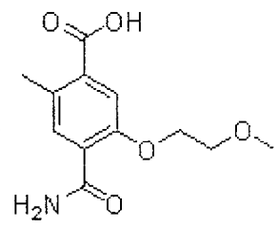


Sintetizado de conformidad con el método del reactivo de la preparación 41 usando cloruro de etilmagnesio

1231

en la etapa 6 de conformidad con el método descrito en Synlett 1996, 5, 473-474 después de proceder con las etapas 7 y 8. ^{1}H NMR (400 MHz, DMSO-d_6): 7.84 (s, 1H), 7.69 (s, 1H), 7.59 (s, 1H), 7.23 (s, 1H), 3.00 (s, 3H), 2.71 (q, 2H), 1.14 (t, 3H). MS (EI) para $C_{11}H_{13}NO_3$: 208 (MH^+).

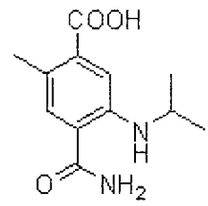
[001074] Ácido 4-(aminocarbonil)-2-metil-5-{[2-(metiloxi)etil]oxi}benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 41 reemplazando la etapa 6 con la conversión de 4-ciano-5-yodo-2-metilbenzoato metilo a 4-ciano-5-hidroxi-2-metilbenzoato de metilo de conformidad con el método descrito en Chemical & Pharmaceutical Bulletin (2007), 55(9), 1361-1364 seguido por alquilación de fenol con 2-bromoetil metil éter después de proceder con las etapas 7 y 8. MS (EI) para $C_{12}H_{15}NO_5$: 254 (MH^+).

1232.

PREPARACIÓN DEL REACTIVO 42: ácido 4-(aminocarbonil)-5-(isopropilamino)-2-metilbenzoico:



[001075] ETAPA 1: Se disuelve 5-amino-4-ciano-2-metilbenzoato de metilo (sintetizado en la preparación del reactivo 41, etapa 4) (240 mg, 1.26 mmol) en 1,2-dicloroetano (7 mL) y se trata con ácido trifluoroacético (0.6 mL, 7.57 mmol), acetona (0.28 mL, 3.79 mmol), y triacetoxiborohidruro de sodio (802 mg, 3.78 mmol) a 45 °C por 20 min. La mezcla de reacción se enfría a temperatura ambiente y se apaga con bicarbonato de sodio acuoso saturado y se divide con diclorometano. La porción acuosa se extrae con diclorometano. La porción orgánica combinada se lava con salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar un aceite amarillo el cual se purifica por cromatografía en columna (gel de sílice, 10% diclorometano en hexanos) para proporcionar 4-ciano-5-(isopropilamino)-2-metilbenzoato de metilo (224 mg, 0.96 mmol, 76% de rendimiento) como un aceite amarillo pálido. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.16 (s, 1H), 4.28 (d, 1H), 3.91 (s, 3H), 3.77-3.74 (m, 1H), 2.40 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H); MS (EI) para $C_{14}H_{16}N_2O_2$: 233 (MH^+).

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[001076] ETAPA 2: Se disuelve 4-ciano-5-(isopropilamino)-2-metilbenzoato de metilo (224 mg, 0.96 mmol) en DMSO (2 mL) y se enfría en un baño de agua fría. Se agrega 30% de peróxido de hidrógeno acuoso (0.2 mL) y carbonato de potasio (42.6 mg, 0.31 mmol), y la mezcla se agita a temperatura ambiente por 1 h. La mezcla de reacción se divide entre acetato de etilo y 10% de cloruro de litio acuoso. La porción acuosa se extrae con acetato de etilo. La porción orgánica combinada se seca sobre sulfato de sodio, después se filtra y se concentra a un aceite amarillo el cual se purifica por cromatografía en columna (gel de sílice, 15-30% de acetato de etilo en hexanos para proporcionar 4-aminocarbonil-5-(isopropilamino)-2-metilbenzoato de metilo (202 mg, 0.81 mmol, 83% de rendimiento) como un aceite amarillo. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, 1H), 7.26 (d, 1H), 7.24-7.22 (m, 2H), 5.70 (br s, 1H), 3.90 (s, 3H), 3.75-3.68 (m, 1H), 2.42 (s, 3H), 1.26-1.24 (m, 6H); MS (EI) para $C_{13}H_{18}N_2O_3$: 251 (MH^+).

[001077] ETAPA 3: Se disuelve 4-aminocarbonil-5-(isopropilamino)-2-metilbenzoato de metilo (202 mg, 0.81 mmol) en metanol (3 mL) y se trata con hidróxido de sodio 1M (3 mL, 3 mmol) a 45 °C por 1.5 h. La mezcla de reacción se enfría a temperatura ambiente y se concentra para proporcionar un residuo acuoso que se acidifica con ácido clorhídrico 1N a pH ~3. Lo precipitado se recolecta por

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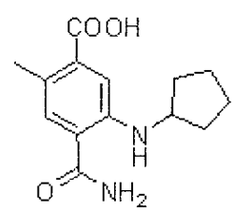
filtración, se lava con agua y se seca para proporcionar ácido 4-aminocarbonil-5-(isopropilamino)-2-metilbenzoico (99.5 mg, 0.42 mmol, 52% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.95 (br s, 1H), 7.90 (br s, 1H), 7.72 (d, 1H), 7.49 (s, 1H), 7.28 (br s, 1H), 7.06 (s, 1H), 3.64-3.54 (m, 1H), 2.33 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H); MS (EI) para $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[001078] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos, se preparan los siguientes reactivos de partida. En casos en donde se usa un aldehído como el sustrato por (etapa 1) ácido acético, generalmente se usa en lugar de ácido trifluoroacético. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

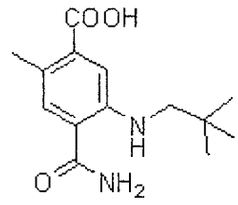
[001079] Ácido 4-(aminocarbonil)-5-(ciclopentilamino)-2-metilbenzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 42 usando ciclopentanona en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.90 (br s, 1H), 7.92 (br s, 1H), 7.87 (d, 1H), 7.49 (s, 1H), 7.28 (br s, 1H), 7.08

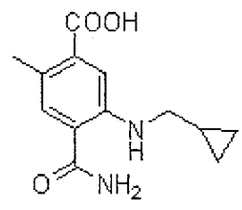
(s, 1H), 3.78-3.73 (m, 1H), 2.34 (s, 3H), 2.02-1.90 (m, 2H), 1.70-1.53 (m, 4H), 1.43-1.33 (m, 2H); MS (EI) para $C_{14}H_{18}N_2O_3$: 263 (MH^+).

[001080] Ácido 4-(aminocarbonil)-2-metil-5-(neopentilamino)benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 42 usando pivalaldehído en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.94 (br s, 1H), 8.12 (t, 1H), 7.93 (br s, 1H), 7.51 (s, 1H), 7.28 (br s, 1H), 7.04 (s, 1H), 2.87 (d, 2H), 2.34 (s, 3H), 0.97 (m, 9H); MS (EI) para $C_{14}H_{20}N_2O_3$: 265 (MH^+).

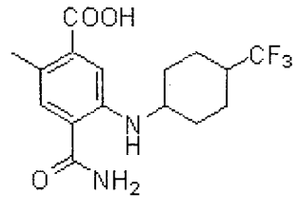
[001081] Ácido 4-(aminocarbonil)-5-(ciclopropilmetilamino)-2-metilbenzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 42 usando ciclopropancarbaldehído

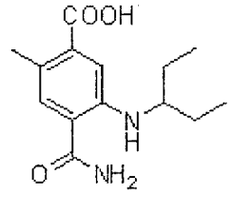
en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.89 (br s, 1H), 7.92 (br s, 1H), 7.85 (t, 1H), 7.50 (s, 1H), 7.29 (br s, 1H), 7.07 (s, 1H), 2.95 (t, 2H), 2.35 (t, 3H), 1.07-1.04 (m, 1H), 0.52-0.47 (m, 2H), 0.25-0.21 (m, 2H); MS (EI) para $C_{13}H_{16}N_2O_3$: 249 (MH^+).

[001082] Ácido 4-aminocarbonil-2-metil-5-[4-(trifluorometil)ciclohexilamino] benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 42 usando 4-(trifluorometil)ciclohexanona en la etapa 1. MS (EI) para $C_{16}H_{19}F_3N_2O_3$: 345 (MH^+).

[001083] Ácido 4-aminocarbonil-2-metil-5-(pentan-3-ilamino)benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 42 usando pentan-3-ona en la etapa 1. ^{1}H NMR (400 MHz, CD_3OD): 7.44 (s, 1H), 7.22 (s, 1H), 3.35-3.29 (m, 1H enterrado), 2.41 (s, 3H), 1.68-1.46 (m, 4H), 0.94

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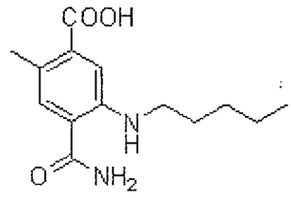
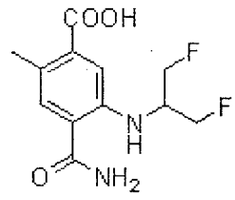
(t, 6H); MS (EI) para $C_{14}H_{20}N_2O_3$: 265 (MH^+).

[001084] Ácido 4-aminocarbonil-2-metil-5-(pentilamino)benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 42 usando *n*-pentanal en la etapa 1. ^{1}H NMR (400 MHz, CD_3OD): 7.45 (s, 1H), 7.20 (s, 1H), 3.15 (t, 2H), 2.42 (s, 3H), 1.70-1.62 (m, 2H), 1.47-1.34 (m, 4H), 0.94 (t, 6H).

[001085] Ácido 4-aminocarbonil-5-(1,3-difluoropropan-2-ilamino)-2-metilbenzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 42 usando 1,3-difluoropropanona en la etapa 1. ^{1}H NMR (400 MHz, CD_3OD): 7.50 (s, 1H), 7.34 (s, 1H), 4.67-4.58 (m, 2H), 4.56-4.46 (m, 2H), 4.11-3.97 (m, 1H), 2.42 (s, 3H); MS (EI) para $C_{12}H_{14}F_2N_2O_3$: 265 (MH^+).

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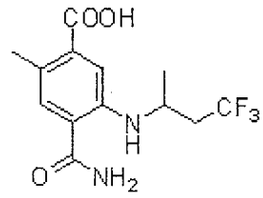
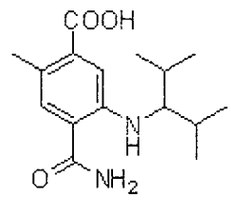
[001086] Ácido 4-(aminocarbonil)-2-metil-5-[(3,3,3-trifluoro-1-metilpropil)amino]-benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 42 usando 4,4,4-trifluorobutan-2-ona en la etapa 1. MS (EI) para $C_{13}H_{15}F_3N_2O_3$: 305 (MH^+).

[001087] Ácido 4-(aminocarbonil)-2-metil-5-{[2-metil-1-(1-metiletil)propil]amino}-benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 42 usando 2,4-dimetilpentan-3-ona en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.85 (br s, 1H), 8.05-7.99 (d, 1H), 7.90 (br. s, 1H), 7.47 (s, 1H), 7.26 (br s, 1H), 7.18 (s, 1H), 3.09-3.00 (m, 1H), 2.31 (s, 3H), 1.89-1.77 (m, 2H), 0.91-0.79 (m, 12H); MS (EI) para $C_{16}H_{24}N_2O_3$: 293 (MH^+).

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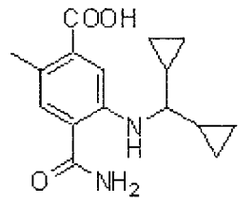
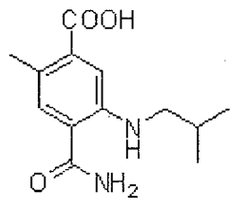
[001088] Ácido 4-(aminocarbonil)-5-[(diciclopropilmetil)amino]-2-metilbenzoico:



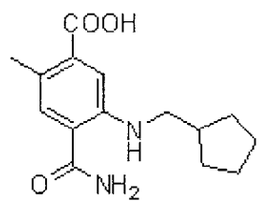
Sintetizado de conformidad con el método del reactivo de la preparación 42 usando diciclopropilmetanona en la etapa 1. MS (EI) para $C_{16}H_{20}N_2O_3$: 293 (MH^+).

[001089] Ácido 4-(aminocarbonil)-2-metil-5-[(2-metilpropil)amino]benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 42 usando isobutiraldehído en la etapa 1. MS (EI) para $C_{13}H_{18}N_2O_3$: 251 (MH^+).

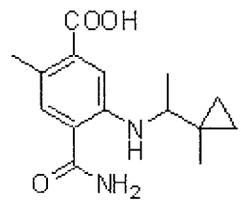
[001090] Ácido 4-(aminocarbonil)-5-[(ciclopentilmetil)amino]-2-metilbenzoico:



Sintetizado de conformidad con el método del

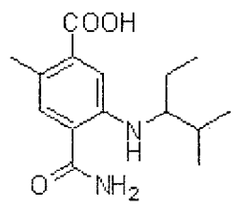
reactivo de la preparación 42 usando ciclopentancarboxaldehído en la etapa 1. MS (EI) para $C_{15}H_{20}N_2O_3$: 277 (MH^+).

[001091] Ácido 4-(aminocarbonil)-2-metil-5-{[1-(1-metilciclopropil)-etil]amino}benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 42 usando 1-metilciclopropil cetona de metilo en la etapa 1. MS (EI) para $C_{15}H_{20}N_2O_3$: 277 (MH^+).

[001092] Ácido 4-aminocarbonil-2-metil-5-(2-metilpentan-3-ilamino)benzoico:



Preparado de conformidad con el método del reactivo de la preparación 42 usando 2-metilpentan-3-ona en la etapa 1.

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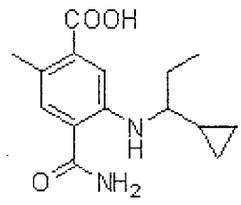
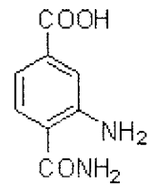
[001093] Ácido 4-aminocarbonil-5-(1-ciclopropilpropilamino)-2-metilbenzoico:



Preparado de conformidad con el método del reactivo de la preparación 42 usando 1-ciclopropilpropan-1-ona en la etapa 1.

PREPARACIÓN DEL REACTIVO 43: Ácido 3-amino-4-(aminocarbonil)benzoico:

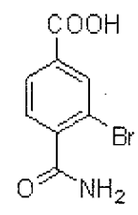


[001094] ETAPA 1: Se recupera ácido 4-(metoxicarbonil)-3-nitrobenzoico (100 g, 0.44 mol) en amoníaco acuoso concentrado (37% en peso, 500 mL), y la solución amarilla resultante se deja agitar a temperatura ambiente durante 12 horas. La solución después se reduce en volumen a aproximadamente 300 mL por evaporación rotatoria, y la solución se acidifica a pH 2 por adición en porciones de ácido clorhídrico acuoso concentrado. Lo precipitado espeso se recolecta por filtración y se seca *in vacuo* para proporcionar 4-(aminocarbonil)-3-nitrobenzoico ácido (51 g,

60% de rendimiento). ^{1}H-NMR (d_6-DMSO): 8.42 (d, 1H), 8.27 (dd, 1H), 8.26 (br s, 1H), 7.86 (br s, 1H), 7.76 (d, 1H).

[001095] ETAPA 2: Se suspende ácido 4-(aminocarbonil)-3-nitrobenzoico (2.00 g, 9.52 mmol) en agua (50 ml) y se agrega bicarbonato de sodio (0.80 g, 9.52 mmol). La solución resultante se hidrogena en la presencia de 10% de paladio en carbono (300 mg) a 30 psi por 16 horas. La mezcla después se filtra a través de Celite. Lo filtrado se acidifica por adición de ácido clorhídrico concentrado y lo sólido resultante se recolecta por filtración y se seca in vacuo para proporcionar ácido 3-amino-4-(aminocarbonil)benzoico (1.70 g, 99% de rendimiento). MS (EI) para $C_8H_8N_2O_3$: 179 (M-H).

PREPARACIÓN DEL REACTIVO 44: ácido 3-bromo-4-(aminocarbonil)benzoico:



[001096] ETAPA 1: Se disuelve 3-bromo-4-cianobenzoato de metilo (preparado como se describe en Wang, G. T. *et al. Bioorg. Med. Chem. Lett.* 2005, *15(1)*, 153) (130 mg, 0.54 mmol) en DMSO (1.5 mL) y se enfría en un baño de agua fría.

Se agregan 30% de peróxido de hidrógeno acuoso (0.1 mL) y carbonato de potasio (23.9.0 mg, 0.17 mmol) y la mezcla se agita a temperatura ambiente por 18.5 h. La mezcla de reacción se divide entre acetato de etilo y 10% de cloruro de litio acuoso. La porción acuosa se extrae con acetato de etilo. Las porciones orgánicas combinadas se secan sobre sulfato de sodio, se filtran y se concentran para proporcionar 3-bromo-4-(aminocarbonil)benzoato de metilo (rendimiento cuantitativo) como un aceite amarillo. GCMS por $C_9H_8BrNO_3$: 257, 259 (M^+).

[001097] ETAPA 2: Se disuelve 3-bromo-4-(aminocarbonil)benzoato de metilo (0.54 mmol) en metanol (1 mL) y se trata con hidróxido de sodio acuoso 1M (1 mL) a 45°C por 3 h. La mezcla de reacción se enfría a temperatura ambiente y se concentra para proporcionar un residuo acuoso que se acidifica con ácido clorhídrico acuoso 1N a pH ~3. Lo precipitado se recolecta por filtración, se lava con agua, y se seca para proporcionar ácido 3-bromo-4-(aminocarbonil)benzoico (69.4 mg, 0.28 mmol, 53% total). ^{1}H NMR (400 MHz, d_6-DMSO): 13.47 (br s, 1H), 8.08 (dd, 1H), 8.00 (br s, 1H), 7.94 (dd, 1H), 7.73 (br s, 1H), 7.51 (d, 1H); MS (EI) para $C_8H_6BrNO_3$: 242, 244(M-H).

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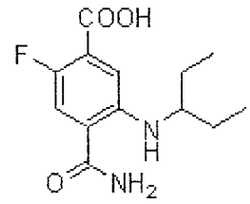
PREPARACIÓN DEL REACTIVO 45: ácido 4-(aminocarbonil)-2-fluoro-5-(pentan-3-ilamino)benzoico:



[001098] ETAPA 1: A una solución de ácido 4-bromo-2-fluorobenzoico (2.0 g, 9.1 mmol) en THF (24 mL) y metanol (6 mL) a 0°C se agrega una solución de (trimetilsilil)diazometano en hexanos (2.0 M, 5.46 mL, 10.9 mmol). La solución amarilla se deja calentar gradualmente a temperatura ambiente durante 1 h. Los materiales volátiles se remueven y el residuo se trata con ácido clorhídrico acuoso (1 M). La mezcla acuosa se extrae con acetato de etilo. El extracto orgánico se seca sobre sulfato de magnesio, se filtra, y se concentra para proporcionar 4-bromo-2-fluorobenzoato de metilo crudo (2.7 g, rendimiento cuantitativo). Este material se usa en la etapa subsecuente sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$): 7.85-7.81 (m, 1H), 7.38-7.33 (m, 2H), 3.93 (s, 3H); MS (EI) para $C_8H_6BrFO_2$: 232, 234 (MH^+).

[001099] ETAPA 2: A una solución de 4-bromo-2-fluorobenzoato de metilo (9.1 mmol) en DMF (50 mL) se agrega cianuro de zinc (641 mg, 5.5 mmol) seguido por

tetraquis(trifenilfosfina)paladio(0) (1.05 g, 0.91 mmol). La mezcla se calienta a 100 °C y se agita por 3 h. En este punto, se agrega tetraquis(trifenilfosfina)-paladio(0) (500 mg, 0.43 mmol) adicional. La mezcla se agita por 30 min adicionales y después se enfría a temperatura ambiente. Se agregan agua y acetato de etilo, y los sólidos insolubles se remueven por filtración a través de celite. Las capas después se separan. La fase acuosa se extrae con acetato de etilo. Los extractos orgánicos se combinan, se lavan con 10% de cloruro de litio acuoso, se secan sobre sulfato de magnesio, se filtran y se concentran. El residuo se purifica por cromatografía en columna (10% de acetato de etilo en hexanos) para proporcionar 4-ciano-2-fluorobenzoato de metilo (1.36 g, 7.6 mmol, 84% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 8.06 (dd, 1H), 7.53 (dd, 1H), 7.47 (dd, 1H), 3.98 (s, 3H); MS (EI) para $C_9H_6FNO_2$: 179 (M^+).

[001100] ETAPA 3: A un matraz que contiene 4-ciano-2-fluorobenzoato de metilo (1.61 g, 9.0 mmol) se agrega ácido nítrico humeante (15 mL) seguido por ácido sulfúrico concentrado (4 mL). La mezcla se calienta a 45 °C por 15 h antes de enfriarse a temperatura ambiente. La solución después se vierte en agua helada y la mezcla resultante se extrae dos veces con acetato de etilo. Los extractos orgánicos combinados se lavan con solución saturada de

bicarbonato de sodio, se secan sobre sulfato de magnesio, se filtran, y se concentran para proporcionar 4-ciano-2-fluoro-5-nitrobenzoato de metilo (859 mg, 3.83 mmol, 43% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 8.95 (d, 1H), 7.72 (d, 1H), 4.04 (s, 3H); MS (EI) para $C_9H_5FN_2O_4$: 224 (M^+).

[001101] ETAPA 4: A una solución de 4-ciano-2-fluoro-5-nitrobenzoato de metilo (785 mg, 3.5 mmol) en ácido acético (15 mL) se agrega polvo de hierro (1.17 g, 21.0 mmol). La mezcla se agita vigorosamente a temperatura ambiente por 2 h. Los sólidos insolubles después se remueven por filtración a través de celite. Se agrega agua a lo filtrado y la mezcla acuosa se extrae con acetato de etilo. El extracto orgánico se lava con bicarbonato de sodio acuoso saturado, se seca sobre sulfato de magnesio, se filtra, y se concentra. El residuo se purifica por cromatografía en columna (30% de acetato de etilo en hexanos) para proporcionar 5-amino-4-ciano-2-fluorobenzoato de metilo (463 mg, 2.38 mmol, 68% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 7.30 (d, 1H), 7.19 (d, 1H), 4.41 (br s, 2H), 3.94 (s, 3H); MS (EI) para $C_9H_7FN_2O_2$: 193 (M-H).

[001102] ETAPA 5: A una solución de 5-amino-4-ciano-2-fluorobenzoato de metilo (437 mg, 2.2 mmol) en THF (13 mL) se agrega yoduro de cobre(I) (419 mg, 2.2 mmol), diyodometano

(890 uL, 11 mmol), y nitrito de isoamilo (890 uL, 6.6 mmol). La solución se calienta a reflujo por 4 h y después se deja enfría a temperatura ambiente. Después de la dilución con acetato de etilo, se agrega agua y la mezcla se filtra a través de celite. Lo filtrado bifásico se divide. La fase orgánica se seca sobre sulfato de magnesio, se filtra, y se concentra. El residuo después se somete a cromatografía en columna para proporcionar 4-ciano-2-fluoro-5-yodobenzoato de metilo impuro (452 mg, ~63% de pureza, ~0.93 mmol). El material restante consiste principalmente de 4-ciano-2-fluorobenzoato de metilo y se lleva hacia adelante en la reacción subsecuente sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$): 8.44 (d, 1H), 7.43 (d, 1H), 3.97 (s, 3H); MS (EI) para $C_9H_5FINO_2$: 305 (M^+).

[001103] ETAPA 6: A un recipiente de presión se agregan el anterior 4-ciano-2-fluoro-5-yodobenzoato de metilo (~0.93 mmol), carbonato de cesio (606 mg, 1.86 mmol), pentan-3-amina (325 uL, 2.79 mmol), XANTPHOS (54 mg, 0.093 mmol), tris(dibencilidenacetona)dipaladio(0) (43 mg, 0.047 mmol), y dioxano (4 mL). El recipiente se sella y se calienta a 95 °C por ~17 h. Después del enfriamiento a temperatura ambiente, la mezcla se filtra a través de celite, y la torta filtrada se enjuaga con acetato de etilo. Lo filtrado después se concentra. El residuo se somete a cromatografía en columna

(10% de acetato de etilo en hexanos). Se recolecta el eluyente que contiene el proyecto deseado y se concentra para proporcionar un residuo deseado. Este residuo se disuelve en DMSO (6 mL) y se trata con carbonato de potasio (111 mg, 0.8 mmol) y 30% de peróxido de hidrógeno acuoso (150 uL). Después de la agitación a temperatura ambiente por 30 min, la mezcla se diluye con acetato de etilo. La solución orgánica se lava con una mezcla de agua y 10% de cloruro de litio acuoso. El lavado acuoso se extrae con acetato de etilo. Los extractos orgánicos combinados se lavan con 10% de cloruro de litio acuoso, se secan sobre sulfato de magnesio, se filtran, y se concentran. El residuo se purifica por cromatografía de gradiente en columna (30% de acetato de etilo en hexanos a 50% de acetato de etilo en hexanos) para proporcionar 4-(aminocarbonil)-2-fluoro-5-(pentan-3-ilamino)benzoato de metilo (73.7 mg, 0.26 mmol, 28% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (d, 1H), 7.18-7.15 (m, 2H), 5.86 (br s, 2H), 3.94 (s, 3H), 3.37-3.29 (m, 1H), 1.67-1.47 (m, 4H), 0.93 (t, 6H).

[001104] ETAPA 7: A una solución de 4-(aminocarbonil)-2-fluoro-5-(pentan-3-ilamino)benzoato de metilo (73.7 mg, 0.26 mmol) en metanol (1 mL) a 0 °C se agrega hidróxido de sodio 1N (520 uL, 0.52 mmol). La mezcla se agita 30 min a 0 °C, y después se calienta a temperatura ambiente. Se agrega

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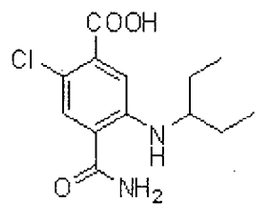
diclorometano (500 uL) para mejorar la solubilidad, y la solución homogénea se agita 3.5 h a temperatura ambiente. Después de la acidificación con ácido clorhídrico 1 N (500 uL), los solventes volátiles se remueven por evaporación rotatoria. Un material sólido insoluble después se aísla a partir del residuo acuoso por filtración. Lo sólido se seca para dar ácido 4-(aminocarbonil)-2-fluoro-5-(pentan-3-ilamino)benzoico (61.7 mg, 0.23 mmol, 88% de rendimiento). ^{1}H NMR (400 MHz, CD_3OD): 7.41 (d, 1H), 7.16 (d, 1H), 3.43-3.28 (m, 1H enterrado), 1.68-1.46 (m, 4H), 0.95 (t, 6H).

PREPARACIÓN DEL REACTIVO 46: ácido 4-(aminocarbonil)-2-cloro-5-(pentan-3-ilamino)benzoico



[001105] ETAPA 1: A un recipiente de presión se agregan 3-bromo-4-cianobenzoato de etilo (500 mg, 1.97 mmol), carbonato de cesio (1.28 g, 3.94 mmol), pentan-3-amina (688 uL, 5.90 mmol), XANTPHOS (114 mg, 0.20 mmol), tris(dibencilidenacetona)dipaladio(0) (90 mg, 0.10 mmol), y dioxano (3 mL). El recipiente se sella y se calienta a 95 °C por 15 h. Después del enfriamiento a temperatura ambiente, la mezcla se filtra a través de celite y la torta filtrada se

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enjuaga con acetato de etilo. Lo filtrado después se concentra y el residuo se purifica por cromatografía en columna (10% de acetato de etilo en hexanos) para proporcionar 4-ciano-3-(pentan-3-ilamino)benzoato de etilo (315 mg, 1.21 mmol, 61% de rendimiento) como un jarabe amarillo. ^{1}H NMR (400 MHz, $CDCl_3$): 7.43 (d, 1H), 7.33 (s, 1H), 7.25 (dd, 1H), 4.44-4.35 (m, 3H), 3.48-3.40 (m ,1H), 1..72-1.48 (m ,4H), 1.40 (t, 3H), 0.96 (t, 6H); MS (EI) para $C_{15}H_{20}N_2O_2$: 261 (MH^+).

[001106] ETAPA 2: A una solución de 4-ciano-3-(pentan-3-ilamino)benzoato de etilo (315 mg, 1.21 mmol) en DMF se agrega *N*-clorosuccinimida (162 mg, 1.21 mmol), y la solución se calienta a 45 °C por 24 h. Después del enfriamiento a temperatura ambiente, la mezcla se diluye con acetato de etilo. La solución orgánica después se lava con una mezcla de agua y 10% de cloruro de litio acuoso. El lavado acuoso se extrae con acetato de etilo y los extractos orgánicos se combinan, se secan sobre sulfato de magnesio, se filtran, y se concentran.

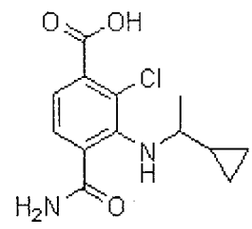
[001107] ETAPA 3: El residuo anterior después se disuelve en DMSO (6 mL) y se trata con carbonato de potasio (167 mg, 1.21 mmol) y 30% de peróxido de hidrógeno acuoso (150 uL) a temperatura ambiente por 5.5 h. Después de la dilución con

acetato de etilo, se agrega agua a la mezcla de reacción. Las capas se separan y la fase acuosa se extrae con acetato de etilo. Los extractos orgánicos combinados se lavan con 10% de cloruro de litio acuoso, se secan sobre sulfato de magnesio, se filtran, y se concentran. El residuo se purifica por cromatografía en columna (30% de acetato de etilo en hexanos) para proporcionar 4-(aminocarbonil)-2-cloro-5-(pentan-3-ilamino)benzoato de etilo (126.5 mg, 0.40 mmol, 33% de rendimiento) como una película amarilla. ^{1}H NMR (400 MHz, $CDCl_3$): 7.73 (d, 1H), 7.41 (s, 1H), 7.04 (s, 1H), 5.86 (br s, 2H), 4.40 (q, 2H), 3.34-3.26 (m, 1H), 1.68-1.47 (m, 4H), 1.41 (t, 3H), 0.93 (t, 6H); MS (EI) para $C_{15}H_{21}ClN_2O_3$: 313 (MH^+).

[001108] ETAPA 4: A una solución de 4-(aminocarbonil)-2-cloro-5-(pentan-3-ilamino)benzoato de etilo (126.5 mg, 0.40 mmol) en metanol (2 mL) se agrega hidróxido de sodio acuoso 2 N (400 uL, 0.80 mmol). La mezcla se agita 4.5 h a temperatura ambiente. Después de la acidificación con ácido clorhídrico 1N (800 uL), los solventes volátiles se remueven. Un material sólido insoluble después se aísla a partir del residuo acuoso por filtración. Lo sólido se seca para dar ácido 4-(aminocarbonil)-2-cloro-5-(pentan-3-ilamino)benzoico (73 mg, 0.26 mmol, 64% de rendimiento). ^{1}H NMR (400 MHz, CD_3OD): 7.65 (s, 1H), 7.07 (s, 1H), 3.35-3.29 (m, 1H enterrado), 1.69-1.47 (m, 4H), 0.94 (t, 6H).

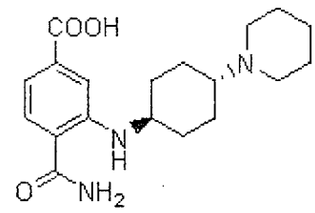
[001109] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos se preparan los siguientes reactivos. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[001110] Ácido 4-(aminocarbonil)-2-cloro-3-[(1-ciclopropiletil)amino]benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 46 primero conduciendo a la etapa 2 para dar una mezcla de 3-bromo-2-cloro-4-cianobenzoato de etilo y 5-bromo-2-cloro-4-cianobenzoato de etilo después de proceder con etapa 1 usando 1-ciclopropiletilamina seguido por etapas 3 y 4. ^{1}HNMR (400 MHz, CD_3OD): 7.49(d, 1H), 7.22 (d, 1H), 2.84 (q, 2H), 1.17(d, 3H), 0.9-0.76(m, 1H), 0.3-0.26(m, 2H), 0.04-0.00 (m, 2H). MS (EI) para $C_{13}H_{15}ClN_2O_3$: 284 (MH^+).

PREPARACIÓN DEL REACTIVO 47: ácido 4-(aminocarbonil)-3-[trans-4-(piperidin-1-il)ciclohexilamino]benzoico:



[001111] ETAPA 1: Una mezcla de 3-bromo-4-cianobenzoato de etilo (0.82 g, 3.24 mmol), (trans-4-aminociclohexil)carbamato de 1,1-dimetiletilo (0.69g, 3.24 mmol), tris(dibencilidenacetona)dipaladio(0) (0.148 g, 0.16 mmol), XANTPHOS (0.19 g, 0.32 mmol) y carbonato de cesio (1.48 g, 4.54 mmol) en dioxano (13 mL) se somete a reflujo por 15 horas. En enfriamiento a temperatura ambiente, la mezcla se filtra a través de Celite, se concentra, y purifica por cromatografía en columna de gel de sílice usando hexanos:acetato de etilo a partir de 5:1 a 4:1 para proporcionar 4-ciano-3-{[trans-4-({[(1,1-dimetiletil)oxi]carbonil}amino)ciclohexil]amino}benzoato de etilo (0.370 g, 30% de rendimiento). ^{1}H NMR (400 MHz, d_6-DMSO): 7.59 (d, 1H), 7.28 (s, 1H), 7.13 (dd, 1H), 6.82 (d, 1H), 6.05 (d, 1H), 4.31 (q, 2H), 3.46-3.37 (m, 1H), 3.28-3.17 (m, 1H), 1.95-1.85 (m, 2H), 1.84-1.76 (m, 2H), 1.46, 1.22 (m, 16H).

[001112] ETAPA 2: Se agita 4-ciano-3-{[trans-4-({[(1,1-dimetiletil)oxi]carbonil}-amino)ciclohexil]amino}benzoato de etilo (0.37 g, 0.97 mmol) en una mezcla de diclorometano (2 mL) y ácido trifluoroacético (2 mL) a temperatura ambiente por 1 hora. El solvente se evapora rotatoriamente, y el residuo se seca in vacuo para dar 3-[(trans-4-aminociclohexil)amino]-4-cianobenzoato de etilo (0.490 g, 99% de rendimiento) como sal del ácido trifluoroacético. MS (EI) para $C_{16}H_{21}N_3O_2$: 288 (MH^+).

[001113] ETAPA 3: Una mezcla de 3-[(trans-4-aminociclohexil)amino]-4-cianobenzoato de etilo (0.490 g, 0.96 mmol), carbonato de potasio (0.66g, 4.78 mmol) y 1,5 dibromopentano (0.130 mL, 0.96 mmol) se agita en dimetilformamida (10 mL) a temperatura ambiente por 48 h. Después se agrega agua (20 mL) a la mezcla, y la fase acuosa se extrae con diclorometano (2x 30 mL). Las capas orgánicas combinadas se secan sobre sulfato de sodio, se filtran y se concentran. El residuo se purifica por cromatografía en columna de gel de sílice usando metanol en diclorometano (5% a 10%) para proporcionar 4-ciano-3-[(trans-4-piperidin-1-ilciclohexil)amino]benzoato de etilo (0.145 g, 43% de rendimiento). MS (EI) para $C_{21}H_{29}N_3O_2$: 356 (MH^+).

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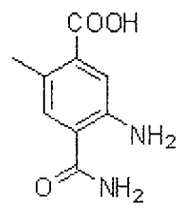
[001114] ETAPA 4: A una solución de 4-ciano-3-[(trans-4-piperidin-1-ilciclohexil)amino]benzoato de etilo (0.145 g, 0.41 mmol) en DMSO (0.5 mL) se agrega una solución al 30% de peróxido de hidrógeno (0.078 mL, 0.81 mmol) y carbonato de potasio (0.014 g, 0.10 mmol). La mezcla de reacción se agita a 50 °C por 3 h. Después se agrega una mezcla de metanol (1.5 mL) y agua (0.5mL) seguido por hidróxido de potasio (0.046 g, 0.81 mmol), y la solución se agita a 55 °C por 2 h. La mezcla se acidifica a pH 5 por adición de ácido clorhídrico acuoso 1N y se liofiliza para proporcionar ácido 4-(aminocarbonil)-3-(trans-4-(piperidin-1-il)ciclohexilamino]benzoico crudo el cual se usa sin purificación adicional. MS (EI) para $C_{19}H_{27}N_3O_3$: 346 (MH^+).

PREPARACIÓN DEL REACTIVO 48: ácido 5-amino-4-(aminocarbonil)-2-metilbenzoico:

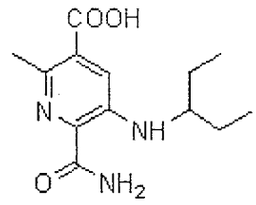


[001115] ETAPA 1: Se disuelve 5-amino-4-ciano-2-metilbenzoato de metilo (151 mg, 0.79 mmol) (sintetizado de conformidad con el reactivo de la preparación 41) en DMSO (1.5 mL). Se agregan 30% de peróxido de hidrógeno acuoso (0.3 mL) y carbonato de potasio (35 mg, 0.25 mmol), y la mezcla se

agita a temperatura ambiente por 1.5 h. La mezcla de reacción se divide entre acetato de etilo y agua. La porción acuosa se extrae (2x) con acetato de etilo. La porción orgánica combinada se seca sobre sulfato de sodio, se filtra y se concentra a un aceite amarillo el cual se purifica por HPLC de fase inversa preparativa para proporcionar 5-amino-4-(aminocarbonil)-2-metilbenzoato de metilo (108 mg, 0.52 mmol, 66% de rendimiento). NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.45 (br s, 1H), 7.26 (s, 1H), 7.19 (br s, 1H), 6.48 (s, 2H), 3.80 (s, 3H), 2.32 (s, 3H); MS (EI) para $C_{10}H_{12}N_2O_3$: 209 (MH^+).

[001116] ETAPA 2: Se disuelve 5-amino-4-(aminocarbonil)-2-metilbenzoato de metilo (108 mg, 0.52 mmol) en metanol (1.5 mL) y se trata con hidróxido de sodio 1M (1.5 mL, 1.5 mmol) por 1 h. La mezcla de reacción se concentra para proporcionar un residuo acuoso que se acidifica con ácido clorhídrico 1N a pH ~3. Lo precipitado se recolecta por filtración, se lava con agua, y se seca in vacuo para proporcionar ácido 5-amino-4-carbamoil-2-metilbenzoico (60.8 mg, 0.31 mmol, 61% de rendimiento). ^1H NMR (400 MHz, d_6-DMSO): δ 12.95 (br s, 1H), 7.99 (br s, 1H), 7.52 (s, 1H), 7.42 (br s, 1H), 7.35 (s, 1H), 4.75 (br s, 2H), 2.33 (s, 3H).

PREPARACIÓN DEL REACTIVO 49: ácido 6-(aminocarbonil)-2-metil-5-(pentan-3-ilamino)nicotínico:



[001117] ETAPA 1: A una solución de 5-amino-2-metilnicotinato de etilo (Fanta, P. E. *J. Am. Chem Soc.* 1953, *75*, 737) (4.1 g, 22.78 mmol) en DMF (50 ml) se agrega NBS (4.46 g, 25.06 mmol), y la mezcla de reacción se agita a temperatura ambiente durante la noche. La mezcla de reacción se diluye con agua (100 ml) y después se extrae con acetato de etilo (3x 100 ml). La capa orgánica se lava con bicarbonato de sodio acuoso saturado y salmuera. Después de la evaporación del solvente, el residuo se tritura con etanol para dar 5-amino-6-bromo-2-metilnicotinato de etilo (5.2 g, 88% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): 7.56 (s, 1H), 4.40 (q, J = 6.8 Hz, 2H), 4.05 (br, s, 2H), 2.75 (s, 3H), 1.39(t, J = 6.8Hz, 3H). MS (EI) para $C_9H_{11}BrN_2O_2$: 259.1 (MH^+).

[001118] ETAPA 2: A una solución de 5-amino-6-bromo-2-metilnicotinato de etilo (1.267 g, 4.89 mmol) en acetato de etilo (30 ml) se agregan 3-pentanona (0.463 g, 5.38 mmol), triacetoxiborohidruro de sodio (1.244 g, 5.868 mmol) y ácido trifluoroacético (1.15 g, 9.78 mmol) a temperatura ambiente.

Después de la agitación durante la noche a temperatura ambiente, se agrega otra porción de triacetoxiborohidruro de sodio (0.6 g, 2.83 mmol). La mezcla de reacción se agita por otras 6 horas. La mezcla de reacción se apaga con agua (20ml). La capa orgánica se lava con bicarbonato de sodio saturado y salmuera. Después de la evaporación del solvente, se purifica 6-bromo-2-metil-5-(pentan-3-ilamino)nicotinato de etilo (1.20g, 74.6% de rendimiento) por cromatografía en columna con 7% de acetato de etilo/Hexano como eluyente. ^{1}H NMR (400 MHz, $CDCl_3$): 7.35(s, 1H), 4.40 (q, J = 6.8 Hz, 2H), 4.10 (br, s, 1H), 3.30 (m, 1H), 2.68 (s, 3H), 1.8-1.5 (m, 4H), 1.42(t, J = 6.8Hz, 3H), 1.0 (t, J = 7.2 Hz, 6H). MS (EI) para $C_{14}H_{21}BrN_2O_2$: 329.1 (MH^+).

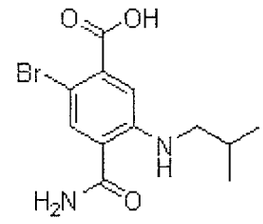
[001119] ETAPA 3: A una solución de 6-bromo-2-metil-5-(pentan-3-ilamino)nicotinato de etilo (1.202 g, 3.65 mmol) en acetonitrilo (30 ml) se agrega cianuro de sodio (0.357 g, 7.3 mmol), cloruro de tributilestaño (1.306 g, 4.015 mmol) y $Pd(dpppf)_3$ (0.298 g, 0.365 mmol). La mezcla de reacción se agita a 88°C durante la noche. La mezcla de reacción se diluye con agua (100 ml), después se extrae con acetato de etilo (3 x 100 ml). La capa orgánica se lava con bicarbonato de sodio acuoso saturado y salmuera. Después de la evaporación del solvente, se obtiene 6-ciano-2-metil-5-(pentan-3-ilamino)nicotinato de etilo (0.59 g, 59% de

rendimiento) por cromatografía en columna. ^{1}H NMR (400 MHz, $CDCl_3$): 7.56(s, 1H), 4.50 (q, J = 6.8 Hz, 2H), 4.35 (br, s, 1H), 3.40 a 9m, 1H), 2.64 (s, 3H), 1.80-1.50 (m, 4H), 1.42(t, J = 6.8Hz, 3H), 1.0 (t, 6H). MS (EI) para $C_{15}H_{21}N_3O_2$: 276.2 (MH^+).

[001120] ETAPA 4: A una solución de 6-ciano-2-metil-5-(pentan-3-ilamino)nicotinato (0.543 g, 1.97 mmol) en DMSO (10 ml) se agregan 50% de peróxido de hidrógeno acuoso (0.2441 g, 3.55 mmol) y carbonato de potasio (0.068 g, 0.49 mmol) a 10°C. La mezcla de reacción se agita a temperatura ambiente por dos horas después se agregan una solución de hidróxido de potasio (0.22 g, 3.94 mmol) en agua (2 ml) y metanol (10 ml) a la mezcla de reacción anterior. Después de ser agitada por otras dos horas a 45°C, la mezcla de reacción se enfría a temperatura ambiente y se neutraliza a pH 7. Se obtiene ácido 6-(Aminocarbonil)-2-metil-5-(pentan-3-ilamino)nicotínico (0.453 g, 87%) por filtración y secado. ^{1}HNMR (400 MHz, MeOH-D_4): 7.62(s, 1H), 3.35 (m, 1H), 2.60 (s, 3H), 1.65 (m, 2H), 1.52(m, 2H), 0.95(t, J = 7.20Hz, 6H). MS (EI) para $C_{13}H_{20}N_3O_3$: 267.2 (MH^+).

d260

PREPARACIÓN DEL REACTIVO 50: 1: ácido 4-(aminocarbonil)-2-bromo-5-[(2-metilpropil)amino]benzoico:



[001121] ETAPA 1: Una mezcla de 3-bromo-4-cianobenzoato de etilo (500 mg, 2.08 mmol), 2-metilpropan-1-amina (250 µL, 4.16 mmol), $Pd_2(dba)_3$ (96 mg, 5 mol%), Xantphos (120 mg, 10 mol%) y fosfato de potasio (959 mg, 4.16 mmol) en dioxano (10 mL) se agita durante la noche a 95 °C. Después del enfriamiento a temperatura ambiente la mezcla se diluye con agua y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio anhidro, se filtra, y se concentra seguido por cromatografía en columna (10% de acetato de etilo en hexanos) para dar 4-ciano-3-[(2-metilpropilamino)]benzoato de etilo (393 mg, 76.7%) como un sólido blanco. ^{1} MS (EI) para $C_{14}H_{18}N_2O_2$: 247.1 (MH^+).

[001122] ETAPA 2: A una solución de 4-ciano-3-[(2-metilpropilamino)]benzoato de etilo (393 mg, 1.60 mmol) en DMF (10 mL) se agrega N-bromsuccinimida (284 mg, 1.60 mmol). La mezcla se agita durante la noche a 45 °C después se enfría a temperatura ambiente y se diluye con agua, después se extrae con acetato de etilo. La capa orgánica se seca sobre

sulfato de sodio anhidro, se filtra y se concentra. El residuo se purifica por cromatografía en columna (10% de acetato de etilo en hexanos) para dar 2-bromo-4-ciano-5-[(2-metilpropil)amino]benzoato de etilo (374 mg, 72.0 %) como un sólido blanco. MS (EI) para $C_{14}H_{17}BrN_2O_2$: 324 (M^+).

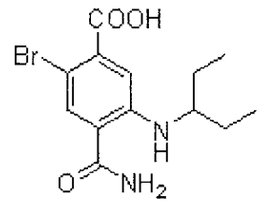
[001123] ETAPA 3: A una solución de 2-bromo 4-ciano-5[(2-metilpropil)amino]benzoato de etilo (374 mg, 1.15 mmol) en DMSO (10 mL), se agregan sucesivamente carbonato de potasio (51 mg, 0.37 mmol) y peróxido de hidrógeno acuoso (645 µl, 6.31 mmol). La mezcla se agita por 3 hr a temperatura ambiente después se diluye con agua, se extrae con acetato de etilo, se seca sobre sulfato de sodio anhidro, se filtra y se concentra. El residuo se purifica por cromatografía en columna para dar 4-(amino)-2-bromo-5-[(2-metilpropil)amino]benzoato de etilo (315 mg, 85.0 %) como un sólido cristalino. MS (EI) para $C_{14}H_{19}BrN_2O_3$: 342.1 (M^+).

[001124] ETAPA 4: A una solución de 2-bromo-4-(aminocarbonil)-5-[(2-metilpropil)amino]benzoato de etilo (315 mg, 0.91 mmol) en metanol (20 mL) se agrega hidróxido de sodio acuoso 1N (15 mL) y la mezcla se agita por 2hr a 45 °C. La mezcla después se concentra por evaporación rotatoria y se diluye con agua, después se ajusta a pH 2 por adición de ácido clorhídrico acuoso 1N y la mezcla se deja reposar por

1 hr a temperatura ambiente. Lo sólido cristalino se recolecta por filtración y se lava con agua, después se seca para dar ácido 4-(aminocarbonil)-2-bromo-5-[(2-metilpropil)amino]benzoico (250 mg, 87.1 %). MS (EI) para $C_{12}H_{15}BrN_2O_3$: 315.1 (MH^+)

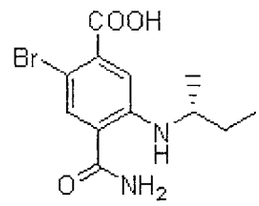
[001125] Usando técnicas sintéticas análogas y sustituyendo con reactivos de partida alternativos se preparan los siguientes reactivos. Se obtienen comercialmente materiales de partida alternativos a menos que se indique de otra manera.

[001126] Ácido 4-(Aminocarbonil)-2-bromo-5-[(1-etilpropil)amino]benzoico.



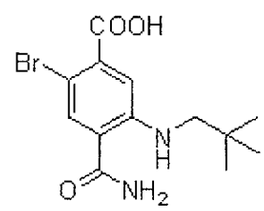
Preparado de conformidad con el método del reactivo de la preparación 50 usando pentan-3-amina en la etapa 1. ^1H NMR (400 MHz, d_6-DMSO): 13.40 (amplio s, 1H), 8.20 (d, 1H), 8.06 (amplio s, 1H), 7.85 (s, 1H), 7.40 (amplio s, 1H), 6.94 (s, 1H), 1.55 (m, 2H), 1.44 (m, 2H), 0.86 (t, 3H). MS (EI) para $C_{13}H_{17}BrN_2O_3$: 330 (MH^+).

[001127] Ácido 4-(Aminocarbonil)-2-bromo-5-{[(1*R*)-1-metilpropil]amino}benzoico.



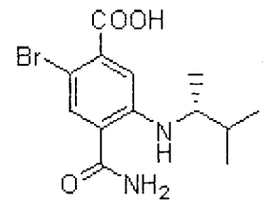
Preparado de conformidad con el método del reactivo de la preparación 50 usando (2*R*)-butan-2-amina en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.42 (amplio s, 1H), 8.16 (d, 1H), 8.06 (amplio s, 1H), 7.84 (s, 1H), 7.40 (amplio s, 1H), 6.92 (s, 1H), 3.47 (m, 1H), 1.49 (m, 2H), 1.10 (d, 3H), 0.87 (t, 3H). MS (EI) para $C_{12}H_{15}BrN_2O_3$: 317 (MH^+).

[001128] Ácido 4-(Aminocarbonil)-2-bromo-5-[(2,2-dimetilpropil)amino]benzoico.



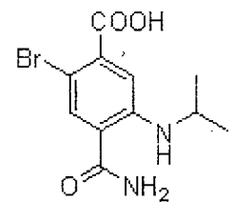
Preparado de conformidad con el método del reactivo de la preparación 50 usando 2,2-dimetilpropan-1-amina en la etapa 1. ^{1}H NMR (400 MHz, CD_3OD): 7.83 (s, 1H), 7.04 (s, 1H), 2.94 (s, 2H), 1.03 (s, 9H); MS (EI) para $C_{13}H_{17}BrN_2O_3$: 329, 331 (MH^+, Br isotopos).

[001129] Ácido 4-(Aminocarbonil)-2-bromo-5-{[(1R)-1,2-dimetilpropil]amino}benzoico.



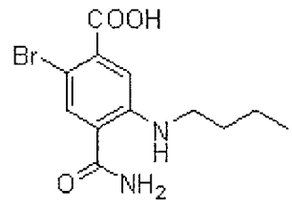
Preparado de conformidad con el método de preparación del reactivo 50 usando (2R)-3-metilbutano-2-amina en la etapa 1. ^{1}H NMR (400 MHz, DMSO- d_6): 13.36 (s, 1H), 8.32 (d, 1H), 8.04 (bs, 1H), 7.84 (s, 1H), 7.38 (bs, 1H), 7.73 (s, 1H), 3.43 (m, 1H), 1.76 (m, 1H), 1.05 (d, 3H), 0.92 (d, 3H), 0.87 (d, 3H). MS (EI) para $C_{13}H_{17}BrN_2O_3$: 330 (MH^+).

[001130] Ácido 4-(Aminocarbonil)-2-bromo-5-[(1-metiletil)amino]benzoico.



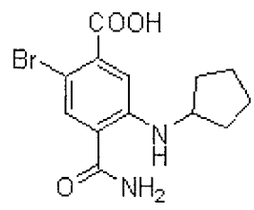
Preparado de conformidad con el método del reactivo de la preparación 50 usando propan-2-amina en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): 8.07 (d, 2H), 7.85 (s, 1H), 7.40 (s, 1H), 6.93 (s, 1H), 3.61-3.69 (m, 1H), 1.15 (d, 6H). MS (EI) para $C_{11}H_{13}BrN_2O_3$: 303 (MH^+).

[001131] Ácido 4-(Aminocarbonil)-2-bromo-5-(butilamino)benzoico.



Preparado de conformidad con el método del reactivo de la preparación 50 usando propan-1-amina en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): δ 13.43 (br s, 1H), 8.18 (m, 1H), 8.07 (br s, 1H), 7.86 (s, 1H), 7.42 (br s, 1H), 6.90 (s, 1H), 3.09-3.05 (m, 2H), 1.60-1.54 (m, 3H), 0.94 (t, 2H); MS (EI) para $C_{11}H_{13}BrN_2O_3$: 299, 301 (MH^+) (patrón isotopo de bromo).

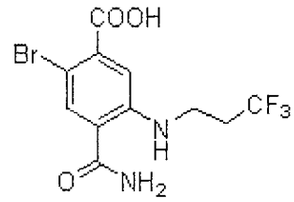
[001132] Ácido 4-(Aminocarbonil)-2-bromo-5-(ciclopentilamino)benzoico.



Preparado de conformidad con el método del reactivo de la preparación 50 usando ciclopentanamina en la etapa 1. ^{1}H NMR (400 MHz, CD_3OD): 7.81(s, 1H), 7.06(s, 1H), 3.83-3.82(m, 1H), 2.06-2.01(m, 2H), 1.77-1.65(m, 4H), 1.54-1.50(m, 2H). MS(EI) para $C_{13}H_{15}BrN_2O_3$: 328(MH^+).

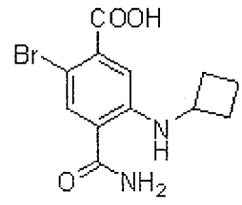
1266

[001133] Ácido 4-(Aminocarbonil)-2-bromo-5-[(3,3,3-trifluoropropil)amino]benzoico.



Preparado de conformidad con el método del reactivo de la preparación 50 usando 3,3,3-trifluoropropan-1-amina en la etapa 1. ^{1}H NMR (400 MHz, d_6-DMSO): 13.47 (br. s, 1H), 8.28 (s, 1H), 8.10 (s, 1H), 7.88 (d, 1H), 7.47 (d, 1H), 6.97 (s, 1H), 3.47-3.39 (m, 2H), 2.66-2.53 (m, 2H). MS (EI) para $C_{11}H_{10}BrF_3N_2O_3$: 356 (MH^+).

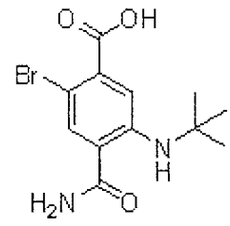
[001134] Ácido 4-(Aminocarbonil)-2-bromo-5-(ciclobutilamino)benzoico.



Preparado de conformidad con el método del reactivo de la preparación 50 usando ciclobutanamina en la etapa 1. ^{1}H NMR (400 MHz, CD_3OD): 7.82 (s, 1H), 6.92 (s, 1H), 4.00-3.89 (m, 1H), 2.50-2.41 (m, 2H), 1.95-1.80 (m, 4H). MS (EI) para $C_{12}H_{13}BrN_2O_3$: 314 (MH^+).

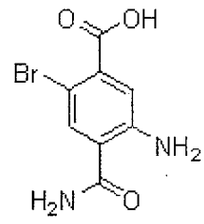
1267

[001135] Ácido 4-(aminocarbonil)-2-bromo-5-[(1,1-dimetiletil)amino]benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 50 usando 1,1-dimetiletilamina en la etapa 1. MS (EI) para $C_{12}H_{15}BrN_2O_3$: 315 (MH^+).

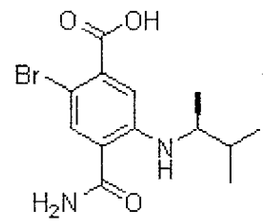
[001136] Ácido 5-amino-4-(aminocarbonil)-2-bromobenzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 50 conduciendo únicamente la etapa 2 usando 3-amino-4-(aminocarbonil)benzoato de 1,1-dimetiletilo (preparación del reactivo 29 etapa 2) seguido por hidrólisis del éster terc-butilo ciclizado del ácido bajo condiciones estándares, véase Green y Wutts en Protective Groups en Organic Synthesis, Wiley-Interscience Ed. ^1H NMR (400 MHz, DMSO-d_6): 13.14 (s, 1H), 8.28 (s, 1H), 8.00 (bs, 2H), 7.80 (s, 1H), 7.28 (bs, 2H). MS (EI) para $C_8H_7BrN_2O_3$: 260 (MH^+).

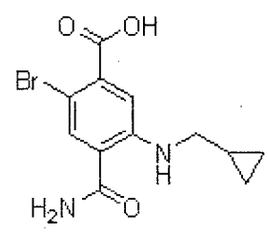
1168

[001137] Ácido 4-(aminocarbonil)-2-bromo-5-{[(1S)-1,2-dimetilpropil]amino}benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 50 usando (1S)-1,2-dimetilpropilamina en la etapa 1. ^{1}H NMR (400 MHz, DMSO-d_6): 13.36 (s, 1H), 8.33 (d, 1H), 8.04 (bs, 1H), 7.82 (s, 1H), 7.38 (bs, 1H), 7.72 (s, 1H), 3.42 (m, 1H), 1.74 (m, 1H), 1.05 (d, 3H), 0.93 (d, 3H), 0.88 (d, 3H). MS (EI) para $C_{13}H_{17}BrN_2O_3$: 330 (MH^+).

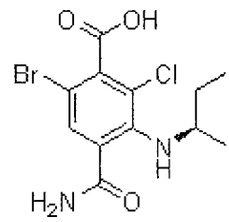
[001138] Ácido 4-(aminocarbonil)-2-bromo-5-[(ciclopropilmetil)amino]benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 50 usando ciclopropilmetilamina en la etapa 1. MS (EI) para $C_{12}H_{13}BrN_2O_3$: 314 (MH^+).

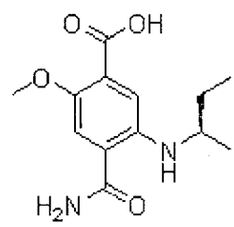
1269

[001139] Ácido 4-(aminocarbonil)-6-bromo-2-cloro-3-{[(1R)-1-metilpropil]amino}benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 50 usando (1R)-1-metilpropilamina en la etapa 1 después de la repetición de la etapa 2 primero usando N-bromosuccinimida después usando N-clorosuccinimida y se prosigue con las etapas 3 y 4.. MS (EI) para $C_{12}H_{14}BrClN_2O_3$: 350 (MH^+).

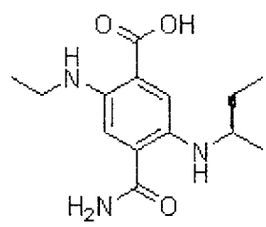
[001140] Ácido 4-(aminocarbonil)-2-(metiloxi)-5-{[(1R)-1-metilpropil]amino}benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 50 usando (1R)-1-metilpropilamina en la etapa 1 después siguiendo la etapa 2 con la conversión de 2-bromo-4-ciano-5-{[(1R)-1-metilpropil]amino}benzoato de etilo a 4-ciano-2-hidroxi-5-{[(1R)-1-metilpropil]amino}benzoato de etilo de conformidad con el

método descrito en Chemical & Pharmaceutical Bulletin (2007), 55(9), 1361-1364 y subsecuente metilación usando yodometano bajo condiciones estándares después de proceder a través de etapas 3 y 4. ^{1}H NMR (400 MHz, d6-DMSO): 12.79-12.74 (s,1H), 8.03-7.95 (s,1H), 7.60-7.52 (d, 1H), 7.35-7.28 (s, 1H), 7.26-7.24 (s, 1H), 6.85-6.81 (s, 1H), 3.72-3.70 (s, 3H), 3.31-3.29 (s, 1H), 1.49-1.40 (m, 2H), 1.08-1.05 (d, 3H), 0.89-0.83 (m, 3H). MS (EI) para $C_{13}H_{18}N_2O_4$: 267 (MH^+).

[001141] Ácido 4-(aminocarbonil)-2-(etilamino)-5-{[(1R)-1-metilpropil]amino}benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 50 usando (1R)-1-metilpropilamina en la etapa 1 después siguiendo la etapa 2 con la conversión de 2-bromo-4-ciano-5-{[(1R)-1-metilpropil]amino}benzoato de etilo a 4-ciano-2-(etilamino)-5-{[(1R)-1-metilpropil]amino}benzoato de etilo de conformidad con el método descrito en la etapa 1 después de proceder a través de etapas 3 y 4. MS (EI) para $C_{14}H_{21}N_3O_3$: 280 (MH^+).

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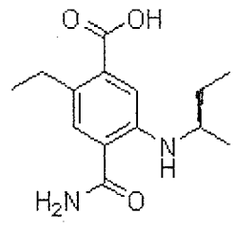
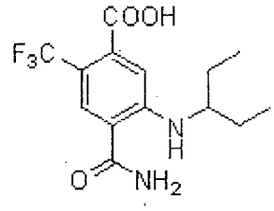
[001142] Ácido 4-(aminocarbonil)-2-etil-5-{[(1R)-1-metilpropil]amino}benzoico:



Sintetizado de conformidad con el método del reactivo de la preparación 50 usando (1R)-1-metilpropilamina en la etapa 1 después siguiendo la etapa 2 con la conversión de 2-bromo-4-ciano-5-{[(1R)-1-metilpropil]amino}benzoato de etilo a 4-ciano-2-etil-5-{[(1R)-1-metilpropil]amino}benzoato de etilo por tratamiento con cloruro de etilmagnesio de conformidad con el método descrito en Synlett 1996, 5, 473-474 después de proceder a través de etapas 3 y 4. ^{1}H NMR (400 MHz, DMSO-d_6): 7.94 (s, 1H), 7.81 (d, 1H), 7.49 (s, 1H), 7.27 (s, 1H), 6.98 (s, 1H), 2.67-2.75 (m, 2H), 1.44-1.53 (m, 2H), 1.06-1.15 (m, 6H), 0.89 (t, 3H). MS (EI) para $C_{14}H_{20}N_2O_3$: 265 (MH^+).

PREPARACIÓN DEL REACTIVO 51: 4-(aminocarbonil)-5-[(1-etilpropil)amino]-2-(trifluorometil)benzoico ácido:



[001143] ETAPA 1: ácido 4-Amino-2-(trifluorometil)benzoico (10 g, 48.8 mmol) se suspende en THF (100 mL) y metanol (30 mL) y se enfría en un baño helado. Se agrega por goteo (trimetilsilil)diazometano (solución 2 M en hexanos; 32 mL). La mezcla se agita por 5 minutos y después se concentra para proporcionar 4-amino-2-(trifluorometil)benzoato de metilo (rendimiento cuantitativo) como un aceite marrón. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, 1H), 6.99 (d, 1H), 6.77 (d, 1H), 4.18 (br s, 2H), 3.88 (s, 3H); GCMS por $C_9H_8F_3NO_2$: 219 (M^+).

[001144] ETAPA 2: Se disuelve 4-amino-2-(trifluorometil)benzoato de metilo (~22 mmol), en THF (100 mL) y la mezcla se rocía con nitrógeno por 15 minutos. Se agregan yoduro de cobre (I) (4.14 g, 21.8 mmol) y diyodometano (8.8 mL, 109 mmol) seguido por nitrito de isoamilo (8.8 mL, 66.2 mmol) y la mezcla se agita a reflujo por 4 h. La mezcla se enfría a temperatura ambiente y después se divide entre acetato de etilo y ácido clorhídrico 1N. La porción acuosa se extrae con acetato de etilo (2x). La porción orgánica combinada se lava secuencialmente con 1:1 solución saturada de bicarbonato de sodio: tiosulfato de sodio 1M (2x) y salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar un aceite marrón el cual se purifica por cromatografía en columna (gel de sílice, 2-40% diclorometano en hexanos) para proporcionar

4-yodo-2-(trifluorometil)benzoato de metilo (5.42 g, 16.4 mmol, ~75% de rendimiento durante 2 etapas) como un aceite amarillo pálido. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.97 (dd, 1H), 7.52 (d, 1H), 3.93 (s, 3H); GCMS por $C_9H_6F_3IO_2$: 330 (M^+).

[001145] ETAPA 3: Se disuelve 4-yodo-2-(trifluorometil)benzoato de metilo (1.65 g, 5.0 mmol) en ácido sulfúrico concentrado (6 mL) y se enfría en un baño helado. Se agrega por goteo ácido nítrico humeante (4 mL) y la mezcla se agita a 70 °C por 1.5 h. La mezcla se enfría a temperatura ambiente y después se vierte en hielo (~100 mL). La mezcla acuosa se extrae con acetato de etilo (2x). La porción orgánica combinada se lava con bicarbonato de sodio saturado (2x), salmuera, se seca sobre sulfato de sodio después se filtra y se concentra para proporcionar (1.7 g, 4.53 mmol, 91% de rendimiento) compuesta de los dos regioisómeros 4-yodo-5-nitro-2-(trifluorometil)benzoato de metilo (Mayor) y 4-yodo-3-nitro-2-(trifluorometil)benzoato de metilo (menor) en una relación 4:1. ^{1}H NMR para el isómero deseado (Mayor) (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.26 (s, 1H), 3.98 (s, 3H); GCMS por $C_9H_5F_3INO_4$: 375 (M^+).

[001146] ETAPA 4: Una mezcla de 4-yodo-5-nitro-2-(trifluorometil)benzoato de metilo (deseado) y 4-yodo-3-

nitro-2-(trifluorometil)benzoato de metilo como se obtiene en la etapa 3 (1.7 g, 4.53 mmol) en ácido acético (20 mL) se trata con polvo de hierro (1.5 g, 26.8 mmol) a 45 °C por 2 h. La mezcla de reacción se enfría a temperatura ambiente y se filtra a través de celite. La torta filtrada se lava con acetato de etilo y lo filtrado se concentra. El residuo se diluye con acetato de etilo, se lava con bicarbonato de sodio saturado y salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar un aceite marrón el cual se purifica por cromatografía en columna (gel de sílice, 10-30% de acetato de etilo en hexanos) para proporcionar los dos regioisómeros 5-amino-4-yodo-2-(trifluorometil)benzoato de metilo (Mayor) y 3-amino-4-yodo-2-(trifluorometil)benzoato de metilo (menor) en una relación 4:1 (1.484 g, 4.30 mmol, 95% de rendimiento). ^{1}H NMR para el isómero deseado (Mayor) (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.06 (s, 1H), 4.55 (br s, 2H), 3.90 (s, 3H); GCMS por $C_9H_7F_3INO_2$: 345 ($M^{+\cdot}$).

[001147] ETAPA 5: Una mezcla de 5-amino-4-yodo-2-(trifluorometil)benzoato de metilo (deseado) y 3-amino-4-yodo-2-(trifluorometil)benzoato de metilo como se obtiene en la etapa 4 (392 mg, 1.14 mmol) se disuelve en 1,2-dicloroetano (12 mL) y se trata con ácido trifluoroacético (0.5 mL, 6.73 mmol), 3-pentanona (0.36 mL, 3.40 mmol) y

triacetoxiborohidruro de sodio (724 mg, 3.42 mmol) a 45 °C por 0.5 h. La GCMS indica la conversión completa del isómero deseado que requiere el producto. Después de 0.5 h adicional a 45 °C, la mezcla de reacción se enfría a temperatura ambiente y se apaga con hidróxido de sodio 1N (5 mL) y bicarbonato de sodio saturado, y se divide con diclorometano. La porción acuosa se extrae con diclorometano. La porción orgánica combinada se lava con salmuera, se seca sobre sulfato de magnesio, después se filtra y se concentra para proporcionar un aceite amarillo el cual se purifica por cromatografía en columna (gel de sílice, 10-40% diclorometano en hexanos) para proporcionar puro 4-yodo-5-(pentan-3-ilamino)-2-(trifluorometil)benzoato de metilo (330 mg, 0.795 mmol, 70% de rendimiento) como un aceite amarillo pálido. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 6.79 (s, 1H), 4.44 (d, 1H), 3.92 (s, 3H), 3.44-3.34 (m, 1H), 1.73-1.48 (m, 4H), 0.95 (t, 6H); GCMS por $C_{14}H_{17}F_3INO_2$: 415 (M^+).

[001148] ETAPA 6: Se disuelve 4-yodo-5-(pentan-3-ilamino)-2-(trifluorometil)benzoato de metilo (401 mg, 0.966 mmol) en DMF (9 mL) y la mezcla se rocía con nitrógeno por 15 minutos. Se agregan cianuro de zinc (79 mg, 0.673 mmol) y tetraquis(trifenilfosfina)paladio(0) (100 mg, 0.086 mmol), y la mezcla se agita a 100 °C por 15 h. La mezcla de reacción se enfría a temperatura ambiente y se filtra a través de

celite. La torta filtrada se lava con acetato de etilo y lo filtrado se lava con 5% de cloruro de litio (2x). El lavado acuoso combinado se extrae nuevamente con acetato de etilo. La porción orgánica combinada se lava con salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar un semi-sólido marrón, el cual se purifica por cromatografía en columna (gel de sílice, 30-50% diclorometano en hexanos) para proporcionar 4-ciano-5-(pentan-3-ilamino)-2-(trifluorometil)benzoato de metilo (262 mg, 0.834 mmol, 86% de rendimiento) como cristales incoloros. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 6.96 (s, 1H), 4.76 (d, 1H), 3.94 (s, 3H), 3.49-3.38 (m, 1H), 1.75-1.63 (m, 2H), 1.61-1.49 (m, 2H), 0.96 (t, 6H); GCMS por $C_{15}H_{17}F_3N_2O_2$: 314 ($M^{+\cdot}$).

[001149] ETAPA 7: Se disuelve 4-ciano-5-(pentan-3-ilamino)-2-(trifluorometil)benzoato de metilo (257 mg, 0.818 mmol) en DMSO (2 mL) y se enfría en un baño de agua fría. Se agrega 30% de peróxido de hidrógeno acuoso (0.2 mL) y carbonato de potasio (38 mg, 0.275 mmol), y la mezcla se agita a temperatura ambiente por 1.5 h. La mezcla de reacción se divide entre acetato de etilo y agua. La porción acuosa se extrae con acetato de etilo. La porción orgánica combinada se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar 4-aminocarbonil-5-(pentan-3-ilamino)-2-(trifluorometil)benzoato de metilo (rendimiento cuantitativo)

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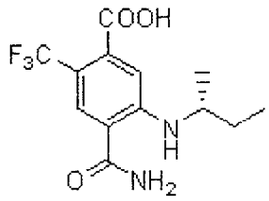
como un aceite amarillo. MS (EI) para $C_{15}H_{19}F_3N_2O_3$: 333 (MH^+).

[001150] ETAPA 8: Se disuelve 4-aminocarbonil-5-(pentan-3-ilamino)-2-(trifluorometil)benzoato de metilo (0.818 mmol) en metanol (2 mL) y se trata con hidróxido de sodio 2M (1 mL, 2 mmol) a 45 °C por 1.5 h. La mezcla de reacción se enfría a temperatura ambiente y se concentra para proporcionar un residuo acuoso que se lava con éter, después se enfría en un baño helado y se acidifica con ácido clorhídrico 1N a pH ~3. Lo precipitado se recolecta por filtración, se lava con agua, después se seca para proporcionar ácido 4-aminocarbonil-5-(pentan-3-ilamino)-2-(trifluorometil)benzoico (233 mg, 0.733 mmol, 90% de rendimiento durante 2 etapas). ^{1}H NMR (400 MHz, d_6-DMSO): δ 13.5 (br s, 1H), 8.74 (d, 1H), 8.21 (br s, 1H), 7.95 (s, 1H), 7.46 (br s, 1H), 6.94 (s, 1H), 3.51-3.43 (m, 1H), 1.63-1.51 (m, 2H), 1.51-1.39 (m, 2H), 0.87 (t, 6H); MS (EI) para $C_{14}H_{17}F_3N_2O_3$: 319 (MH^+).

PREPARACIÓN DEL REACTIVO 52: ácido 4-(aminocarbonil)-5-{[(1R)-1-metilpropil]amino}-2-(trifluorometil)benzoico:



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[001151] ETAPA 1: Una mezcla de 5-amino-4-yodo-2-(trifluorometil)benzoato de metilo (Mayor) y 3-amino-4-yodo-2-(trifluorometil)benzoato de metilo (menor) en una relación 4:1 (preparada en el Ejemplo 51 Etapa 4) (1.08 g, 3.13 mmol) se disuelve en DMF (17 mL), y la mezcla se rocía con nitrógeno por 15 minutos. Se agregan cianuro de zinc (257 mg, 2.19 mmol) y tetraquis(trifenilfosfina)paladio(0) (362 mg, 0.313 mmol) y la mezcla se agita a 100 °C por 15 h. La mezcla de reacción se enfría a temperatura ambiente y se filtra a través de celite. La torta filtrada se lava con acetato de etilo y lo filtrado se lava con 5% cloruro de litio. El lavado acuoso se extrae nuevamente con acetato de etilo (2x). La porción orgánica combinada se lava con 10% de cloruro de litio y salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar un residuo el cual se purifica por cromatografía en columna (gel de sílice, 30-50% de acetato de etilo en hexanos) para proporcionar 5-amino-4-ciano-2-(trifluorometil)benzoato de metilo puro (556 mg, 2.28 mmol, 73% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.10 (s, 1H), 4.88 (br s, 2H), 3.93 (s, 3H); GCMS por $C_{10}H_7F_3N_2O_2$: 244 (M^+).

[001152] ETAPA 2: Se disuelve 5-amino-4-ciano-2-(trifluorometil)benzoato de metilo (250 mg, 1.02 mmol) en THF (6 mL), y la mezcla se rocía con nitrógeno por 15 minutos. Se

agregan yoduro de cobre (I) (195 mg, 1.02 mmol) y diyodometano (0.4 mL, 4.95 mmol) seguido por nitrito de isoamilo (0.4 mL, 3.01 mmol), y la mezcla se agita a reflujo por 2.5 h. La mezcla se enfría a temperatura ambiente y después se divide entre acetato de etilo y ácido clorhídrico 1N. La porción acuosa se extrae con acetato de etilo (2x). La porción orgánica combinada se lava secuencialmente con 1:1 de solución saturada de bicarbonato de sodio:tiosulfato de sodio 1M (2x) y salmuera, se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar un semi-sólido, el cual se purifica por cromatografía en columna (gel de sílice, 20-50% diclorometano en hexanos) para proporcionar 4-ciano-5-yodo-2-(trifluorometil)benzoato de metilo (174 mg, 0.49 mmol, 48% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.93 (s, 1H), 3.98 (s, 3H); GCMS por $C_{10}H_5F_3INO_2$: 355 (M^+).

[001153] ETAPA 3: Se disuelve 4-ciano-5-yodo-2-(trifluorometil)benzoato de metilo (174 mg, 0.49 mmol) en dioxano (2 mL) y se rocía con nitrógeno por 15 minutos. Se agregan XANTPHOS (57 mg, 0.098 mmol), carbonato de cesio (350 mg, 1.07 mmol), (R)-sec-butilamina (0.1 mL, 0.986 mmol), y tris(dibencilidenacetona)dipaladio (45 mg, 0.049 mmol), y la mezcla se agita en un tubo sellado a 95 °C por 20 h. La mezcla de reacción se enfría a temperatura ambiente y se filtra a través de celite. La torta filtrada se lava con acetato de

etilo y lo filtrado se concentra para proporcionar un aceite anaranjado el cual se purifica por cromatografía en columna (gel de sílice, 5-15% de acetato de etilo en hexanos) para proporcionar 5-(sec-butilamino)-4-ciano-2-(trifluorometil)benzoato de (R)-metilo (45 mg, 0.150 mmol, 31% de rendimiento) como un aceite amarillo. GCMS por $C_{14}H_{15}F_3N_2O_2$: 300 (M^+).

[001154] ETAPA 4: Se disuelve 5-(sec-butilamino)-4-ciano-2-(trifluorometil)benzoato de (R)-metilo (45 mg, 0.150 mmol) en DMSO (1 mL) y se trata con 30% de peróxido de hidrógeno acuoso (0.05 mL) y carbonato de potasio (6 mg, 0.043 mmol) a temperatura ambiente por 2 h. La mezcla de reacción se divide entre acetato de etilo y agua. La porción acuosa se extrae con acetato de etilo. La porción orgánica combinada se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar un aceite amarillo el cual se purifica por cromatografía en columna (gel de sílice, 10-40% de acetato de etilo en hexanos) para proporcionar 5-(sec-butilamino)-4-aminocarbonil-2-(trifluorometil)benzoato de (R)-metilo (27 mg, 0.085 mmol, 57% de rendimiento). Se suspende 5-(sec-butilamino)-4-aminocarbonil-2-(trifluorometil)benzoato de (R)-metilo (27 mg, 0.085 mmol) en metanol (1 mL) y se trata con hidróxido de sodio 1M (0.2 mL, 0.2 mmol) a 45 °C por 1 h. Se agrega diclorometano (0.5 mL) e hidróxido de sodio 1M (0.2

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mL, 0.2 mmol) y la mezcla se agita a 45 °C por 1.5 h adicionales. Se agregan diclorometano (0.5 mL) e hidróxido de sodio 1M (0.2 mL, 0.2 mmol), y la mezcla se agita a 45 °C por 1 h adicional y después a temperatura ambiente por 15 h. La mezcla de reacción se concentra para proporcionar un residuo acuoso que se enfría en un baño helado, se acidifica con ácido clorhídrico 1N a pH ~2, después se extrae con acetato de etilo (2x). La porción orgánica se seca sobre sulfato de sodio, después se filtra y se concentra para proporcionar ácido 4-(aminocarbonil)-5-{[(1R)-1-metilpropil]amino}-2-(trifluorometil)benzoico (23 mg, 0.076 mmol, 89% de rendimiento). MS (EI) para $C_{13}H_{15}F_3N_2O_3$: 305 (MH^+).

PREPARACIÓN DEL REACTIVO 53: 1,1,1-trifluorobutan-2-amina:

[001155] ETAPA 1: A una solución de 1,1,1-trifluorobutan-2-ona (5.0 g, 39.9 mmol) y clorhidrato de hidroxilamina (3.22 g, 46.3 mmol) en agua (28 mL) se agrega una solución de hidróxido de sodio (1.84 g, 46.0 mmol) en agua (14 mL), después la mezcla se lleva a reflujo por 4hr. Después del enfriamiento a temperatura ambiente, la mezcla se extrae con diclorometano (3 x 50 mL) y las capas orgánicas combinadas se lavan con agua, salmuera, después se secan sobre sulfato de sodio anhidro. La filtración y la concentración después de la destilación usando una columna de 10 cm Vigreux (b.p. 123-

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124°C) proporciona oxima de (*E*)-1,1,1-trifluorobutan-2-ona (2.50 g, 44.5% de rendimiento) como un líquido claro. ^{1}H NMR (400 MHz, $CDCl_3$): 9.18 (br s, 1H), 2.52 (q, 2H), 1.21 (t, 3H).

[001156] ETAPA 2: A una solución de hidruro de aluminio 1M y litio en éter de etilo (40 ml) se agrega oxima de (*E*)-1,1,1-trifluorobutan-2-ona (2.50 g, 17.7 mmol) disuelta en éter de etilo (25 mL) a temperatura ambiente. La mezcla de reacción se agita por 3hr, después cuidadosamente se apaga por adición de agua y la solución acuosa se extrae con acetato de etilo (3x 50 mL) y se seca sobre sulfato de sodio anhidro. Después de la filtración, se agrega cloruro de hidrógeno 4.0 M en dioxano (10 mL). La solución después se evapora rotatoriamente casi al 80 % en volumen, y se agrega éter de etilo (30 mL) para dar un precipitado. Lo sólido se recolecta por filtración y se seca para dar sal clorhidrato de 1,1,1-trifluorobutan-2-amina (2.46 g, 85.6 % de rendimiento). ^{1}H NMR (400 MHz, d6-DMSO): 9.30 (br s, 2H), 4.18 (m, 1H), 1.81 (q, 2H), 1.02 (t, 3H).

ENSAYOS HSP90:

Protocolo de Transferencia (TR-FRET) de Energía de Resonancia Fluorescencia de Resolución Temporal Hsp90

[001157] La determinación de los valores IC50 de inhibidores

1183

HSP90 se conducen usando ensayo de enlace de desplazamiento de transferencia de energía (TR-FRET) de resonancia fluorescencia de resolución temporal. El ensayo emplea una sonda de geldanamamicina biotinilada (biotin-GM) y dominio de enlace ATP N-terminal Hsp90 humano etiquetado con His6 (Hsp90N). Los compuestos de prueba se diluyen serialmente en DMSO y se transfieren 0.5 µL de alícuotas a placas de ensayo microtituladores de enlace medio, negras de 384 cavidades (Greiner). Se prepara el reactivo 1 mezclando 80 nM de biotina-GM, 1 nM de quelado anti-His-Eu y 100 nM de aloficocianina de estreptavidina (SA-APC) en amortiguador de enlace (50 mM de Tris-HCl, pH 7.5, 1 mM de EDTA, 150 mM de NaCl, 0.1% de Triton X-100, 0.05% de BSA y 1 mM de DTT) y se transfiere 10 µL a la placa de ensayo. Se prepara el reactivo 2 mezclando 80 nM de HSP90N en amortiguador de enlace y 10 µL se transfiere a las columnas 3-24 de la placa de ensayo. Se agrega el amortiguador de ensayo (10 µL) a las columnas 1-2 como 100% de control de inhibición. La placa se incuba por 180 minutos a temperatura ambiente. Se miden las señales TR-FRET en un lector de placa Envision (Perkin Elmer) usando el protocolo de detección de ensayo LANCE®. Se calculas los valores IC(50) como un porcentaje del desplazamiento de biotin-GM a partir de HSP90N por compuestos a concentraciones molares variables.

[001158] Los compuestos tanto en la Tabal 1 como II se ha

probado por su actividad inhibitoria a HSP90 (valores IC_{50}), y estos compuestos tienen valores IC_{50} para HSP90 menores que 10,000 nM. Un grupo preferido de compuestos de la Tabla I tienen valores IC_{50} para HSP90 menores que 5,000 nM. Otro grupo preferido de compuestos de la Tabla I tienen valores IC_{50} para HSP90 menores que 2,000 nM. Otro grupo preferido de compuestos de la Tabla I tienen valores IC_{50} para HSP90 menores que 1,000 nM. Otro grupo preferido de compuestos de la Tabla I tienen valores IC_{50} para HSP90 menores que 500 nM. Otro grupo preferido de compuestos de la Tabla I tienen valores IC_{50} para HSP90 menores que 200 nM. Otro grupo preferido de compuestos de la Tabla I tienen valores IC_{50} para HSP90 menores que 100 nM. Otro grupo preferido de compuestos de la Tabla I tienen valores IC_{50} para HSP90 menores que 50 nM. Otro grupo preferido de compuestos de la Tabla I tienen valores IC_{50} para HSP90 menores que 25 nM.

Ejemplos de Composiciones Farmacéuticas

[001159] Las siguientes son formulaciones farmacéuticas representativos que contienen un compuesto de Fórmula I, II o III.

1285

Formulación de Tableta

[001160] Los siguientes ingredientes se mezclan íntimamente y se comprimen en tabletas de registro único

Ingrediente	Cantidad por tableta, mg
Fórmula I, II o III	400
Almidón de maíz	50
croscarmelosa de sodio	25
Lactosa	120
Estearato de magnesio	5

Formulación de Cápsula

[001161] Los siguientes ingredientes se mezclan íntimamente y se cargan en una cápsula de gelatina de cáscara dura.

Ingrediente	Cantidad por tableta, mg
Fórmula I, II o III	200
Lactosa, secada por rocío	148
Estearato de magnesio	2

1286

Formulación de Suspensión

[001162] Los siguientes ingredientes se mezclan para formar una suspensión para administración oral.

Ingrediente	Cantidad
Fórmula I, II o III	1.0 g
Ácido fumárico	0.5 g
Cloruro de sodio	2.0 g
Metil parabeno	0.15 g
Propil parabeno	0.05 g
Azúcar granulada	25.5 g
sorbitol (70% de	12.85 g
solución)	1.0 g
Veegum K (Vanderbilt Co.)	0.035 ml
Saborizante	0.5 mg
Colorantes	c.s para 100 ml
agua destilada	

Formulación Inyectable

[001163] Los siguientes ingredientes se mezclan para formar una formulación inyectable.

Ingrediente	Cantidad
Fórmula I, II o III	1.2 g
solución amortiguadora de	
acetato de sodio	2.0 ml, 0.4 M
HCl (1N) o NaOH (1M)	c.s para pH adecuado
agua (destilada, estéril)	c.s para 20 ml

1287

[001164] Todos los ingredientes anteriores, excepto agua, se combinan y calientan a 60°-70° con agitación. Entonces se agrega una cantidad suficiente de agua a 60°C con agitación vigorosa para emulsificar los ingredientes, y entonces se agrega c.s. de agua a 100 g.

Formulación de Supositorio

[001165] Se prepara un supositorio de peso total 2.5 g mezclando el compuesto descrito en la presente (compuestos de Fórmula I, II o III) con Witepsol® H15 (triglicéridos de ácidos grasos vegetales saturados; Riches-Nelson, Inc., New York), y tiene la siguiente composición.

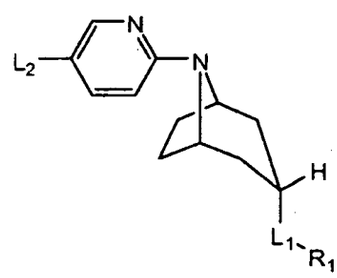
Ingrediente	Cantidad por tableta, mg
Fórmula I, II o III	500
Witepsol ® H-15	Balance

[001166] La descripción precedente se ha descrito en algún detalle por medio de ilustración y ejemplo, para propósitos de claridad y entendimiento. La invención se ha descrito con referencia a varias modalidades y técnicas específicas y preferidas. Sin embargo, se entenderá que se pueden hacer muchas variaciones y modificaciones mientras permanezcan dentro del espíritu y alcance de la invención. Será obvio para un experto en la técnica que se pueden practicar cambios y modificaciones dentro del alcance de las reivindicaciones

anexas. Por lo tanto, se entenderá que la descripción anterior se planea ser ilustrativa y no restrictiva. El alcance de la invención por lo tanto, se debe determinar no con referencia a la anterior descripción, pero en cambio se debe determinar con referencia a las siguientes reivindicaciones anexas, junto con el alcance completo de equivalentes a los cuales las reivindicaciones están tituladas.

REIVINDICACIONES

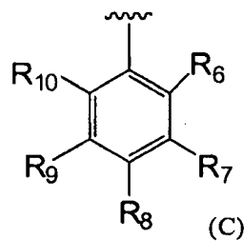
1. Un compuesto de acuerdo con la Fórmula I:



I

o una sal farmacéuticamente aceptable del mismo, en donde:

R_1 se selecciona de



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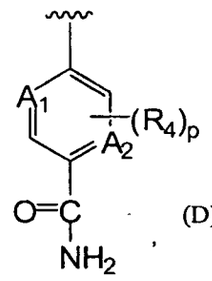

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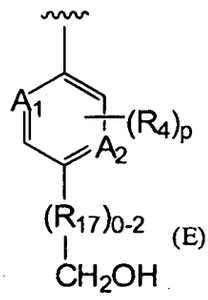

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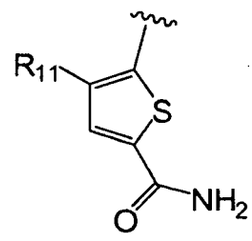


(Q) ;

R_3 se selecciona de hidrógeno, $-CF_3$, $-NH_2$, $-OH$, alquilo opcionalmente sustituido con 1, 2 o 3 R_5, alcoxi, dialquilaminoalquilo, cicloalquilo opcionalmente sustituido con arilalcoxi, arilo opcionalmente sustituido con 1, 2 o 3

grupos seleccionados de halógeno, alquilo, alcoxi, dialquilaminoalcoxi y heterocicloalquilo opcionalmente sustituido con alquilo o arilo, alquenilo, alquinilo, heterocicloalquilo opcionalmente sustituido con un grupo seleccionado de alquilo, -C(O)O-alquilo y arilalquilo, arilalquilo opcionalmente sustituido con alquilheterocicloalquilo en cualquier posición del anillo del grupo arilo, y heteroarilo;

R_4, R_7, R_8, R_9 y R_{11} cada uno se seleccionan independientemente de hidrógeno, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hidroxi, alquenilo, alquinilo, hidroxialquinilo, halógeno, hidroxialquilo, dihidroxialquilo, $-O-C(O)-NH_2$, amino(imino)alquilo, $-C(O)-NH_2$, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógeno, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, $-NH_2$, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de alquilo, alcoxi y halógeno;

R_5 se selecciona de halógeno, cicloalquilo, cicloalquilalquilamino, heteroarilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de halógeno, alquilo y

alcoxi, alquiltio, heterocicloalquilo opcionalmente sustituido con 1, 2, o 3 grupos seleccionados de alquilo, halógeno, fenilo y oxo, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de halógeno, alquilo, alcoxi, dialquilaminoalcoxi, y heterocicloalquilo opcionalmente sustituido con alquilo, alcoxi, dialquilamino, -OH, -C(O)-NH_2, -C(O)-O-CH_3, -C(O)-N(H)alquilo (C_1-C_3), heteroarilamino opcionalmente sustituido con halógeno, y -OCF_3;

R_6 y R_{10} cada uno se seleccionan de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, alquiltio, alquenilo, alquinilo, hidroxialquinilo, halógeno, hidroxialquilo, dihidroxialquilo, amino(imino)alquilo, -C(O)-NH_2, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilamino opcionalmente sustituido con 1-8 halógenos, dialquilamino, alcoxialquilamino, -N(H)alquilheterocicloalquilo, cicloalquilalquilamino, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalquilamino opcionalmente sustituido con un grupo seleccionado de -OH, alquilo, -CF_3 y heterocicloalquilo, -N(H)cicloalquilo opcionalmente sustituido con -OH o -NH_2, -NH_2, -N(H)-heteroarilo, -N(H)-arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de alcoxi, heterocicloalquilalcoxi y dialquilaminoalcoxi, alquilsulfonilalquilamino y -

N(H)heterocicloalquilo;

R_{16} se selecciona de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados de -OH, $-NH_2$, alquilo, heterocicloalquilo, y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalquilo, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo;

R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-;

cada uno es A_1 o A_2 es N o C(H), en donde A_1 y A_2 pueden ser iguales o diferentes, siempre que A_1 se pueda sustituir con R_4 solamente cuando A_1 es C(H), y siempre que A_2 se pueda sustituir con R_4 solamente cuando A_2 es C(H);

L_1 se selecciona de -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, $-(CH_2)_nC(O)NH-$, $-(CH_2)_nNHC(O)-$, $-(CH_2)_mNH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)_nNHSO_2-$, $-(CH_2)_mC(O)-$, $-(CH_2)_mO-$, y $-(CH_2)_mNH-(CH_2)_n-$;

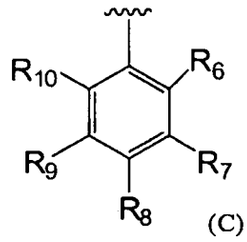
L_2 es $-C(O)-NH-R_3$, -CN, $-C(O)-N(CH_3)-OCH_3$, o $-C(O)-R_3$;

n es 0 o 1;

m es 0, 1 o 2; y

cada p es independientemente 0, 1, 2, 3 o 4.

2. El compuesto de acuerdo con la reivindicación 1, en donde R_1 se selecciona de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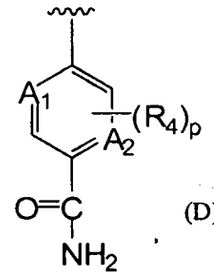
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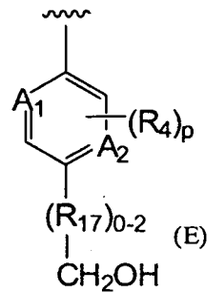
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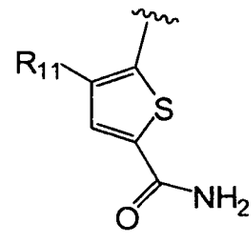

(Q) ;

R_3 se selecciona de hidrógeno, $-CF_3$, $-NH_2$, -OH, alquilo opcionalmente sustituido con 1, 2 o 3 R_5, alcoxi, dialquilaminoalquilo, cicloalquilo opcionalmente sustituido con arilalcoxi, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de halógeno, alquilo, alcoxi, dialquilaminoalcoxi y heterocicloalquilo opcionalmente sustituido con alquilo o arilo, alquenilo, alquinilo, heterocicloalquilo opcionalmente sustituido con un grupo seleccionado de alquilo, -C(O)O-alquilo y arilalquilo, arilalquilo opcionalmente sustituido con alquilheterocicloalquilo en cualquier posición del anillo del grupo arilo, y heteroarilo;

R_4, R_7, R_8, R_9 y R_{11} cada uno se seleccionan independientemente de hidrógeno, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hidroxi, alquenilo, alquinilo, hidroxialquinilo, alcoxi,

halógeno, hidroxialquilo, dihidroxialquilo, -O-C(O)-NH_2, amino(imino)alquilo, -C(O)-NH_2, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógeno, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, -NH_2, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de alquilo, alcoxi y halógeno;

R_5 se selecciona de halógeno, cicloalquilo, cicloalquilalquilamino, heteroarilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de halógeno, alquilo y alcoxi, alquiltio, heterocicloalquilo opcionalmente sustituido con 1, 2, o 3 grupos seleccionados de alquilo, halógeno, fenilo y oxo, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de halógeno, alquilo, alcoxi, dialquilaminoalcoxi, y heterocicloalquilo (opcionalmente sustituido con alquilo), alcoxi, dialquilamino, -OH, -C(O)-NH_2, -C(O)-O-CH_3, -C(O)-N(H)alquilo (C_1-C_3), heteroarilamino opcionalmente sustituido con halógeno, y -OCF_3;

R_6 y R_{10} cada uno se seleccionan de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, alquiltio, alquenilo, alquinilo, hidroxialquinilo, halógeno,

hidroxialquilo, dihidroxialquilo, amino(imino)alquilo, -C(O)-NH_2, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilamino opcionalmente sustituido con 1-8 halógenos, dialquilamino, alcoxialquilamino, -N(H)alquilheterocicloalquilo, cicloalquilalquilamino, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalquilamino opcionalmente sustituido con un grupo seleccionado de -OH, alquilo, $-CF_3$ y heterocicloalquilo, -N(H)cicloalquilo opcionalmente sustituido con -OH o $-NH_2$), $-NH_2$, -N(H)-heteroarilo, -N(H)-arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de alcoxi, heterocicloalquilalcoxi y dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo;

R_{16} se selecciona de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados de -OH, $-NH_2$, alquilo, heterocicloalquilo, y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalcoxi, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalcoxi;

cada uno es A_1 o A_2 es -N= o -CH=, en donde A_1 y A_2 pueden ser iguales o diferentes;

L_1 se selecciona de -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)_nC(O)NH-$, $-(CH_2)_nNHC(O)-$, $-(CH_2)_mNH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)_nNHSO_2-$, $-(CH_2)_mC(O)-$, $-(CH_2)_mO-$, y $-(CH_2)_mNH-$;

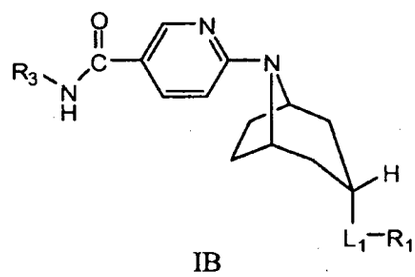
L_2 es $-C(O)-NH-R_3$, -CN o $-C(O)-R_3$;

n es 0 o 1;

m es 0, 1 o 2; y

cada p es independientemente 0, 1, 2, 3 o 4.

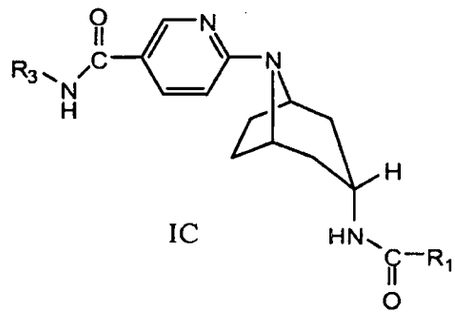
3. El compuesto de acuerdo con la reivindicación 1, caracterizado porque se selecciona de:



IB

o una sal farmacéuticamente aceptable del mismo,

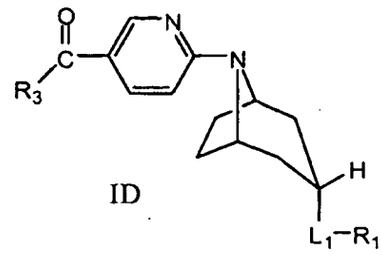
en donde L_1, R_1 y R_3 son como se definen de acuerdo con la reivindicación 1,



IC

o una sal farmacéuticamente aceptable del mismo,

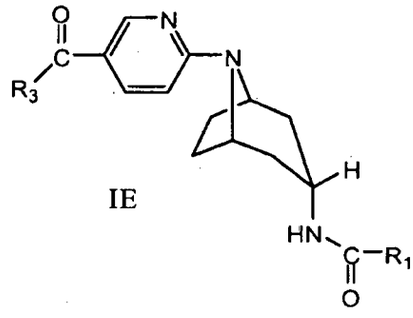
en donde R_1 y R_3 son como se definen de acuerdo con la reivindicación 1,



ID

o una sal farmacéuticamente aceptable del mismo,

en donde R_1, R_3 y L_1 son como se definen de acuerdo con la reivindicación 1, y



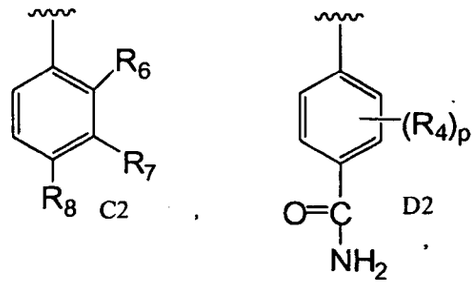
IE

o una sal farmacéuticamente aceptable del mismo,

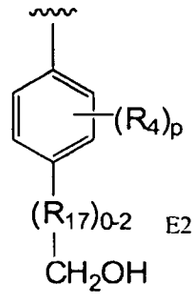
en donde R_1 y R_3 son como se definen de acuerdo con la reivindicación 1.

4. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde:

R_1 se selecciona de



y



R_3 se selecciona de CF_3, ciclopropilo, ciclobutilo, ciclohexilo opcionalmente sustituido con hidroxilo, ciclopropilmetilo, N-propilo, 3-metilbutilo, (1S)-2-hidroxi-1-metiletilo, (2S)-2-hidroxipropilo, metoxietilo, etoxietilo, metilfenilo, fenilo, dimetilfenilo, metoxifenilo, dimetilaminoetilo, dimetilaminopropilo, dietilaminoetilo, dietilaminopropilo, ciclopentilo, halofenilo, fenilmetilo, feniletilo opcionalmente sustituido con hidroxilo en la posición etilo de feniletilo, fenilpropilo, fenilpiperidinilo, dietilaminoetiloxifenilmetilo, dietilaminoetiloxifeniletilo, pirrolidinilfenilmetilo, dietilaminoetiloxi-2-fluorofeniletilo, fenilalquilo (C_1-C_3) opcionalmente sustituido en la posición fenilo de fenilalquilo (C_1-C_3) con 1-3 grupos seleccionados de metoxi, halo y metilo, metilfenilalquilo (C_1-C_4) en donde la porción

alquilo (C_1-C_4) de metilfenilalquilo (C_1-C_4) se sustituye opcionalmente con $-C(O)NH_2$, $-C(O)NHCH_3$ o $-C(O)NHCH_2CH_3$, tienilmetilo, furanilmetilo, piridiniletilo, piridinilmetilo, metilpirazinilmetilo, metilo, etilo, metilpropilo, 2-metilpropilo, 2,3-dihidroxipropilo, (1S)-1-metilpropilo, (1S)-1,2-dimetilpropilo, (1R)-1,2-dimetilpropilo, metiloxipropilo, etiloxipropilo, (1S)-1-metil-2-(metiloxi)etilo, 1,3-benzodioxolilo, 1,3-benzodioxlilmetilo, N-prop-2-in-1-ilo, N-[3-(4-metilpiperazin-1-il)propilo, N-[2-(etiltio)etilo], (1S,2S)-2-[(fenilmetil)oxi]ciclopentilo, 6-cloropiridinilmetilo, 2-cloro-6-fluorofenilmetilo, metiltioetilo, N-butilo, 1-metiletiloxietilo, 1-metiletiloxipropilo, 4,4-bismetiloxibutilo, metilpirazinilmetilo, propiloxipropilo, trifluorometiloxifenilmetilo, metiloxifeniletilo, (2,2-dimetil-1,3-dioxolan-4-il)metilo, fenilmetilpirrolidinilo, oxopirrolidinilpropilo, pirrolidiniletilo, metilpirrolidiniletilo, etilpirrolidinilmetilo, N-(1R,2R,4S)-biciclo[2.2.1]hept-2-ilo, 3,3-dimetilbutilo, etiloxifenilmetilo, fenilmetilpiperidinilo, etoxicarbonilpiperidinilo, trifluorometilfenilmetilo, imidazolilpropilo, (3R)-pirrolidin-3-ilo, morfoliniletilo, morfolinilpropilo, piperidiniletilo, pirrolidinilo, piperidinilo, pirrolidinilmetilo, 1-metiletilpirrolidinilo, etilpirrolidinilo, metilpirrolidinilo, metiletilpiperidinilo,

metilpiperidinilo, etilpiperidinilo, etilazetidinilo, azetidinilo, metilazetidinilo, 1-metiletilazetidinilo, metilpiperazinilfenilmetilo, piperazinilfenilmetilo, metilpiperazinilfenilo, metilpiperidinilfenilo, piperidinilfenilalquilo (C_1-C_3) opcionalmente sustituido con 1-4 halo, metilpiperazinilfenil(halo)metilo, metilpiperidinilfenilmetilo, metilpiperazinilfeniletilo, 2-metilpropilpiperazinilfenilmetilo, morfolinilfenilmetilo, piperazinilpiridiniletilo, $-CH(CH_3)C(O)-NH_2$, dimetilaminoetiloxifenilo, isopropilo, alquilo (C_1-C_5) opcionalmente sustituido con 1-7 halo,-OH, $-NH_2$, ciclohexilalquilo (C_1-C_5) opcionalmente sustituido con 1-2 grupos hidroxilo, fenilaminoetilo opcionalmente sustituido con halo, morfoliniletilo, fenilpiperaziniletilo, y metilpiperaziniletilo;

cada R_4, cuando se presenta, es independientemente seleccionado de halo, 1-etilpropilamino, metilo, etilo, ciclohexilamino opcionalmente sustituido con hidroxilo, ciclobutilamino, 1-metilpropiloxi, metoxietoxi, $-CF_3$, piperidinilo o amino, morfolinilamino, dimetilaminobutilo, metiletilaminopropilo, metiletilaminopropilamino, ciclopentilamino, piperidinilamino, metiletilamino, etilamino, 2-metilpropilamino, tetrahidropiranilamino, etilpiperidinilamino, 2,2-dimetilpropilamino, pirrolidinilamino, 1-metilpropilamino, 2-metilpropilamino,

amino, 1,1 dimetiletilamino, tetrahidropiranilmetilamino, piperidinilamino opcionalmente sustituido con metilsulfonilo, fenilamino opcionalmente sustituido con 1-3 grupos seleccionados de metoxi y dimetilaminoetiloxi, metilsulfoniletilamino, metoxietilamino, morfoliniletiloxi, -N(H)C(O)CH_3, ciclobutilamino, metoxi, ciclobutiloxi, ciclobutilamino, piridinilamino, etilamino, 1-metilciclopropiletilamino, metiletiloxietilamino, butilamino, piperidinilo, pentilamino, azetinilo, 1,2-dimetilpropilamino, 1-metiletilpropilamino, propilamino, 1-ciclopropilpropilamino, 1-propilbutilamino, 1-ciclopropiletilamino, diciclopropilmetilamino, 1,2,2-trimetilpropilamino, tetrahidrofuranilamino, alquilamino (C_1-C_5) sustituido con 1-7 halo, morfoliniletiloxi y ciclopropilmetilamino;

R_6 se selecciona de hidrógeno, alquilo (C_1-C_4) opcionalmente sustituido con hidroxi, alquilamino o dimetilamino (C_1-C_3), alquinilo (C_1-C_4) opcionalmente sustituido con hidroxilo, y halo;

R_7 se selecciona de hidrógeno, -OH, -Oalquilo (C_1-C_3), -Salquilo (C_1-C_3), -N(H)alquilo (C_1-C_3), cicloalquilamino (C_5-C_6) opcionalmente sustituido con hidroxilo, alquilamino o dimetilamino (C_1-C_3), -C(O)NH_2, y -O-C(O)NH_2;

R_8 se selecciona de hidrógeno, -Oalquilo (C_1-C_3), -O-C(O)NH_2, y -C(=NH)-NH_2;

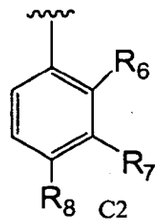
L_1 es -N(H)C(O)-;

L_2 es -C(O)-NH-R_3 o -C(O)-R_3; y

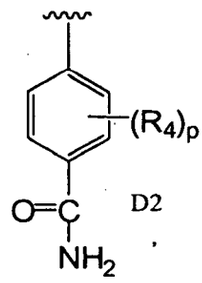
cada p es independientemente 0, 1, 2 o 3.

5. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde:

R_1 se selecciona de

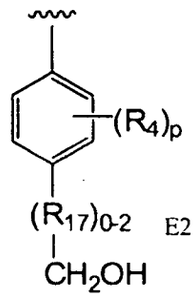


C2 ,



D2 ,

y



E2

R_3 se selecciona de hidrógeno, $-CF_3$, $-NH_2$, -OH, alquilo opcionalmente sustituido con 1, 2 o 3 R_5, alcoxi, dietilaminoetoxi, etilmetilaminoetoxi, dimetilaminoetoxi, ciclopentilo opcionalmente sustituido con arilalcoxi, ciclobutilo opcionalmente sustituido con arilalcoxi, ciclopropilo opcionalmente sustituido con arilalcoxi, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de halógeno, alquilo, alcoxi, dialquilaminoalcoxi, piperazinilo

opcionalmente sustituido con alquilo o fenilo, morfolinilo opcionalmente sustituido con alquilo o fenilo, azetidinilo y piperidinilo opcionalmente sustituido con alquilo o fenilo, alquenilo, alquinilo, heterocicloalquilo seleccionado de piperidinilo, pirrolidinilo, morfolinilo y piperizinilo, en donde el heterocicloalquilo es opcionalmente sustituido con un grupo seleccionado de alquilo, -C(O)O-alquilo y arilalquilo, arilalquilo opcionalmente sustituido con alquilheterocicloalquilo en cualquier posición del anillo del grupo arilo, y heteroarilo;

cada R_4, cuando se presenta, se selecciona independientemente de metilo, 1-metiletilamino, etilamino, 1-etilpropilamino, 2-metilpropilamino, (2,2-dimetilpropil)amino, (2-aminoetil)amino, (2,2,3,3,3-pentafluoropropil)amino, 1-metilpropilamino, (1S)-1-metilpropilamino, (2,2,2-trifluoroetil)amino, 1-propilbutilamino, propilamino, 1,2-dimetilpropilamino, (3,3,3-trifluoropropil)amino, (2,2,3,3,4,4,4-heptafluorobutil)amino, butilamino, 1,2,2-trimetilpropilamino, 1-[(metiloxi)metil]propilamino, 1-metiletiloxietilamino, 1-metilpropilamino, pentilamino, (2,2,3,3,3-pentafluoropropil)amino, butilamino, 2-[(1-metiletil)oxi]etilamino, (1S)-1-metilpropilamino, (1R)-1-metilpropilamino, (1S)-1,2-dimetilpropilamino, 1-ciclopropiletilamino, (1R)-1,2-dimetilpropilamino, 1-etil-2-

metilpropilamino, y 3-[(1-metiletil)amino]propilamino;

R_6 se selecciona de hidrógeno, alquilo (C_1-C_4) opcionalmente sustituido con hidroxi, alquilamino o dimetilamino (C_1-C_3), alquinilo (C_1-C_4) opcionalmente sustituido con hidroxilo, y halo;

R_7 se selecciona de hidrógeno, -OH, -Oalquilo (C_1-C_3), -Salquilo (C_1-C_3), -N(H)alquilo (C_1-C_3), cicloalquilamino (C_5-C_6) opcionalmente sustituido con hidroxilo, alquilamino o dimetilamino (C_1-C_3), -C(O)NH_2, y -O-C(O)NH_2;

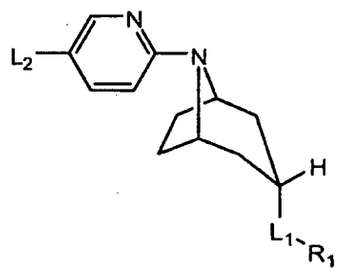
R_8 se selecciona de hidrógeno, -Oalquilo (C_1-C_3), -O-C(O)NH_2, y -C(=NH)-NH_2;

L_1 es -N(H)C(O)-;

L_2 es -C(O)-NH-R_3 o -C(O)-R_3; y

cada p es independientemente 0, 1, 2 o 3.

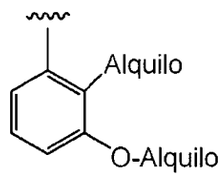
6. El compuesto de acuerdo con la reivindicación 1 que tiene la Fórmula I:



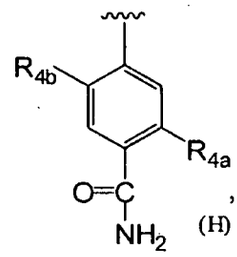
I

una sal farmacéuticamente aceptable del mismo, en donde:

R_1 se selecciona a partir de:

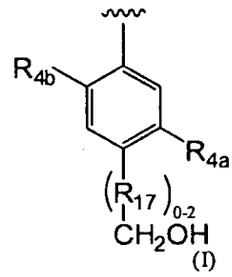


(G) ,



(H) ,

y



(I)

en donde R_{4a} se selecciona de hidrógeno, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hidroxi, alquenilo, alquinilo, hidroxialquinilo, alcoxi, halógeno, hidroxialquilo, dihidroxialquilo, $-O-C(O)-NH_2$, amino(imino)alquilo, $-C(O)-NH_2$, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógenos, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, $-NH_2$, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de alquilo, alcoxi y halógeno;

R_{4b} se selecciona de H, halógeno y metilo

opcionalmente sustituido con 1-3 halógenos;

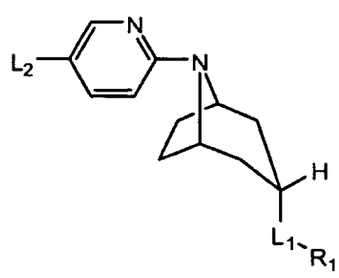
R_{16} se selecciona de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados de -OH, $-NH_2$, alquilo, heterocicloalquilo, y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalquilo, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo;

R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-;

L_1 se selecciona de -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)C(O)NH-$, $-(CH_2)NHC(O)-$, $-(CH_2)NH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)NHSO_2-$, $-(CH_2)C(O)-$, $-(CH_2)O-$, y $-NH-(CH_2)-$; y

L_2 es -C(O)-NH-ciclopropilo o $-NH-C(O)-CH_3$.

7. El compuesto de acuerdo con la reivindicación 1 que tiene la Fórmula I:

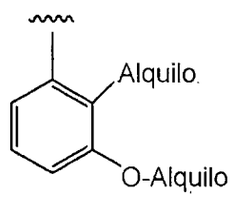


I

una sal farmacéuticamente aceptable del mismo, en

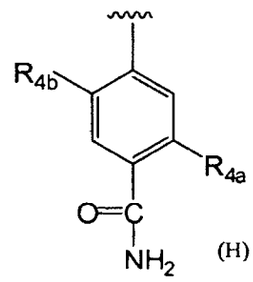
donde:

R_1 se selecciona a partir de:



(G)

y



(H)

en donde R_{4a} se selecciona de hidrógeno, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hidroxi, alquenilo, alquinilo, hidroxialquinilo, alcoxi, halógeno, hidroxialquilo, dihidroxialquilo, $-O-C(O)-NH_2$, amino(imino)alquilo, $-C(O)-NH_2$, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógenos, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, $-NH_2$, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de alquilo, alcoxi y halógeno;

R_{4b} se selecciona de H, halógeno y metilo opcionalmente sustituido con 1-3 halógenos;

R_{16} se selecciona de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados de -

OH, $-NH_2$, alquilo, heterocicloalquilo, y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalquilo, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo;

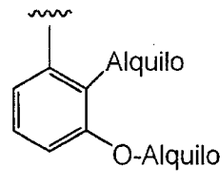
L_1 se selecciona de -NHC(O)-, $-NHSO_2-$, -NHC(O)O-, -C(O)O-, -C(O)NH-, $-C(O)NHSO_2-$, -C(O)-, $-(CH_2)C(O)NH-$, $-(CH_2)NHC(O)-$, $-(CH_2)NH-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)NHSO_2-$, $-(CH_2)C(O)-$, $-(CH_2)O-$, y $-NH-(CH_2)-$; y

L_2 es -C(O)-NH-ciclopropilo o $-NH-C(O)-CH_3$.

8. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde L_2 es -C(O)-NH-ciclopropilo, $-C(O)-NH-CH_3$, -C(O)-ciclopropilo, o $-C(O)-CH_3$.

9. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde R_1 se selecciona de uno de los siguientes del Grupo Z:

<u>Grupo Z</u>



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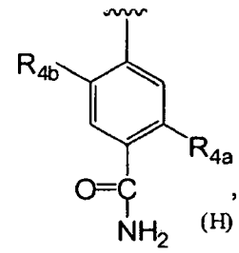

(H) ,

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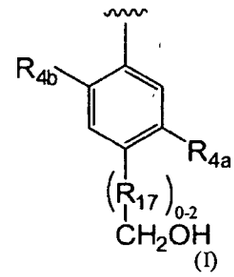


(I)

en donde R_{4a} se selecciona de hidrógeno, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hidroxi, alquenilo, alquinilo, hidroxialquinilo, alcoxi, halógeno, hidroxialquilo, dihidroxialquilo, $-O-C(O)-NH_2$, amino(imino)alquilo, $-C(O)-NH_2$, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógenos, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, $-NH_2$, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de alquilo, alcoxi y halógeno;

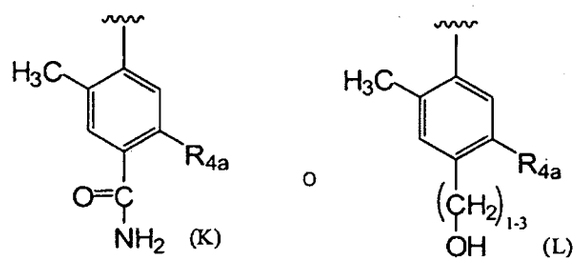
R_{4b} se selecciona de H, halógeno y metilo opcionalmente sustituido con 1-3 halógenos;

R_{16} se selecciona de hidrógeno, alquilo

opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados de -OH, $-NH_2$, alquilo, heterocicloalquilo, y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heterocicloalquilalquilo, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo; y

R_{17}, cuando se presenta, es $-CH_2-$ o -CH(OH)-.

10. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde R_1 es

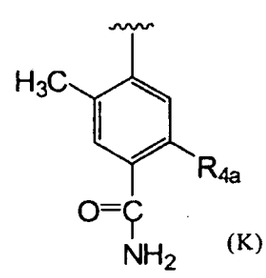


en donde R_{4a} se selecciona de $-N(H)R_{16}$, $-OR_{16}$, y $-SR_{16}$; y

R_{16} se selecciona de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados de -OH, $-NH_2$, $-CH_3$ y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo

opcionalmente sustituido con 1, 2 o 3 alcoxi, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo.

11. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde R_1 es

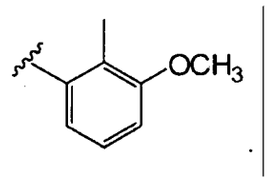


(K)

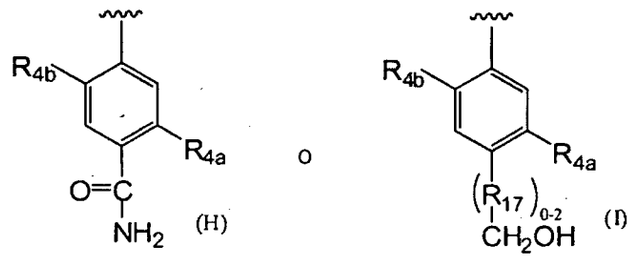
en donde R_{4a} se selecciona de $-N(H)R_{16}$, $-OR_{16}$, y $-SR_{16}$; y

R_{16} se selecciona de hidrógeno, alquilo opcionalmente sustituido con 1-8 halógenos, cicloalquilo opcionalmente sustituido con 1 o 2 grupos seleccionados de -OH, $-NH_2$, $-CH_3$ y $-CF_3$, cicloalquilalquilo, heterocicloalquilo opcionalmente sustituido con -OH o $-NH_2$, alcoxialquilo, arilo opcionalmente sustituido con 1, 2 o 3 alcoxi, heteroarilo, gem-dicicloalquilalquilo y dialquilaminoalquilo.

12. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde R_1 es



13. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde R_1 es



en donde R_{4a} es alquilamino opcionalmente sustituido con 1-8 halógenos;

R_{4b} se selecciona de H, halógeno y metilo opcionalmente sustituido con 1-3 halógenos;

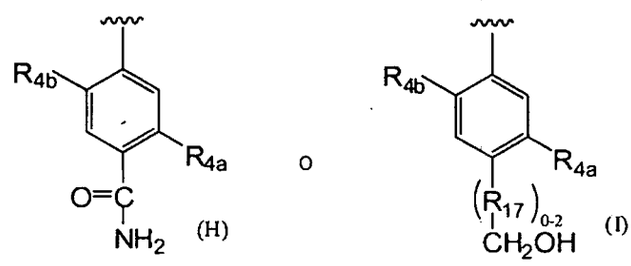
R_{17}, cuando se presenta, es $-CH_2-$ o $-CH(OH)-$; y

L_1 es $-N(H)C(O)-$.

14. El compuesto de acuerdo con la reivindicación 13, o una sal farmacéuticamente aceptable del mismo, en donde R_{4a} es 1-metiletilamino, etilamino, 1-etilpropilamino, 2-metilpropilamino, (2,2-dimetilpropil)amino, (2-aminoetil)amino, (2,2,3,3,3-pentafluoropropil)amino, 1-

metilpropilamino, (1S)-1-metilpropilamino, (2,2,2-trifluoroetil)amino, 1-propilbutilamino, propilamino, 1,2-dimetilpropilamino, (3,3,3-trifluoropropil)amino, (2,2,3,3,4,4,4-heptafluorobutil)amino, butilamino, 1,2,2-trimetilpropilamino, 1-[(metiloxi)metil]propilamino, 1-metiletiloxietilamino, 1-metilpropilamino, pentilamino, (2,2,3,3,3-pentafluoropropil)amino, butilamino, 2-[(1-metiletil)oxi]etilamino, (1S)-1-metilpropilamino, (1R)-1-metilpropilamino, (1S)-1,2-dimetilpropilamino, 1-ciclopropiletilamino, (1R)-1,2-dimetilpropilamino, 1-etil-2-metilpropilamino, o 3-[(1-metiletil)amino]propilamino.

15. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde R_1 es



en donde R_{4a} es heterocicloalquilamino opcionalmente sustituido con alquilo;

R_{4b} se selecciona de H, halógeno y metilo opcionalmente sustituido con 1-3 halógenos;

R_{17}, cuando se presenta, es $-CH_2-$ o $-CH(OH)-$; y

L_1 es -N(H)C(O)-.

16. El compuesto de acuerdo con la reivindicación 15, o una sal farmacéuticamente aceptable del mismo, en donde R_{4a} es tetrahidrofuran-3-ilamino, piperidin-4-ilamino, tetrahidro-2H-piran-4-ilamino, (1-etilpiperidin-4-il)amino, (tetrahidrofuran-2-ilmetil)amino, pirrolidin-3-ilamino, (piperidin-3-ilmetil)amino, (pirrolidin-3-ilmetil)amino, (3S)-tetrahidrofuran-3-ilamino, (3R)-tetrahidrofuran-3-ilamino, azetidin-1-ilo, piperidin-1-ilamino, o (3S)-tetrahidrofuran-3-ilamino.

17. El compuesto de acuerdo con la reivindicación 1, en donde el compuesto de Fórmula I se selecciona de uno de los siguientes compuestos:

NOMBRE
N-ciclopropil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(metiloxi)etil]piridin-3-carboxamida;
N-[2-(dimetilamino)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-morfolin-4-iletil)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(piridin-3-ilmetil)piridin-3-carboxamida;
N-ciclopentil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida
N-[(2-clorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(4-clorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;

NOMBRE
N-{2-[3,4-bis(metiloxi)fenil]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-(furan-2-ilmetil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-metilpropil)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(metiloxi)fenil]metil}piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(metiloxi)propil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-metilfenil)metil]piridin-3-carboxamida;
N-(1,3-benzodioxol-5-ilmetil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-prop-2-in-1-ilpiridin-3-carboxamida;
N-{[3,4-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(4-metilpiperazin-1-il)propil]piridin-3-carboxamida;
N-[2-(etiltio)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S,2S)-2-[(fenilmetil)oxi]ciclopentil}piridin-3-carboxamida;
N-[(6-cloropiridin-3-il)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(2-cloro-6-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(metiltio)etil]piridin-3-carboxamida;;
N-butil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;

NOMBRE
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(3-morfolin-4-ilpropil)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-piridin-4-iletil)piridin-3-carboxamida;
N-{2-[(1-metiletil)oxi]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-piridin-3-iletil)piridin-3-carboxamida;
N-[4,4-bis(metiloxi)butil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(5-metilpirazin-2-il)metil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-endo-(propiloxi)propil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[3,4,5-tris(metiloxi)fenil]metil}piridin-3-carboxamida;
N-{[3,5-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-({4-[(trifluorometil)oxi]fenil}metil)piridin-3-carboxamida;
N-(ciclopropilmetil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{[2,4-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(4-bromofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(2,2-dimetil-1,3-dioxolan-4-il)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3S)-1-(fenilmetil)pirrolidin-3-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3R)-1-(fenilmetil)pirrolidin-3-il]piridin-3-carboxamida;

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NOMBRE
N-[3-(dietilamino)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{3-[(1-metiletil)oxi]propil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-propilpiridin-3-carboxamida
N-[2-(dietilamino)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida
N-(3-metilbutil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3-metilfenil)metil]piridin-3-carboxamida;
N-[(3-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2-metilfenil)metil]piridin-3-carboxamida;
N-[(3-clorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(tetrahidrofuran-2-ilmetil)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(2-oxopirrolidin-1-il)propil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(1-metilpirrolidin-2-il)etil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-piperidin-1-iletil)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[2-(metiloxi)fenil]metil}piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[3-(metiloxi)fenil]metil}piridin-3-carboxamida;

NOMBRE
N-[(2-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(4-fluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(1R,2R,4S)-biciclo[2.2.1]hept-2-il]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-(3,3-dimetilbutil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{[2,3-bis(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{[2-(etiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[1-(fenilmetil)piperidin-4-il]piridin-3-carboxamida;
4-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino]piperidine-1-carboxilato de etilo;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-tienilmetil)piridin-3-carboxamida;
N-ciclobutil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[3-(etiloxi)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[3-(dimetilamino)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(trifluorometil)fenil]metil}piridin-3-carboxamida;
N-[(2,4-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(2,5-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(2,6-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;

NOMBRE
N-[(3,4-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[3-(1H-imidazol-1-il)propil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(2-metilfenil)piridin-3-carboxamida;
N-(3,5-dimetilfenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-1,3-benzodioxol-5-il-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(4-metilfenil)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(3-metilfenil)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[2-(metiloxi)fenil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[3-(metiloxi)fenil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[4-(metiloxi)fenil]piridin-3-carboxamida;
N-(3-clorofenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-(4-fluorofenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[3-(metiloxi)fenil]etil}piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-morfolin-4-ilfenil)metil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3R)-pirrolidin-3-il]piridin-3-carboxamida;

NOMBRE
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-piperidin-3-ilpiridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-piperidin-4-ilpiridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(pirrolidin-3-ilmetil)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(1-metilpiperidin-4-il)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida;
N-(1-metiletil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-ciclohexil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-metil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-etil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(1S)-1,2-dimetilpropil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(1R)-1,2-dimetilpropil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(1S)-1-metil-2-(metiloxi)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-azetidin-3-il-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(1-metilpiperidin-4-il)fenil]metil}piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(metiloxi)fenil]etil}piridin-3-carboxamida;

NOMBRE
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-piperidin-3-ilpiridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-piperidin-4-ilpiridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(pirrolidin-3-ilmetil)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(1-metilpiperidin-4-il)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida;
N-(1-metiletil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-ciclohexil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-metil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-etil-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(1S)-1,2-dimetilpropil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(1R)-1,2-dimetilpropil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(1S)-1-metil-2-(metiloxi)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-azetidin-3-il-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[4-(1-metilpiperidin-4-il)fenil]metil}piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(metiloxi)fenil]etil}piridin-3-carboxamida;

NOMBRE
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1R)-1-[4-(metiloxi)fenil]etil}piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1R)-1-feniletil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1S)-1-feniletil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1S)-1-fenilpropil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-((1-feniletil)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida;
N-[(1S)-1-(4-clorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{(1S)-1-[2-fluoro-4-(metiloxi)fenil]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{[2-fluoro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(2-cloro-3,6-difluorofenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(4-{[2-(dietilamino)etil]oxi}fenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(1S)-2-amino-1-metil-2-oxoetil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(3-{[2-(dietilamino)etil]oxi}fenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{[4-fluoro-3-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{[3-fluoro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;

NOMBRE
N-{[2-cloro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2,4,6-trifluorofenil)metil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[3-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida;
N-{[2,6-difluoro-4-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(2-cloro-6-fluoro-3-metilfenil)metil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[1-(4-clorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(1-fenilpiperidin-4-il)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-pirrolidin-1-ilfenil)metil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2,3,6-trifluorofenil)metil]piridin-3-carboxamida;
N-{[2-fluoro-6-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{[4-fluoro-2-(metiloxi)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{[2-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(2,4,5-trifluorofenil)metil]piridin-3-carboxamida;
N-{[3-fluoro-4-(4-metilpiperazin-1-il)fenil]metil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-(8-{5-[({[4-(4-metilpiperazin-1-il)fenil]metil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;

NOMBRE
N-[(1S)-1-(4-{[2-(dietilamino)etil]oxi}-2-fluorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[4-(4-metilpiperazin-1-il)fenil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[4-(1-metilpiperidin-4-il)fenil]piridin-3-carboxamida;
N-(4-{[2-(dimetilamino)etil]oxi}fenil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-hidroxi-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{8-[5-(hidrazinocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-3-(metiloxi)benzamida;
N-[(1S)-1-(4-{[2-(dietilamino)etil]oxi}fenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[1-(6-piperazin-1-ilpiridin-3-il)etil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(4-piperazin-1-ilfenil)metil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-({4-[4-(2-metilpropil)piperazin-1-il]fenil}metil)piridin-3-carboxamida;
N-[1-(4-bromo-2-fluorofenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{1-[3,4-bis(metiloxi)fenil]etil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(1S)-1-metilpropil]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3R)-1-metilpirrolidin-3-il]piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(3S)-1-metilpirrolidin-3-il]piridin-3-carboxamida;

NOMBRE
N-(2,3-dihidroxipropil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(1S,2S)-2-hidroxiciclopentil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(1S,2S)-2-hidroxiciclohexil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(1S)-2-hidroxi-1-metiletil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[(2S)-2-hidroxipropil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-(2-hidroxietil)-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
2-[(1-etilpropil)amino]-N4-[8-(5-{[(3R)-pirrolidin-3-ilamino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
2-[(1-etilpropil)amino]-N4-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-
2-[(1-etilpropil)amino]-N4-{8-[5-({[(3S)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-
2-[(1-etilpropil)amino]-N4-{8-[5-({[(3R)-1-etilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
5-[(1-etilpropil)amino]-2-metil-N-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-
2-[(1-etilpropil)amino]-N4-[8-(5-{[(3S)-piperidin-3-ilamino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
5-[(1-etilpropil)amino]-2-metil-N-{8-[5-({[(3R)-1-(1-metiletil)piperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-
6-(3-endo-{[(2,3-dimetilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida;

NOMBRE
6-(3-endo-{[(3-hidroxi-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida;
6-(3-endo-{[(3-amino-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida;
N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
2-metil-N1-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida;
2-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,3-dicarboxamida;
3-metil-4-({[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]amino}carbonil)fenilcarbamato;
2-metil-3-({[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]amino}carbonil)fenilcarbamato;
6-[3-endo-({[4-(hidroximetil)-2-metilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida;
6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(piridin-3-ilmetil)piridin-3-carboxamida;
N-[8-(5-{[(piridin-3-ilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-[(5-metilpirazin-2-il)metil]piridin-3-carboxamida;
N-{8-[5-({[(5-metilpirazin-2-il)metil]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
6-[3-endo-({[4-(hidroximetil)-2-metilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(piridin-3-ilmetil)piridin-3-carboxamida;
6-{3-endo-[({4-[amino(imino)metil]fenil}carbonil)amino]-8-azabiciclo[3.2.1]oct-8-il}-N-(fenilmetil)piridin-3-carboxamida;

NOMBRE
6-[3-endo-({[2-metil-3,4-bis(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida;
6-[3-endo-({[3-(metiloxi)-2-propilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida;
6-[3-endo-({[3-(metiloxi)-2-prop-2-en-1-ilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida;
6-[3-endo-({[2-bromo-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida;
6-[3-endo-({[2-iodo-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida;
2,6-dimetil-N1-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino}bencen-1,4-dicarboxamida;
N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[2-(metilsulfonil)etil]amino}bencen-1,4-dicarboxamida;
N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-[(4-trans-hidroxiciclohexil)amino]bencen-1,4-dicarboxamida;
2-[(4-trans-hidroxiciclohexil)amino]-N4-{8-[5-({[1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-[8-(5-{[metil(metiloxi)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
N4-(8-{5-[(ciclopentilamino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
5-[(1-etilpropil)amino]-N-{8-[5-({[(1-etilpirrolidin-2-il)metil]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida;
6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;

NOMBRE
6-[3-endo-({[2-fluoro-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-cloro-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-(3-endo-{[(4-amino-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
6-[3-endo-({[4-(hidroximetil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
6-[3-endo-({[4-(hidroximetil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-(4-hidroxibut-1-in-1-il)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[2-(metiloxi)etil]amino}bencen-1,4-dicarboxamida;
N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(2-morfolin-4-iletil)oxibencen-1,4-dicarboxilato;
N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(4-hidroxiciclohexil)amino]bencen-1,4-dicarboxamida;
2-(acetilamino)-N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[2-(metilsulfonil)etil]amino}bencen-1,4-dicarboxamida;
N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(ciclobutilamino)bencen-1,4-dicarboxamida;
2,5-dimetil-N-{8-[5-({[(3S)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
6-(3-endo-{[(3-hidroxi-2-metilfenil)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida;

NOMBRE
4-metil-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1H-1,2,3-benzotriazol-5-carboxamida;
2-(metiloxi)-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
6-[3-endo-({[2-metil-3-(metilamino)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida;
6-[3-endo-({[3-(dimetilamino)-2-metilfenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida;
6-[3-endo-({[2-metil-3-(metiltio)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida;
2-(ciclobutiloxi)-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
2-metil-3-(metiloxi)-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
2-(ciclobutilamino)-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[3,4,5-tris(metiloxi)fenil]amino}bencen-1,4-dicarboxamida;
N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-(fenilamino)bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-(piridin-4-ilamino)bencen-1,4-dicarboxilato;
N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[1-(metilsulfonil)piperidin-4-il]amino}bencen-1,4-dicarboxamida;
3-(etilamino)-2,5-dimetil-N1-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
2-[(4-hidroxiciclohexil)amino]-N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;

NOMBRE
N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-{[2-(metilsulfonil)etil]amino}bencen-1,4-dicarboxamida;
6-{3-endo-[({3-[(4-hidroxiciclohexil)amino]fenil}carbonil)amino]-8-azabiciclo[3.2.1]oct-8-il}-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida;
2,5-dimetil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
2,5-dicloro-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
2,5-dimetil-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
N-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida;
2,5-dimetil-N-{8-[5-({[(3R)-1-(1-metiletil)pirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2,5-dimetil-N-{8-[5-({[(3S)-1-metilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
N-{8-[5-({[(3R)-1-etilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida;
2,5-dimetil-N-{8-[5-({[(3R)-1-metilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2,5-dimetil-N-{8-[5-({[(3R)-1-metilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2,5-dimetil-N-[8-(5-{[(1-metilpiperidin-4-il)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
N-[8-(5-{[(1-etilpiperidin-4-il)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2,5-dimetilbencen-1,4-dicarboxamida;
2,5-dimetil-N-{8-[5-({[1-(1-metiletil)piperidin-4-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
N-{8-[5-({[(3S)-1-etilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida;

NOMBRE
2,5-dimetil-N-{8-[5-({[(3R)-1-(1-metiletil)piperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
N-{8-[5-({[(3S)-1-etilpiperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida;
2,5-dimetil-N-{8-[5-({[(3S)-1-(1-metiletil)piperidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2,5-dimetil-N-{8-[5-({[(3S)-1-metilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
N-{8-[5-({[(3R)-1-etilpirrolidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2,5-dimetilbencen-1,4-dicarboxamida;
N-[8-(5-{[(1-etilazetidin-3-il)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2,5-dimetilbencen-1,4-dicarboxamida;
2,5-dimetil-N-{8-[5-({[1-(1-metiletil)azetidin-3-il]amino}carbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2,5-dimetil-N-[8-(5-{[(1-metilazetidin-3-il)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
(2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoato de metilo;
Ácido (2S)-[({6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-il}carbonil)amino][4-(metiloxi)fenil]etanoico;
N-{(1S)-2-amino-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{(1S)-2-(metilamino)-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-{(1S)-2-(etilamino)-1-[4-(metiloxi)fenil]-2-oxoetil}-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N4-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2-[(2-morfolin-4-iletil)amino]bencen-1,4-dicarboxamida;
N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino}bencen-1,4-dicarboxamida;

NOMBRE
N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(trans-4-aminociclohexil)amino]bencen-1,4-dicarboxamida;
N-[1-(2-fluoro-4-piperidin-4-ilfenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
N-[1-(2,6-difluoro-4-piperidin-4-ilfenil)etil]-6-[3-endo-({[2-metil-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida;
6-[3-endo-({[2-(3-hidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[2-{3-[(1-metiletil)amino]propil}-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida;
6-[3-endo-({[2-(4-hidroxibutil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-{3-endo-[({2-[4-(dimetilamino)butil]-3-(metiloxi)fenil}carbonil)amino]-8-azabiciclo[3.2.1]oct-8-il}piridin-3-carboxamida;
6-[3-endo-({[2-(2,3-dihidroxipropil)-3-(metiloxi)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]piridin-3-carboxamida;
6-[3-endo-({[4-(1,2-dihidroxietil)fenil]carbonil}amino)-8-azabiciclo[3.2.1]oct-8-il]-N-(fenilmetil)piridin-3-carboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(trans-4-hidroxiciclohexil)amino]bencen-1,4-dicarboxamida;
N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-metil-3-(metiloxi)benzamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(ciclohexilamino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(ciclopentilamino)bencen-1,4-dicarboxamida;

NOMBRE
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(piperidin-4-ilamino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-metiletil)amino]bencen-1,4-dicarboxamida;
N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-5-[(trans-4-hidroxiciclohexil)amino]-2-metilbencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(etilamino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-etilpropil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(ciclopropilamino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2-metilpropil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(tetrahidrofuran-3-ilamino)bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-metilbutanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-[8-(5-propanoilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(tetrahidro-2H-piran-4-ilamino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-etilpiperidin-4-il)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2-dimetilpropil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(tetrahidrofuran-2-ilmetil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(pirrolidin-3-ilamino)bencen-1,4-dicarboxamida;

NOMBRE
2-[(ciclopropilmetil)amino]-N4-{8-[5-(4,4,4-trifluorobutanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(fenilamino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2-aminoetil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2,3,3,3-pentafluoropropil)amino]bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-(2-metilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(piperidin-3-ilmetil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(pirrolidin-3-ilmetil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-butanoylpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(fenilmetil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(3S)-tetrahidrofuran-3-ilamino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-metilpropil)amino]bencen-1,4-dicarboxamida;
N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-5-[(1-etilpropil)amino]-2-metilbencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2,2-trifluoroetil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(3R)-tetrahidrofuran-3-ilamino]bencen-1,4-dicarboxamida;
;N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-{[3-{[2-(dimetilamino)etil]oxi}-4-(metiloxi)fenil]amino}bencen-1,4-dicarboxamida;

NOMBRE
N4-{8-[5-(ciclopentilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclobutilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-aminobencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1-propilbutil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(propilamino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-azetidin-1-ilbencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-bromobencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1,2-dimetilpropil)amino]bencen-1,4-dicarboxamida;
N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-5-[(1-etilpropil)amino]-2-fluorobencen-1,4-dicarboxamida;
N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-metil-5-{[4-(trifluorometil)ciclohexil]amino}bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(2,2,3,3,4,4,4-heptafluorobutil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(3,3,3-trifluoropropil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(butilamino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(3-{[2-(dimetilamino)etil]oxi}fenil)amino]bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-[(1,2,2-trimetilpropil)amino]bencen-1,4-dicarboxamida;

NOMBRE
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-(piperidin-1-ilamino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({1-[(metiloxi)metil]propil}amino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({2-[(1-metiletil)oxi]etil}amino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-{[(1S)-1-metilpropil]amino}bencen-1,4-dicarboxamida;
N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-metil-5-(pentilamino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({4-(metiloxi)-3-[(2-morfolin-4-iletil)oxi]fenil}amino)bencen-1,4-dicarboxamida;
N4-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2-({3-[(1-metiletil)amino]propil}amino)bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(1-etilpropil)amino]bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]-2-metilbencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(piridin-4-ilamino)bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(2,2,3,3,3-pentafluoropropil)amino]bencen-1,4-dicarboxamida;
2-cloro-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]bencen-1,4-dicarboxamida;
2-(ciclopentilamino)-N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(3S)-tetrahidrofuran-3-ilamino]bencen-1,4-dicarboxamida;

NOMBRE
2-(butilamino)-N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-({2-[(1-metiletil)oxi]etil}amino)bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(cis-4-hidroxi-4-metilciclohexil)amino]bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1S)-1-metilpropil]amino}bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(1-metilpropil)amino]bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-(propilamino)bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]-2-fluorobencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(trans-4-piperidin-1-ilciclohexil)amino]bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1S)-1,2-dimetilpropil]amino}bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(1-ciclopropiletil)amino]bencen-1,4-dicarboxamida;
N4-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-{[(1R)-1,2-dimetilpropil]amino}bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etil-2-metilpropil)amino]-2-metilbencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-ciclopropiletil)amino]-2-metilbencen-1,4-dicarboxamida;

NOMBRE
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-ciclopropilpropil)amino]-2-metilbencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[(1R)-1,2,2-trimetilpropil]amino}bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1R)-1,2-dimetilpropil]amino}-2-metilbencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(3,3,3-trifluoro-1-metilpropil)amino]bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[2-metil-1-(trifluorometil)propil]amino}bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[2-metil-1-(1-metiletil)propil]amino}bencen-1,4-dicarboxamida;
2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(1-metiletil)amino]bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(diciclopropilmetil)amino]-2-metilbencen-1,4-dicarboxamida;
5-(ciclopentilamino)-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[1-(trifluorometil)propil]amino}bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(2-metilpropil)amino]bencen-1,4-dicarboxamida;
5-[(ciclopentilmetil)amino]-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida;
5-(ciclobutilamino)-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metilbencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[(1S)-1-metilpropil]amino}bencen-1,4-dicarboxamida;

NOMBRE
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-etilpropil)amino]-2-(trifluorometil)bencen-1,4-dicarboxamida;
2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1R)-1-metilpropil]amino}bencen-1,4-dicarboxamida;
2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(1-metiletil)amino]bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(2,2-dimetilpropil)amino]-2-metilbencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(ciclopropilmetil)amino]-2-metilbencen-1,4-dicarboxamida;
2-bromo-5-(ciclopentilamino)-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(2-metilpropil)amino]bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-[(3,3,3-trifluoropropil)amino]bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-(propilamino)bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-metil-5-{[1-(1-metilciclopropil)etil]amino}bencen-1,4-dicarboxamida;
2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(2,2-dimetilpropil)amino]bencen-1,4-dicarboxamida;
2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1R)-1,2-dimetilpropil]amino}bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[2-fluoro-1-(fluorometil)etil]amino}-2-metilbencen-1,4-dicarboxamida;
2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-(propilamino)bencen-1,4-dicarboxamida;
N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-{[(1R)-1-metilpropil]amino}-2-(trifluorometil)bencen-1,4-dicarboxamida;

NOMBRE
2-bromo-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-5-[(3,3,3-trifluoropropil)amino]bencen-1,4-dicarboxamida;
2-bromo-5-(ciclobutilamino)-N-{8-[5-(ciclopropilcarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-(8-{5-[3-(1-metilpiperidin-4-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-hidroxi-4-metilpentanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-fenilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-hidroxi-3-fenilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-(4-metilpentanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
N4-{8-[5-(3-ciclohexilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-2-[(ciclopropilmetil)amino]bencen-1,4-dicarboxamida;
5-[(1-etilpropil)amino]-2-metil-N-(8-{5-[3-(1-metilpiperidin-4-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-piperidin-4-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-(N,N-dimetil-beta-alanil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-(8-{5-[3-(metiloxi)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-piperidin-1-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-(8-{5-[3-(etiloxi)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-(8-{5-[N-(4-fluorofenil)-beta-alanyl]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;

NOMBRE
2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-morfolin-4-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-(8-{5-[3-(4-metilpiperazin-1-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-(3-pirrolidin-1-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-(8-{5-[3-(4-fenilpiperazin-1-il)propanoil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)bencen-1,4-dicarboxamida;
2-[(1-etilpropil)amino]-N4-{8-[5-(3-piperidin-1-ilpropanoil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
2-[(ciclopropilmetil)amino]-N4-{8-[5-(piperidin-1-ilacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
N-[8-(5-acetilpiridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-2,5-dimetilbencen-1,4-dicarboxamida; y
2-[(ciclopropilmetil)amino]-N4-{8-[5-(trifluoroacetil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}bencen-1,4-dicarboxamida;
o una sal farmacéuticamente aceptable de cualquiera de los compuestos anteriores

18. Una composición farmacéutica que comprende el compuesto de acuerdo con cualquiera de las reivindicaciones 1-17, o una sal farmacéuticamente aceptable del mismo, y un portador, excipiente o diluyente farmacéuticamente aceptable.

19. Un método para inhibir HSP90 en una célula, que comprende poner en contacto la célula, en la cual se desea la inhibición de HSP90, con el compuesto de acuerdo con cualquiera de las reivindicaciones 1-17, o una sal

farmacéuticamente aceptable del mismo.

20. Un método para tratar una enfermedad o afección que involucra HSP90, que comprende administrar a un animal, en necesidad de dicho tratamiento, el compuesto de acuerdo con cualquiera de las reivindicaciones 1-17, o una sal farmacéuticamente aceptable del mismo.

21. El método de acuerdo con la reivindicación 20, en donde la enfermedad que se trata se selecciona de cáncer de mama, CML, carcinoma colorrectal, glioma, melanoma, mieloma múltiple, cáncer de pulmón no microcítico, cáncer de ovario, cáncer de próstata, carcinoma de células renales, cáncer de pulmón microcítico y respuesta a proteína no plegada.

22. El método de acuerdo con la reivindicación 20, en donde la enfermedad que se tratase selecciona de enfermedad neurodegenerativa, enfermedad infecciosa, enfermedad inflamatoria, trastorno autoinmune, apoplejía, isquemia, trastorno cardiaco, sepsis, trastorno fibrogenético y enfermedad metabólica.

23. El método de acuerdo con la reivindicación 20, en donde la enfermedad que se trata es una enfermedad

neurodegenerativa caracterizada por la acumulación de formas hiperfosforiladas o mutadas de la proteína Tau asociada al microtúbulo.

24. Un método para tratar proteínas Tau aberrantes en un animal, que comprende administrar un compuesto de acuerdo con cualquiera de las reivindicaciones 1-17 a dicho animal.

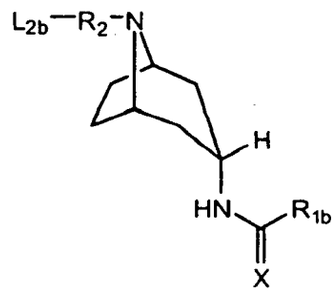
25. El método de acuerdo con la reivindicación 20, en donde la enfermedad que se trata es infección de los virus de ARN de cepa negativa, virus de la influenza, hepatitis B, hepatitis C o virus del herpes simple tipo 1.

26. El método de acuerdo con la reivindicación 20, que comprende adicionalmente administrar tratamiento de radiación o uno o más agentes terapéuticos seleccionados a partir de Camptotecina, Topotecano, 9-Nitrocamptotecina, 9-Aminocamptotecina, Carenitecina, Irinotecano, Etopósido, Fosfato de Etopósido, Tenipósido, Amsacrina, Razoxano, Dexrazoxano, Mecloretamina, Ciclofosfamida, Ifosfamida, Clorambucilo, Melfalano, Tiotepa, Trenimon, Trietilenmelamina, Dianhidrogalactitol, Dibromodulcitol, Busulfan, dimetilsulfato, Cloroetilnitrosourea, Carmustina, Lomustina, Metil-Lomustina, Estreptozotocina, Clorozotocina,

Prednimustina, Estramustina, Procarbazina, Dacarbazina, Hexametilmelamina, Pentametilmelamina, Temozolomida, Cisplatino, Carboplatino, Oxaliplatino, Bleomicina, Dactinomicina, Mitramicina, Rapamicina, Mitomicina C, Daunorubicina, Doxorubicina, Epirubicina, Idarubicina, Metotrexato, Edatrexato, Trimetoprim, Nolatrexed, Raltitrexed, Hidroxiurea, 5-fluorouracilo, Ftorafur, Capecitabina, Furtulon, Eniluracilo, ara-C, 5-azacitidina, Gemcitabina, Mercaptopurina, Tioguanina, Petostatina, ADN antisentido, ARN antisentido, un híbrido ARN/antisentido ADN, una ribozima, radiación ultravioleta, Vincristina, Vinblastina, Paclitaxel, Docetaxel, L-Asparaginasa, un inhibidor de cinasa, Imatinib, Mitotano, Aminoglutetimida, Dietilestilbestrol, Etinil estradiol, Tamoxifen, Anastrozol, Propionato de testosterona, Fluoximesterona, Flutamida, Leuprólido, Prednisona, Caproato de hidroxiprogesterona, Acetato de medroxiprogesterona, Acetato de megestrol, Alfa-interferón, e Interleucina.

27. El método de acuerdo con la reivindicación 20, que compende adicionalmente administrar tratamiento de radiación o uno o más agentes terapéuticos seleccionados de inhibidores de proteosoma, inhibidores EGFR y agentes que dañan el ADN.

28. Un compuesto de acuerdo con la Fórmula II:



II

o una sal farmacéuticamente aceptable del mismo, en donde:

R_{1b} se selecciona de heteroarilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de halógeno, fenilo y alquilo;

R_2 es un fenilo o un heteroarilo que puede contener 1, 2 o 3 heteroátomos, en donde el arilo o heteroarilo puede ser sustituido con 1, 2 o 3 grupos seleccionados de alquilo, -OH, alcoxi, y halógeno;

R_{3b} se selecciona de hidrógeno, $-CF_3$, $-NH_2$, -OH, alquilo opcionalmente sustituido con 1, 2 o 3 R_{5b}, alcoxi, dialquilaminoalquilo, cicloalquilo opcionalmente sustituido con arilalcoxi, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de halógeno, alquilo, alcoxi, dialquilaminoalcoxi y heterocicloalquilo opcionalmente sustituido con alquilo o arilo, alquenilo, alquinilo, heterocicloalquilo opcionalmente sustituido con un grupo seleccionado de alquilo, -C(O)O-alquilo y arilalquilo,

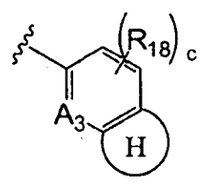
arilalquilo opcionalmente sustituido con alquilheterocicloalquilo en cualquier posición del anillo del grupo arilo, y heteroarilo;

R_{5b} se selecciona de halógeno, cicloalquilo, heteroarilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de halógeno, alquilo y alcoxi, alquiltio, heterocicloalquilo opcionalmente sustituido con 1, 2, o 3 grupos seleccionados de alquilo, halógeno, fenilo y oxo, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados de halógeno, alquilo, alcoxi, dialquilaminoalcoxi y heterocicloalquilo opcionalmente sustituido con alquilo, alcoxi, dialquilamino, -OH, -C(O)-NH_2, -C(O)-O-CH_3, -C(O)-N(H)alquilo (C_1-C_3), heteroarilamino opcionalmente sustituido con halógeno y -OCF_3;

L_{2b} es -C(O)-NH-R_{3b}, -CN o -C(O)-R_{3b}; y

X es O u S.

29. El compuesto de acuerdo con la reivindicación 28, en donde R_{1b} es



(O)

en donde:

A_3 es =N- o =CH-;

cada R_{18} se selecciona independientementede $-NH_2$, halógeno y alquilo;

el anillo (H) es un anillo heterocíclico de 5 o 6 elementos fusionado a los dos átomos de carbono a los cuales el anillo (H) se une, en donde el anillo (H) contiene 1, 2 o 3 heteroátomos seleccionado de N, O u S; y

c es 0, 1 o 2.

30. El compuesto de acuerdo con la reivindicación 29, en donde la Fórmula (O) se selecciona de 1H-bencimidazol opcionalmente sustituido con 1 o 2 grupos metilo, 1H-indol opcionalmente sustituido con 1 o 2 grupos metilo, benzofuran, 3,4-dihidro-2H-cromenilo opcionalmente sustituido con 1 o 2 grupos metilo, 2,3-dihidrobenzofuranilo opcionalmente sustituido con 1 o 2 grupos metilo, 2,3-dihidro-1,4-benzodioxin-6-ilo opcionalmente sustituido con 1 o 2 grupos metilo, 1H-1,2,3-benzotriazol opcionalmente sustituido con 1, 2 o 3 grupos metilo, 9H-purin-9-ilo opcionalmente sustituido con 1 o 2 grupos seleccionados de halógeno y amino, 1,3-benzotiazol opcionalmente sustituido con 1 o 2 grupos metilo, y 2,3-dihidro-1-benzofuran opcionalmente sustituido con 1 o 2 grupos metilo.

31. El compuesto de acuerdo con la reivindicación 28, en donde el compuesto de Fórmula II se selecciona de uno

de los siguientes compuestos:

1,4-dimetil-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1H-bencimidazol-5-carboxamida;
N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1,3-benzotiazol-5-carboxamida;
4-metil-N-(8-{5-[({(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1H-1,2,3-benzotriazol-5-carboxamida;
6-(3-endo-{[(8-metil-3,4-dihidro-2H-cromen-7-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida;
6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;

6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida;
6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(1-metilpiperidin-4-il)fenil]metil}piridin-3-carboxamida;
6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida;
N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-bencimidazol-5-carboxamida;
N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-indol-4-carboxamida;
6-(3-endo-{[(2-amino-6-cloro-9H-purin-9-il)acetil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida;
6-(3-endo-{[(7-metil-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida;
6-(3-endo-{[(5-metil-2,3-dihidro-1,4-benzodioxin-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida;
6-(3-endo-{[(4-metil-1,3-benzodioxol-5-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida;
8-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]quinoline-7-carboxamida;
6-(3-endo-{[(8-metil-3,4-dihidro-2H-cromen-7-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(fenilmetil)piridin-3-carboxamida;
4-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-bencimidazol-5-carboxamida;
4-metil-N-(8-{5-[({[4-(4-metilpiperazin-1-il)fenil]metil}amino)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-1H-bencimidazol-5-carboxamida;
6-(3-endo-{[(5-metil-2,3-dihidro-1,4-benzodioxin-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida;

N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-indol-6-carboxamida;
1-metil-N-[8-(5-{[(fenilmetil)amino]carbonil}piridin-2-il)-8-azabiciclo[3.2.1]oct-3-endo-il]-1H-indol-4-carboxamida;
N4-{8-[5-(aminocarbonil)piridin-2-il]-8-azabiciclo[3.2.1]oct-3-endo-il}-1H-indol-4,7-dicarboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[3-(metiloxi)fenil]etil}piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(4-metilpiperazin-1-il)fenil]metil}piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{(1S)-1-[4-(4-metilpiperazin-1-il)fenil]etil}piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-{[4-(1-metilpiperidin-4-il)fenil]metil}piridin-3-carboxamida;
N-[(4-{[2-(dietilamino)etil]oxi}fenil)metil]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
N-(ciclopropilmetil)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
N-[2-(dietilamino)etil]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-metilpirrolidin-3-il]piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-metilpirrolidin-3-il]piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-(1-metilpiperidin-4-il)piridin-3-carboxamida;
N-[(1S)-1-(4-{[2-(dietilamino)etil]oxi}fenil)etil]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;

7-metil-N-(8-{5-[(4-metilpiperazin-1-il)carbonil]piridin-2-il}-8-azabiciclo[3.2.1]oct-3-endo-il)-2,3-dihidro-1-benzofuran-6-carboxamida;
N-(1-etilpiperidin-3-il)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-(1-metiletil)pirrolidin-3-il]piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-metilpiperidin-3-il]piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-(1-metiletil)pirrolidin-3-il]piridin-3-carboxamida;
N-[(3S)-1-etilpirrolidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[1-(1-metiletil)piperidin-4-il]piridin-3-carboxamida;
N-(1-etilpiperidin-4-il)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
N-[(3R)-1-etilpiperidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
N-(1-etilazetidin-3-il)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[1-(1-metiletil)azetidin-3-il]piridin-3-carboxamida;
N-(1-metilazetidin-3-il)-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
N-[(3R)-1-etilpirrolidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-(1-metiletil)piperidin-3-il]piridin-3-carboxamida;
N-[(3S)-1-etilpiperidin-3-il]-6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)piridin-3-carboxamida;

6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3S)-1-(1-metiletil)piperidin-3-il]piridin-3-carboxamida; y
6-(3-endo-{[(7-metil-2,3-dihidro-1-benzofuran-6-il)carbonil]amino}-8-azabiciclo[3.2.1]oct-8-il)-N-[(3R)-1-metilpiperidin-3-il]piridin-3-carboxamida,
o una sal farmacéuticamente aceptable de cualquiera de los compuestos anteriores

32. Una composición farmacéutica que comprende el compuesto de acuerdo con cualquiera de las reivindicaciones 28-31, o una sal farmacéuticamente aceptable del mismo, y un portador, excipiente o diluyente farmacéuticamente aceptable.

33. Un método para tratar una enfermedad o afección que involucra HSP90 que comprende administrar a un animal, en necesidad de dicho tratamiento, el compuesto de acuerdo con cualquiera de las reivindicaciones 28-31, o una sal farmacéuticamente aceptable del mismo.

34. El método de acuerdo con la reivindicación 33, en donde la enfermedad que se trata se selecciona de cáncer de mama, CML, carcinoma colorrectal, glioma, melanoma, mieloma múltiple, cáncer de pulmón no microcítico, cáncer de ovario, cáncer de próstata, carcinoma de células renales, cáncer de pulmón microcítico, respuesta de proteína no plegada, enfermedad neurodegenerativa, enfermedad infecciosa, enfermedad inflamatoria, trastorno autoinmune, apoplejía,

isquemia, trastorno cardiaco, sepsis, trastorno fibrogenético, enfermedad metabólica, infección a partir del virus de ARN de cepa negativa, virus de la influenza, hepatitis B, hepatitis C, y virus del herpes simple tipo 1.

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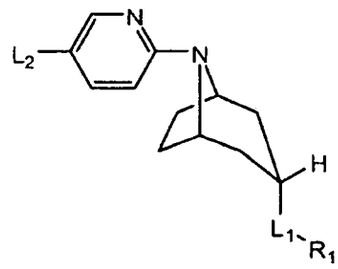
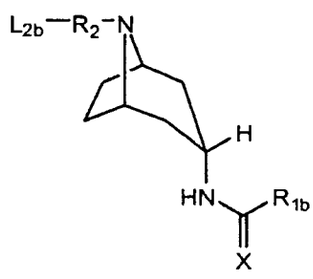
RESUMEN DE LA INVENCIÓN

La presente invención se refiere a un compuesto de conformidad con la Fórmula I o II:



I

o



II

en donde R_1, R_{1b}, R_2, L_1, y L_2 y L_{2b} son como se definen en la especificación, composiciones farmacéuticas de los mismos y métodos de uso de los mismos.

1336

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/012221

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D451/02 A61K31/46 A61P35/00

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)
C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BARRIL ET AL: "4-Amino derivatives of the Hsp90 inhibitor CCT018159" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 16, no. 9, 16 March 2006 (2006-03-16), pages 2543-2548, XP005932896 ISSN: 0960-894X the whole document	1-34
A	WO 2004/113334 A (NEUROSEARCH AS [DK]; PETERS DAN [DK]; ERIKSEN BIRGITTE L [DK]; NIELSEN) 29 December 2004 (2004-12-29) page 1; claim 1	1-34
A	WO 2005/033107 A (PFIZER LTD [GB]; STUPPLE PAUL ANTHONY [GB]; PFIZER [US]) 14 April 2005 (2005-04-14) page 1; claim 1	1-34

☐ 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 document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 2009	10/02/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lauro, Paola

1357

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/012221

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004113334 A	29-12-2004	AU 2004249441 A1	29-12-2004
		BR PI0411608 A	08-08-2006
		CA 2530023 A1	29-12-2004
		CN 1798745 A	05-07-2006
		EP 1638965 A1	29-03-2006
		HK 1089157 A1	18-07-2008
		IS 8212 A	30-12-2005
		KR 20060030482 A	10-04-2006
		UA 82517 C2	25-04-2008
		US 2008269229 A1	30-10-2008
		US 2006142331 A1	29-06-2006
WO 2005033107 A	14-04-2005	AT 380813 T	15-12-2007
		AU 2004278158 A1	14-04-2005
		BR PI0414862 A	28-11-2006
		CA 2540834 A1	14-04-2005
		DE 602004010708 T2	04-12-2008
		DK 1682545 T3	17-03-2008
		EC SP066475 A	10-10-2006
		EP 1682545 A1	26-07-2006
		ES 2295924 T3	16-04-2008
		HR 20080052 T3	29-02-2008
		JP 2007507483 T	29-03-2007
		KR 20060070571 A	23-06-2006
		MX PA06003749 A	14-06-2006
		PA 8614301 A1	10-05-2005
		TW 280244 B	01-05-2007
		US 2005131011 A1	16-06-2005
		UY 28546 A1	31-05-2005

1358

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) ***Prioridad*** **61/000,687** (32) ***Fecha*** **25/10/2007** (33) ***País*** **US**

(51) Int Cl: **C07D 451/002**

(71)Solicitante(s) **EXELIXIS , INC.**

(72) Inventor(es) **KENNETH D. RICE Y OTROS**

(74) Apoderado: **LUZ CLEMENCIA DE PAEZ**

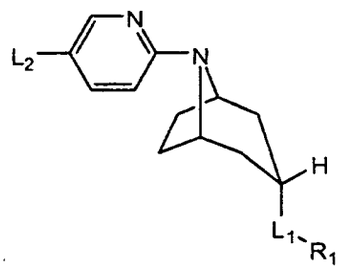
(85) Fecha limite inicio fase nacional: 25/05/2010
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 27/10/2008
No. de solicitud PCT/US2008/012221

(87) Publicación internacional
Fecha: 30/04/2009
N° publicación: ***WO 2009/055077 A1***

(54) Titulo: **COMPUESTOS DE TROPANO**

Reivindicación(es):

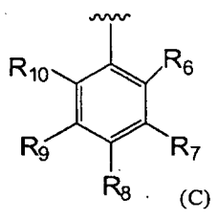
1. Un compuesto de conformidad con la Fórmula I:



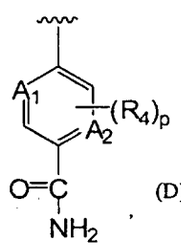
I

o una sal del mismo farmacéuticamente aceptable, caracterizado porque:

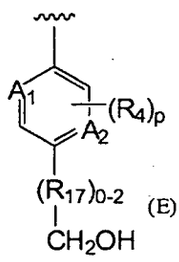
R_1 se selecciona a partir de



(C)

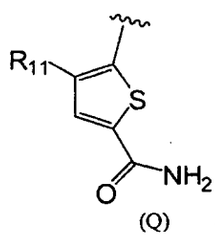


(D)



(E)

y

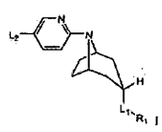


(Q) ;

R_3 se selecciona a partir de hidrógeno, $-CF_3$, $-NH_2$, -OH, alquilo opcionalmente sustituido con 1, 2 o 3 R_5, alcoxi, dialquilaminoalquilo, cicloalquilo opcionalmente sustituido con arilalcoxi, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo, alcoxi, dialquilaminoalcoxi y heterocicloalquilo opcionalmente sustituido con alquilo o arilo, alquenilo, alquinilo, heterocicloalquilo opcionalmente sustituido con un grupo seleccionado a partir de alquilo, -C(O)O-alquilo y arilalquilo, arilalquilo opcionalmente sustituido con alquilheterocicloalquilo en cualquier posición del anillo del grupo arilo, y heteroarilo;

R_4, R_7, R_8, R_9 y R_{11} son cada uno seleccionados independientemente a partir de hidrógeno, $-OR_{16}$, $-SR_{16}$, $-N(H)R_{16}$, hidroxi, alquenilo, alquinilo, hidroxialquinilo, halógeno, hidroxialquilo, dihidroxialquilo, $-O-C(O)-NH_2$, amino(imino)alquilo, $-C(O)-NH_2$, -N(H)C(O)alquilo, alquilaminoalquilo, alquilaminoalquilamino, aminoalquilamino, arilalquilamino, heterocicloalquilo, dialquilaminoalquilo, alquilo opcionalmente sustituido con 1-8 halógeno, dialquilamino, -N(H)alquilheterocicloalquilo, alquilsulfonilheterocicloalquilamino, cicloalquilalquilamino, cicloalcoxi, $-NH_2$, -O-alquilo-heterocicloalquilo, dialquilaminoalcoxi, alquilsulfonilalquilamino y -N(H)heterocicloalquilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de alquilo, alcoxi y halógeno;

R_5 se selecciona a partir de halógeno, cicloalquilo, cicloalquilalquilamino, heteroarilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo y alcoxi, alquiltio, heterocicloalquilo opcionalmente sustituido con 1, 2, o 3 grupos seleccionados a partir de alquilo, halógeno, fenilo y oxo, arilo opcionalmente sustituido con 1, 2 o 3 grupos seleccionados a partir de halógeno, alquilo, alcoxi, dialquilaminoalcoxi, y heterocicloalquilo opcionalmente sustituido con alquilo, alcoxi, dialquilamino, -OH, $-C(O)-NH_2$, $-C(O)-O-CH_3$, $-C(O)-N(H)$alquilo (C_1-C_3), heteroarilamino opcionalmente sustituido con halógeno, y $-OCF_3$;



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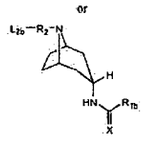

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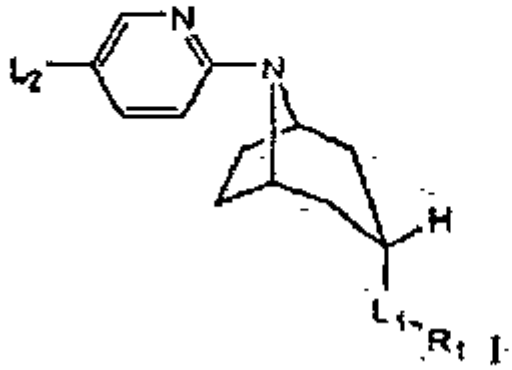
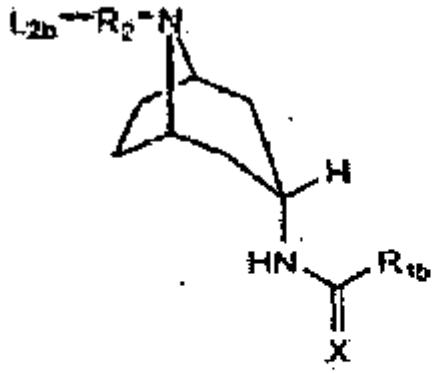


(I)

or



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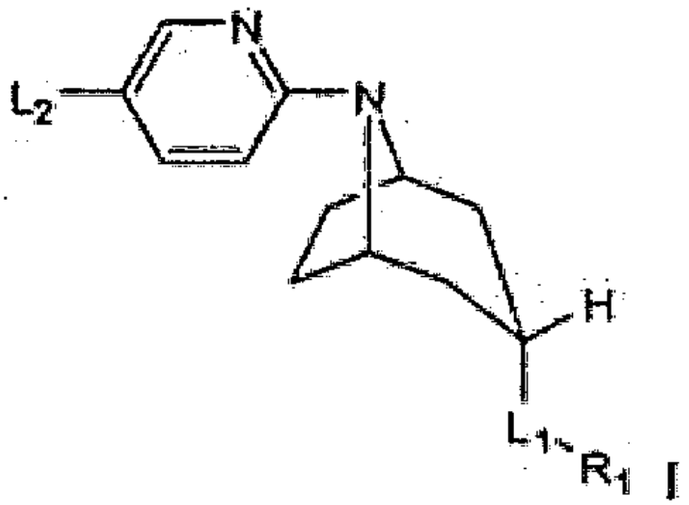

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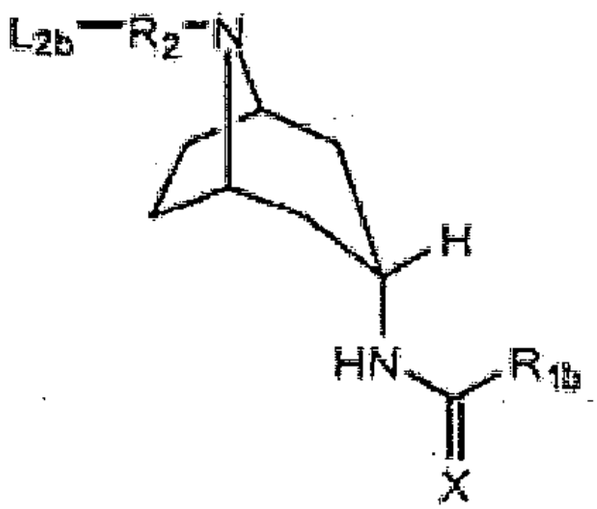
or



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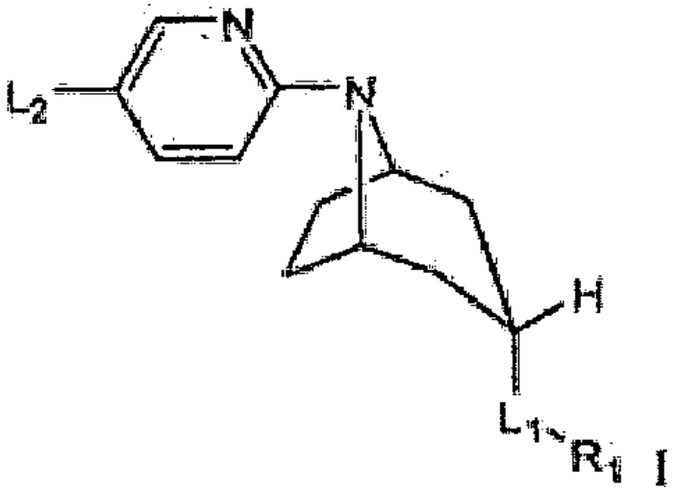

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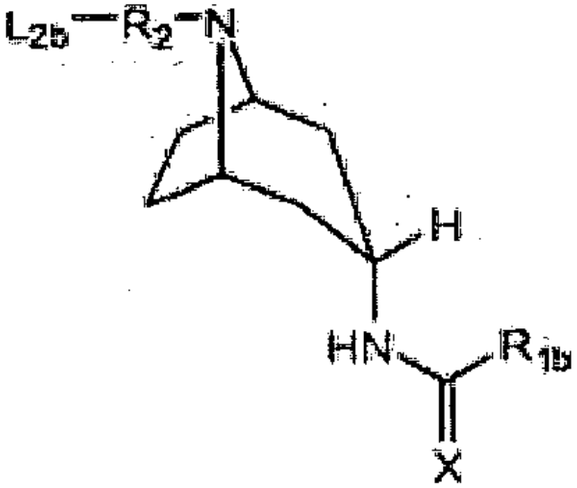
or



(II)

1360

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 34,601
FECHA : MAYO 4 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-061824- -00000-0000

Fecha: 2010-05-24 15:37:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1362

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	175534520	03/05/2010	61,670,000.00

***** 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	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 15391-841-002-5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

126R

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 24,645
FECHA : ABRIL 5 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-061824- -00000-0000

Fecha: 2010-05-24 15:37:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1362

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	175534531	31/03/2010	95,531,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	83 INVOCACION DE UNA PRIORIDAD EN SI	155,000.00
		TOTAL : $	155,000.00

SON: CIENTO CINCUENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 15391-841-002-5

1362

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 34,573
FECHA : MAYO 4 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-061824- -00000-0000

Fecha: 2010-05-24 15:37:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1362

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	175534520	03/05/2010	61,670,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	470,000.00
		TOTAL : $	470,000.00

SON: CUATROCIENTOS SETENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 15391-841-002-5

~~COLO: 17626-841-001-4~~

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-061824- -00000-0000

Fecha: 2010-05-24 15:37:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1362

PATENTE DE INVENCIÓN ☐ **MODELO DE U1**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
EXELIXIS, INC

REFERENCIA	Radicación No.	10 061824
	Solicitud internacional	PCT/US2008/012221
	Fecha inicio fase nacional	25/05/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	E 07147

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

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

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.

Continua en la página siguiente...

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5 , 7 y 10 PBX: 5870000
Sede CAN: Av. Cra 50 No. 26-55 int. 2 Tel: 5880070
Call Center 6513240. Linea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co

Industria y Comercio
SUPERINTENDENCIA

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

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 04 JUN. 2010.
adpa11

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5 , 7 y 10 PBX: 5870000
Sede CAN: Av. Cra 50 No. 26-55 int. 2 Tel: 5880070
Call Center 6513240. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co

Industria y Comercio
SUPERINTENDENCIA

Folio 1401

2020
Bogotá D.C.,

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
EXELIXIS, INC

REFERENCIA	Radicación No.	10 61824
	Solicitud internacional	PCT/US2008/012221
	Fecha inicio fase nacional	25/05/2010
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	13527
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC,

2 JUN. 2011

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (C)

jfernand