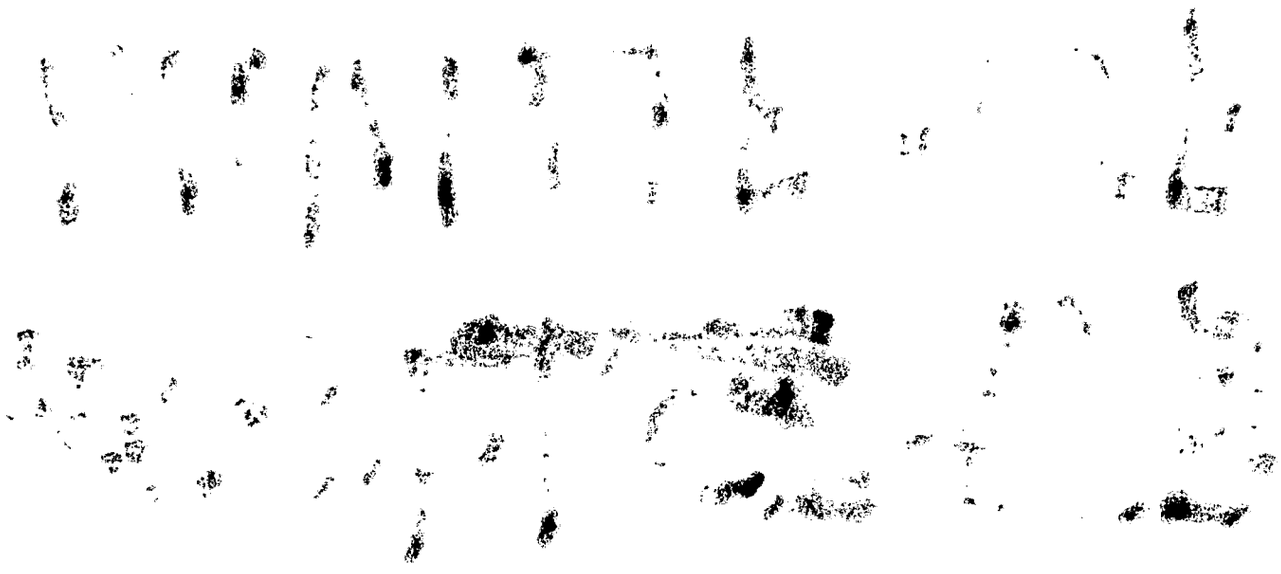


PCT

Industria y Comercio

SUPERINTENDENCIA

10.159479 OK

Delegatura de Propiedad Industrial

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

División de Nuevas Creaciones

[redacted]

PATENTE DE INVENCION

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-159479- -00000-0000
Fecha: 2010-12-20 11:46:04 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 294

21. **EXPEDIENTE No.** _____

54. **TÍTULO** DERIVADOS ADAMANTIL DIAMINA Y USOS DELOS MISMOS

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** H. LUNDBECK A/S

DOMICILIO VALBY-COPENHAGEN, DINAMARCA

74. **APODERADO** LUZ CLEMENCIA D EPAEZ

C.C. [35.456.344 de Usaquén

22. **BOGOTÁ, D. C.,** _____

25-02-2011

(FORMA P-10)

Cuad. 22 folios
25-01-2011

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-159479- -00000-0000
Fecha: 2010-12-20 11:46:04 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 294

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: **H. LUNDBECK A/S**
sociedad constituida y existente bajo las leyes de Dinamarca.

Dirección: Ottiliavej 9,
2500 Valby-Copenhagen,
Dinamarca

Domicilio: Valby-Copenhagen,
Dinamarca

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

3 REPRESENTANTE O APODERADO

Nombre: LUZ CLEMENCIA DE PÁEZ
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

4 INVENTOR (ES) (72)

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Englewood,
New Jersey 07631,
Estados Unidos de América

5 PCT (86)

Solicitud Internacional No. PCT/US2009/050934 Fecha: 17 de julio de 2009
Publicación Internacional No. WO 2010/011570 A1 Fecha: 28 de enero de 2010

6 Título (54)

DERIVADOS ADAMANTIL DIAMINA Y USOS DE LOS MISMOS

7 Clasificación Internacional (51) C07D 233/079

8 Prioridad SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US US	25 de julio de 2008 17 de marzo de 2009	61/083,563 61/160,804

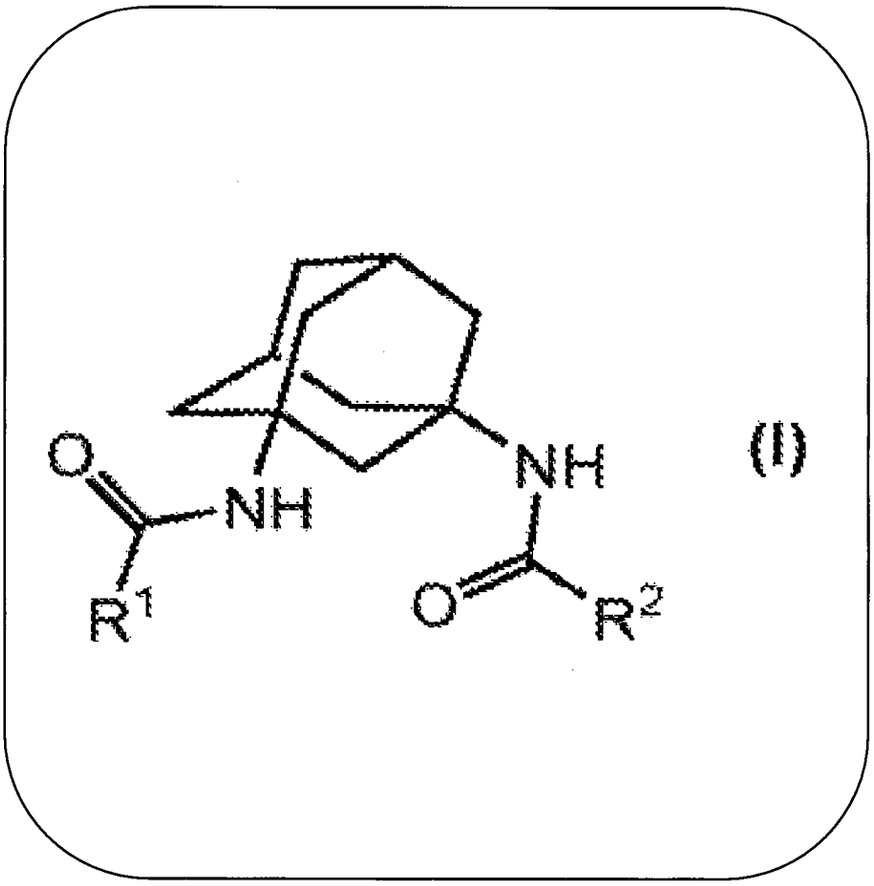
9 **Comprobante de pago No.:** 10-104,309 **Fecha:** Diciembre 7, 2010
10-106,127 **Fecha:** Diciembre 13, 2010
10-106,151 **Fecha:** Diciembre 13, 2010
10-106,196 **Fecha:** Diciembre 13, 2010

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 554.000.oo.
- ☒ Comprobante de pago por 36 reivindicaciones adicionales después de la décima reivindicación por $936.000.oo.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



(I)

12 Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PÁEZ

FIRMA : Luz Clemencia de Páez

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

JGG

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2010/011570 A1

   Descripción:

   Páginas 110 en el idioma original

   Páginas 107 en español

   Reivindicaciones: Número (s) 46

   Figuras: Número (s)

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

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

EDIFICIO
CARRERA
BOGOTA, D - COLOMBIA

240 09 5

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

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

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

03003
06049

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

H. LUNDBECK A/S

of/domiciliado (s) en 9, Ottiliavej, DK-2500, Copenhagen, DENMARK

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

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

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

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

Given and signed this/Dado y firmado hoy

11 June 1998

in/en Copenhagen

H. Lundbeck A/S

John Meidahl Pet

Signature Firma

John Meidahl Petersen

Patent Department

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
17 DIC. 2010
AMPARO QUINTERO ARTURO
NOTARIA

© CAVELIER ABOGADOS

164033 06 0001.2101 12.06.98 RA
60100-02364/98 200.00 K

LEGALIZACION

El Señor Cónsul de Colombia debe expedir un *certificado consular* sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a *consular certificate*, on (1) the legal existence of the company which grants the Power-of-Attorney, (2) that it is in actual exercise of its company purposes, and (3) that the persons who execute the Power of Attorney is autorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).

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
17 DIC. 2010
AMPARO QUINTERO ARTURO
NOTARIA

NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.

La suscrita Ilse Greby, notario público de Copenhague, Dinamarca, certifica que el señor

John Meidahl Petersen,

que en la fecha de hoy ha firmado ante mí el presente documento, está autorizado, según documentos justificativos que juzgo suficientes, para usar la firma de la sociedad denominada

H. LUNBECK A/S,

domiciliada en 9, Ottiliavej, DK-2500 Copenhague, Dinamarca, y que legalmente existe y actualmente ejerce su objeto social de acuerdo con las leyes del Dinamarca.

En fé de lo cual pongo mi firma y el sello notarial.

Notaría de Copenhague, a 11 de Junio de 1998.

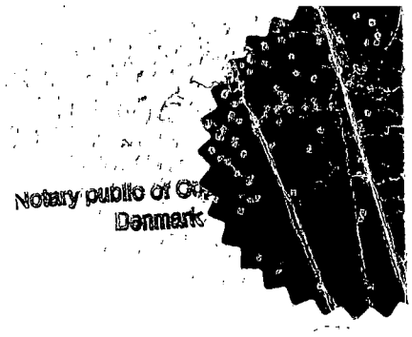
Ilse Greby
notario público

Derechos: 200,- DKK.

MINISTERIO DE RELACIONES EXTERIORES

SE LEGALIZA LA FIRMA QUE ANTECEDE DE
ILSE GREBY
COPENHAGUE, EL 10 JUNI 1998
POR EL MINISTRO DE RELACIONES EXTERIORES
P. A.
INGER ELGAARD

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTÁ D.C., HAGO CONSTAR QUE LA PRESENTE COPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
17 DIC. 2010
AMPARO QUINTERO ARTURO
NOTARIA



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

17 DIC. 2010

AMPARO QUINTERO ARTURO
NOTARIA

ERHVERVS- OG SELSKABSSTYRELSEN
ERHVERVSMINISTERIET

The Danish Commerce and Companies Agency
certifies and attests that

"H. LUNDBECK A/S"
Ottiliavej 7-9
DK-2500 Valby
Denmark

of the municipality of Copenhagen
which company was established 14th October 1950
under registration number A/S 22.472
in the Danish Commerce and Companies Agency incorporated with limited liability, is legally existing as a Danish Public Company, limited by shares, and duly registered and incorporated under the provisions of the Company Legislation of the Kingdom of Denmark.

Copenhagen, 11th May 1998

Pia Sødequist

THE TRUE SIGNATURE OF
P.P. S.SØDEQUIST
LIMITED.
18 MAJ 1998
FOR THE MINISTER FOR FOREIGN AFFAIRS.
E.A.
INGRID ELGAART

KAMPMANNSGADE 1 1780 KOBENHAVN V TELEFON 33 30 77 00

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

C O N S U L A D O D E C O L O M B I A

No 33-98

El suscrito, Cónsul de Colombia en Copenhague, Dinamarca, vistos los documentos presentados por los interesados,

C E R T I F I C A :

Que la Sra. Inger Elgaard quien autoriza el documento adjunto, ejercía legalmente, en la fecha allí expresada, sus funciones como Funcionario del Ministerio de Relaciones Exteriores de Dinamarca, y que su firma y sellos corresponden a los registrados en este Consulado.

Que la firma H. LUNDBECK A/S. existe legalmente, que ejerce su objeto social de acuerdo a las leyes danesas y que el Sr. John Meidahl Petersen está autorizado para firmar el documento, de cuerdo al Resumen expedido por la Dirección de Industrias y Comercio Nr. A/S 22472, cuya copia se adjunta.

El suscrito Cónsul de Colombia no asume responsabilidad por el contenido del documento.

"Se pagarán en Colombia los impuestos de Timbre que se ocasionen al ejecutar en Colombia las obligaciones emanadas del presente documento de conformidad con el artículo 519 del Estatuto tributario."

Copenhague, Junio 23 de 1.998.

CARLOS ARTURO MORALES
Cónsul de Colombia

Pagado : Impuesto Timbre USD. 6.oo
Derechos Consulares USD: 100.oo

CONSULADO DE COLOMBIA
COPENHAGUE

OTRO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HACE CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
17 DIC. 2010
AMPARO QUINTERO ARTURO
NOTARIA

MINISTERIO DE RELACIONES EXTERIORES

051248

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

98 JUL - 1 PM 2:40

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

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

BOGOTA D.C., REPUBLICA DE COLOMBIA

17 DIC. 2010

AMPARO QUINTERO LOPEZ

NOTARIA SEXTA

TRADUCCIÓN OFICIAL N° 0807981 al español de un documento escrito en inglés, preparada por Jaime Armando Garavito Burgos, Traductor Oficial debidamente reconocido por el Ministerio de Relaciones Exteriores y aprobado por el Ministerio de Justicia de la República de Colombia mediante Resolución N° 034 de enero 11 de 1983

(En la parte superior central de las tres primeras páginas aparece sello redondo en relieve de la Embajada de Colombia en Copenhague, Dinamarca)

(Adherido en la esquina superior izquierda de las dos primeras hojas del documento aparece sello rojo de oblea, junto con sello en tinta del Notario Público de Copenhague, Dinamarca)

Documento escrito en inglés y español por medio del cual **H. LUNDBECK A/S**, otorga poder a favor de **GERMÁN CAVELIER, GONZALO PERDOMO, EMILIO FERRERO y LUZ CLEMENCIA DE PÁEZ.** Dado y firmado el 11 de junio de 1998 en [illegible] (firmado) John Meidahl Petersen, Departamento de Patentes

---

CERTIFICACIÓN NOTARIAL (SOCIEDAD) en español [illegible] a la existencia legal de la sociedad **H. LUNDBECK A/S** y su representante autorizado **John Meidahn Petersen**, expedida el 11 de junio de 1998 en Copenhague, Dinamarca. (firmado) Ilse Greby, Notario Público (Aparece adherido sello notarial rojo de oblea)

17 DIC. 2010
AMPARO QUINTERO ARTURO
NOTARIA

consulares. (firmado) CARLOS ARTURO MORALES, Cónsul de Colombia

---

EL MINISTERIO DE RELACIONES EXTERIORES en Santafé de Bogotá, D.C. certifica la firma y las funciones de Carlos Morales, el 1 de julio de 1998. **N° 051248.** (firmado) Jefe de Legalizaciones.

Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Santafé de Bogotá, D.C., julio 8 de 1998

COLO: 3003-801-001-0
WPCL3003- ID # 19

NO SE ASUME RESPONSABILIDAD DEL TEXTO

98 JUL 14 PM 12:18

JEFE DEL LEGALIZACIONES SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

051248

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

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
17 DIC. 2010
AMPARO QUINTERO ARTURO
NOTARIA

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) ...

Paul A Gonzalez

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

SANTAFE DE BOGOTA, 14 JUL. 1998

COMO NOTARIA SEXTA DEL CÍRCULO 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

17 DIC. 2010

AMPARO QUINTERO ARTURO
NOTARIA

CAVELIER
ABOGADOS

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

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

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

12

Señor Jefe de la

DIVISION DE SIGNOS DISTINTIVOS

Superintendencia de Industria y Comercio

E. S. D.

Poderdante: H. LUNDBECK A/S

Poder conferido el: 11-06-98

Yo, GERMAN CAVELIER, obrando en mi calidad de apoderado principal del poderdante arriba mencionado, atentamente manifiesto a Usted que sustituyo el poder que me ha sido conferido en la persona del doctor EMILIO FERRERO, Abogado con Tarjeta Profesional N° 31.929, con todas las facultades que me fueron conferidas.

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

Señor Jefe,

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

Acepto:

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

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

N I T. 860.041.367-3

NOTARIA SEXTA DE BOGOTA
RECONOCIMIENTO Y PRESENTACION PERSONAL

Santafé de Bogotá D. C. 19 MAYO 1999

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BOGOTA D.C. REPUBLICA DE COLOMBIA
17 DIC. 2010
AMPARO QUINTERO ARTURO
NOTARIA

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Poderdante : **H. LUNDBECK A/S**

Poder conferido el : 11/06/1998

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.

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T.P.A. N° 31.929
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COMO NOTARIA SEXTA DEL CÍRCULO DE BOGOTÁ D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
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Acepto:

LUZ CLEMENCIA DE PAEZ
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NOTARIA SEXTA DE BOGOTA
RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá, D.C.
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Luz Clemencia Suárez

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NOTARIA
NOTARIA SEXTA DE BOGOTA

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
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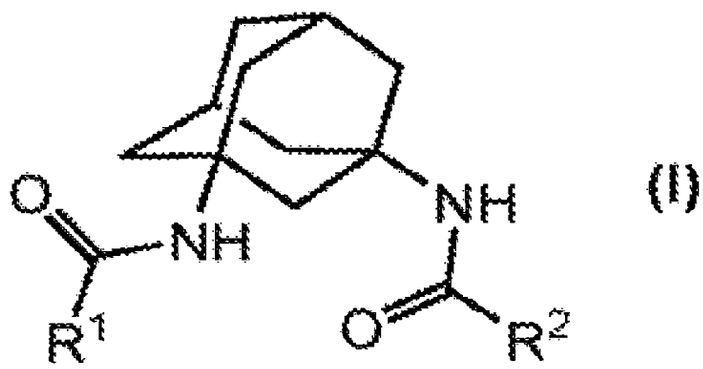
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(54) Title: ADAMANTYL DIAMIDE DERIVATIVES AND USES OF SAME



(I)

(57) Abstract: The present invention provides adamantyl-diamide derivatives of formula (I): wherein R^1 and R^2 are as defined herein, or a pharmaceutically acceptable salt thereof; and pharmaceutical compositions and methods using the same

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ADAMANTYL DIAMIDE DERIVATIVES AND USES OF SAME

FIELD OF THE INVENTION

The present invention provides adamantyl diamide derivatives, as well as pharmaceutical compositions and methods of treatment using same.

BACKGROUND OF THE INVENTION

This invention concerns adamantyl diamide derivatives, which act as allosteric modulators of the metabotropic glutamate receptor 5 (mGlu5 receptors or mGluR5), as well as pharmaceutical compositions and methods of treatment utilizing these compounds.

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. One means of modulating glutamate neurotransmission is through metabotropic glutamate receptors (mGluRs); another means being ionotropic receptors. Presently, eight mGluRs have been cloned and classified into three groups based on sequence homology, preferred signal transduction pathway and pharmacology. Group I of mGluRs includes mGluR1 and mGluR5, while Group II comprises mGluR2 and mGluR3 and Group III comprises mGlu4, 6, 7 and 8 receptors.

mGlu receptors have an essential role in normal brain functions, as well as in neurological, psychiatric, and neuromuscular disorders. mGlu5 receptors are located primarily postsynaptically and highly expressed in the limbic brain regions. mGlu5 receptors also are expressed in the thalamus, spinal cord, and vagal nerve systems, as well as peripherally in the skin on nerve endings and C fibers.

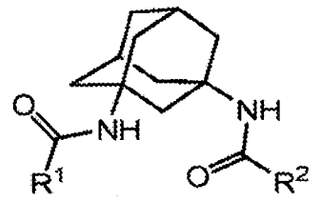
Ligands to the mGlu5 receptors have been shown to have promise for peripheral and central nervous system disorders. *See e.g.*, G. Jaeschke *et al.*, "mGlu5 receptor antagonists and their therapeutic potential," *Expert Opin. Ther. Patents*, **2008**, *18*, 2: 123-142. Yet some proffer that glutamate analogs targeting the orthosteric binding site may be limited by low brain penetration and insufficient selectivity with respect to the different mGluRs subtypes. Synthetic agonists may lead to continuous stimulation of the receptor since they are often designed to be metabolically stable. This continuous stimulation is not necessarily desirable,

due to potential receptor desensitization issues. Also, with respect to receptor occupancy, synthetic antagonists may lead to prolonged blockade of receptor function, which may not be compatible with the kinetics of the pathology of a central nervous system disorder.

However, a more selective and controlled "fine-tuning" action on the mGlu5 receptor is feasible through allosteric modulation. *See e.g.*, P. Bach *et al.*, "Metabotropic glutamate receptor 5 modulators and their potential therapeutic applications," *Expert Opin. Ther. Patents*, **2007**, *17*, 4: 371-381. Allosteric modulation refers to binding by a modulator ligand to a site on a receptor that is different from the orthosteric primary substrate or ligand binding site. This ligand binding process results in conformational changes, which may profoundly influence the function of the protein (*e.g.*, G protein-coupled receptors such as mGluRs, including mGluR5). Novel mGluR5 ligands that allosterically modulate the mGlu5 receptor may improve the therapeutic window of traditional central nervous system agents and/or the treatment of central nervous system disorders. The present invention is directed these, and other important, ends.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula (I):



(I)

;

wherein:

R^1 and R^2 are each independently alkyl, cycloalkyl, ketocycloalkyl, heterocyclyl, aryl or heteroaryl, which is optionally mono-, di-, or tri-substituted independently with alkyl, alkoxy, halogen, cyano, nitro, trifluoroalkyl, amino, alkylamino, dialkylamino, acyl, aryl, heteroaryl, heterocyclyl, heterocyclyl-R^3, -NHR^3, -N(alkyl)R^3, -$C(O)NHR^3$, -$C(O)N(alkyl)R^3$, -$NHC(O)R^3$, -$N(alkyl)C(O)R^3$, -OH or -OR^3, wherein:

R^3 is C_1-C_6alkyl or C_1-C_6cycloalkyl, which is optionally substituted with halogen, C_1-C_3alkoxy, OH, -CN, -NH_2, -NH(C_1-C_3alkyl), -N(C_1-C_3alkyl)$_2$, C_1-$_3$alkylheterocyclyl, C_1-C_3alkylcarbamate, -C(O)NH(C_1-C_3alkyl), -C(O)N(C_1-C_3alkyl)$_2$, -NHC(O)-C_1-C_3alkyl, -N(C_1-C_3alkyl)-C(O)-C_1-C_3alkyl, OH, or –O-C_1-C_6alkyl;

with the proviso that the compound of formula (I) is not:

N, N'-(1,3-adamantylene)bis(3-methoxy-benzamide);

N, N'-(1,3-adamantylene)bis(4-ethoxy-benzamide);

N, N'-(1,3-adamantylene)bis(4-methoxy-benzamide);

N,N'-(1,3-adamantylene)bis(3,4,5-trimethoxybenzamide);

N, N'-(1,3-adamantylene)bis(2-iodo-benzamide);

N,N'-(1,3-adamantylene)bis-benzamide;

N,N'-(1,3-adamantylene)bis(3-nitrobenzamide); and

N,N'-(1,3-adamantylene)bis-(3-pyridinecarboxamide); or

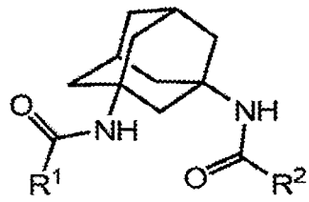
a pharmaceutically acceptable salt thereof.

The present invention also provides a pharmaceutical composition comprising at least one compound of the invention or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

The present invention also provides a method of treating a disease or disorder, the method comprises administering a therapeutically effective amount of at least one compound of the present invention or a pharmaceutically acceptable salt thereof to a mammal in need thereof, wherein the disease or disorder is a central nervous system disease or disorder. In some embodiments of the method, a symptom of the disease or disorder is treated.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the present invention provides adamantyl diamide derivatives. The present invention comprises a compound of formula (I):



(I)

;

wherein:

R^1 and R^2 are each independently alkyl, cycloalkyl, ketocycloalkyl, heterocyclyl, aryl or heteroaryl, which is optionally mono-, di-, or tri-substituted independently with alkyl, alkoxy, halogen, cyano, nitro, trifluoroalkyl, amino, alkylamino, dialkylamino, acyl, aryl, heteroaryl, heterocyclyl, heterocyclyl-R^3, -NHR^3, -N(alkyl)R^3, -C(O)NHR^3, -C(O)N(alkyl)R^3, -NHC(O)R^3, -N(alkyl)C(O)R^3, -OH or -OR^3, wherein:

R^3 is C_1-C_6alkyl or C_1-C_6cycloalkyl, which is optionally substituted with halogen, C_1-C_3alkoxy, OH, -CN, -NH_2, -NH(C_1-C_3alkyl), -N(C_1-C_3alkyl)$_2$, C_1-C_3alkylheterocyclyl, C_1-C_3alkylcarbamate, -C(O)NH(C_1-C_3alkyl), -C(O)N(C_1-C_3alkyl)$_2$, -NHC(O)-C_1-C_3alkyl, -N(C_1-C_3alkyl)-C(O)-C_1-C_3alkyl, OH, or –O-C_1-C_6alkyl;

with the proviso that the compound of formula (I) is not:

N, N'-(1,3-adamantylene)bis(3-methoxy-benzamide) (*i.e.*, the compound having CAS registry number 899289-36-2);

N, N'-(1,3-adamantylene)bis(4-ethoxy-benzamide) (*i.e.*, the compound having CAS registry number 899289-24-8);

N, N'-(1,3-adamantylene)bis(4-methoxy-benzamide) (*i.e.*, the compound having CAS registry number 899259-96-2);

N,N'-(1,3-adamantylene)bis(3,4,5-trimethoxybenzamide) (*i.e.*, the compound having CAS registry number 173068-46-7);

N, N'-(1,3-adamantylene)bis(2-iodo-benzamide) (*i.e.*, the compound having CAS registry number 899259-92-8);

N,N'-(1,3-adamantylene)bis-benzamide (*i.e.*, the compound having CAS registry number 103307-81-9);

N,N'-(1,3-adamantylene)bis(3-nitrobenzamide) (*i.e.*, the compound having CAS registry number 350024-39-4); and

N,N'-(1,3-adamantylene)bis-(3-pyridinecarboxamide) (*i.e.*, the compound having CAS registry number 371933-95-8); or

a pharmaceutically acceptable salt thereof.

The term "alkyl", employed alone or as part of a group, is defined herein, unless otherwise stated, as either a straight-chain or branched saturated hydrocarbon of 1 to 8 carbon atoms. In some embodiments, the alkyl moiety contains 8, 7, 6, 5, 4, 3, 2 or 1 carbon atoms. Where the term "alkyl" appears herein without a carbon atom range it means a range of C_1-C_8. Examples of saturated hydrocarbon alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, *iso*propyl, *n*-butyl, *tert*-butyl, *iso*-butyl, *sec*-butyl, *n*-pentyl, *n*-hexyl, and the like.

The term "alkoxy", employed alone or in combination with other terms, is defined herein, unless otherwise stated, as –O-alkyl, where "alkyl" is as previously defined herein. Examples of alkoxy moieties include, but are not limited to, chemical groups such as methoxy, ethoxy, *iso*-propoxy, *sec*-butoxy, *tert*-butoxy, and homologs, isomers, and the like. Alkoxy also refers to –O-alkyl moieties where the alkyl group is substituted by hydroxy, cyano, alkoxy, alkylamino, dialkylamino, alkylamide, dialkylamide, and the like, including without limitation, -OC_1-C_4alkyl-OH, -OC_1-C_4alkyl-OCH_3, -OC_1-C_4alkyl-$NHCH_3$, -OC_1-C_4alkyl-$N(CH_3)_2$, -OC_1-C_4alkyl-$CONHCH_3$, -OC_1-C_4alkyl-$CON(CH_3)_2$, -OC_1-C_4alkyl-$NHCOCH_3$, and -OC_1-C_4alkyl-$N(CH_3)COCH_3$.

As used herein, the term "cycloalkyl", employed alone or in combination with other terms, is defined herein, unless otherwise stated, as a cyclized alkyl group having from 3 to 8 ring carbon atoms, where "alkyl" is as defined herein. Examples of cycloalkyl moieties include, but are not limited to, chemical groups such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein, the term "ketocycloalkyl", employed alone or in combination with other terms, is defined herein, unless otherwise stated, as a cycloalkyl having a keto radical attached thereto, where "cycloalkyl" is as defined herein. Examples include cyclopentanone or cyclohexanone.

The terms "halo" or "halogen", employed alone or in combination with other terms, is defined herein, unless otherwise stated, as fluoro, chloro, bromo, or iodo.

The term "aryl", employed alone or in combination with other terms, is defined herein, unless otherwise stated, as an aromatic hydrocarbon of up to 14 carbon atoms, which can be a single ring (monocyclic) or multiple rings (*e.g.*, bicyclic, tricyclic, polycyclic) fused together or linked covalently. Any suitable ring position of the aryl moiety can be covalently linked to the defined chemical structure. Examples of aryl moieties include, but are not limited to, chemical groups such as phenyl, benzyl, 1-naphthyl, 2-naphthyl, and the like. An aryl group can be unsubstituted or substituted as described herein.

The term "heteroaryl" employed alone or in combination with other terms, is defined herein, unless otherwise stated, as a monocyclic or polycyclic (fused together or linked covalently) aromatic hydrocarbon ring comprising one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. A heteroaryl group comprises up to 14 carbon atoms and 1 to 6 heteroatoms. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3,)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, 2-quinolinyl, 2-quinazolinyl, 3-phenyl-2-quinolinyl and the like. A heteroaryl group can be unsubstituted or substituted as described herein.

The term "heterocyclyl" employed alone or in combination with other terms, is defined herein, unless otherwise stated, as a univalent group formed by removing a hydrogen atom from any ring atom of a heterocycle.

The term "acyl" employed alone or in combination with other terms, is defined herein, unless otherwise stated, as groups of formula -C(O)-alkyl, where alkyl is a previously described herein; *i.e.*, an alkylcarbonyl, such as formyl, acetyl and the like.

The term "aminoalkyl" employed alone or in combination with other terms, is defined herein, unless otherwise stated, as alkyl-amino, where the term "alkyl" is as previously defined herein and the term "amino" is $-NH_2$, $-NH-$, or $-N<$. Non-limiting examples include - CH_3NH-, CH_3CH_2NH-, $(C_1\text{-}C_3alkyl)NH$-, $(C_1\text{-}C_3alkyl)_2N$-, and the like.

The term "alkylamino" employed alone or in combination with other terms, is defined herein, unless otherwise stated, as amino-alkyl, where the term "alkyl" is as previously defined herein and the term "amino" is $-NH_2$, $-NH-$, or $-N<$. Non-limiting examples include $-NHCH_3$, $-NHCH_2CH_3$, $-NH(C_1\text{-}C_3alkyl)$, $-N(C_1\text{-}C_3alkyl)_2$, and the like.

In some embodiments of the invention, R^1 and R^2 are both aryl. In some embodiments, R^1 and R^2 are both heteroaryl. In some embodiments, R^1 is aryl and R^2 is heteroaryl. In some embodiments of the invention, at least one aryl is phenyl. In some embodiments, at least one heteroaryl is pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl, pyrazolyl, indazolyl, thiophenyl, furanyl, or benzofuranyl. In some embodiments, both aryls are phenyl. In some embodiments, both heteroaryls are selected from a group consisting of pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl, pyrazolyl, indazolyl, thiophenyl, furanyl, and benzofuranyl.

In some embodiments of the invention, at least one aryl or heteroaryl is substituted as previously described. In some such embodiments, the 1, 2, or 3 substituents are independently selected from the group consisting of methyl, methoxy, dimethylamino-ethoxy, amino, methylamino, dimethylamino, cyano, chloro, fluoro, furanyl and thiophenyl.

In some embodiments, R^1 and R^2 each are independently selected from a group consisting of phenyl, 3 or 4-methyl-phenyl, 3 or 4-chloro-phenyl, 3 or 4-fluoro-phenyl, 3 or 4-dimethylamino-ethoxy-phenyl, 3 or 4-dimethylamino-phenyl, 3 or 4-cyano-phenyl, 3-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl, 1*H*-indole-5-yl, 1*H*-indole-6-yl, 1*H*-benzimidazole-5-yl, pyridyl, 2-pyridyl, 4-pyridyl, 4- or 5-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl, 6-chloro-pyridin-2-yl, pyrazin-2-yl, thiazol-2-yl, 5-(thiophen-2-yl)-*1H*-pyrazol-3-yl, 1-methyl-5-(thiophen-2-yl)-*1H*-pyrazol-3-yl, 5-(furan-2-yl)-1-methyl-*1H*-pyrazol-3-yl, indazol-3-yl, 2-methyl-*2H*-indazol-3-yl, benzofuranyl, benzofuran-5-yl.

In some embodiments, the compound of the present invention is a compound disclosed in the Experimental Section below. In some embodiments, the compound is one from Table 1, 2, 3, or 4, below.

In some embodiments of the invention, R^1 and R^2 are both aryl. In some embodiments, R^1 and R^2 are both heteroaryl. In some embodiments, R^1 is aryl and R^2 is heteroaryl. In some embodiments, either R^1 or R^2 is heteroaryl. In some embodiments, either R^1 or R^2 is aryl.

In some embodiments of the invention, at least one aryl is phenyl. In some embodiments, at least one heteroaryl is benzofuranyl, benzo[c]isoxazolyl, benzooxazolyl, benzothiazolyl, dihydrothieno[3,4-b][1,4]dioxinyl, furanyl, imidazo[1,2-a]pyridinyl, indazolyl, indolinyl, indolyl, isoquinolinyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolo[3,2-c]pyridine, quinolinyl, quinoxalinyl, thiazolyl, or thiophenyl.

In some embodiments, both aryls are phenyl. In some embodiments, both heteroaryls are selected from a group consisting of at least one heteroaryl is benzofuranyl, benzo[c]isoxazolyl, benzoxazolyl, benzothiazolyl, dihydrothieno[3,4-b][1,4]dioxinyl, furanyl, imidazo[1,2-a]pyridinyl, indazolyl, indolinyl, indolyl, isoquinolinyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolo[3,2-c]pyridinyl, quinolinyl, quinoxalinyl, thiazolyl, or thiophenyl.

In some embodiments, the heteroaryl is pyridinyl, and the pyridinyl is mono-, di-, or tri-substituted as previously defined. In some such embodiments, the mono-, di-, or tri-substitutions are independently heteroaryl, heterocyclyl, heterocyclyl-R^3, -NHR^3, -$N(alkyl)R^3$, wherein R^3 is as previously defined.

In some embodiments of the invention, R^1 is aryl or heteroaryl and R^2 is cycloalkyl, ketocycloalkyl or heterocyclyl. In some embodiments, either R^1 or R^2 is cycloalkyl. In some embodiments, at least one cycloalkyl is cyclobutyl, cyclohexyl, cyclopentyl, or cyclopropyl. In some embodiments, the cycloalkyl is further substituted beyond the tri-substitution previously defined, i.e., the cycloalkyl is substituted more than three times as previously described; for example, the cycloalkyl is tetra-substituted with fluorine.

In some embodiments of the invention, at least one cycloalkyl, ketocycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted as previously described. In some such embodiments, the 1, 2, or 3 substituents are independently selected from the group consisting of methyl, methoxy, dimethylamino-ethoxy, amino, methylamino, dimethylamino, cyano, chloro, fluoro, furanyl and thiophenyl.

In some embodiments, the mono-, di-, or tri-substituents are independently selected from the group consisting of amino, chloro, cyano, dimethylamino, dimethylamino-ethoxy, methyl, methylamino, methoxy, fluoro, -C(O)NHCH$_3$, furanyl, pyrrolidinyl, thiophenyl and trifluoromethyl.

In some embodiments, the compound of the present invention is a compound disclosed in the Experimental Section below. In some embodiments, the compound is one from Table 1, Table 2, Table 3 or Table 4, below.

Another aspect of the present invention is a composition that comprises a pharmaceutically effective amount of a compound according to the present invention, and a pharmaceutically acceptable carrier or excipient.

A composition of the present invention may be adapted to any mode of administration, such as orally (including sublingually), *via* implants, parentally (including intravenous, intraperitoneal, intraarticularly and subcutaneous injections), rectally, intranasally, topically, ocularly (*via* eye drops), vaginally, and transdermally.

A compound of the present invention can be used either as a free base or in the form of a salt derived from pharmaceutically acceptable acids or bases. The salt includes without limitation the following: salts with inorganic acids, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid, and organic acids *e.g.*, acetic acid, oxalic acid, citric acid, tartaric acid, succinic acid, maleic acid, benzoic acid, benzene sulfonic acid, fumaric acid, malic acid, methane sulfonic acid, pamoic acid, and para-toluene sulfonic acid. Other salts include salts with alkali metals or alkaline earth metals, *e.g.*, sodium, potassium, calcium and magnesium, or with organic bases, including quaternary ammonium salts. Further non-limiting examples of pharmaceutically acceptable inorganic and organic acid

addition salts include those listed in [S.M. Berge *et al.*, *J. Pharm. Sci.* **1977**, *66*, 1: 2, and G.S. Paulekuhn, *et al.*, *J. Med. Chem.* **2007**, *50*, 26: 6665-6672].

A compound of the present invention can also be used in the form of an ester, carbamate and other conventional prodrug form, which generally will be a functional derivative of the compound that is readily converted to the active moiety *in vivo*. Also included are metabolites of a compound of the present invention defined as active species produced upon introduction of the compound into a biological system.

When a compound of the present invention is employed as described above, it may be combined with one or more pharmaceutically acceptable excipients or carriers, *e.g.*, solvents, diluents and the like. Such pharmaceutical preparations may be administered orally in such forms as tablets, capsules (including, *e.g.*, time release and sustained release formulations), pills, lozenges, aerosols, dispersible powders, granules, solutions, suspensions (containing, *e.g.*, a suspending agent, at, *e.g.*, from about 0.05 to about 5% of suspending agent), syrups (containing, *e.g.*, sugar or a sugar substitute such as aspartame, at, *e.g.*, about 10 to about 50% sugar or sugar substitute), elixirs and the like, or parenterally in the form of sterile injectable solutions, suspensions or emulsions containing, *e.g.*, from about 0.05 to about 5% suspending agent in an isotonic medium. Such preparations may contain, *e.g.*, from about 25 to about 90% of the active ingredient in combination with the carrier, more customarily from about 5% and about 60% by weight. The effective dosage of an active ingredient (*e.g.*, a compound or salt of the present invention and a prodrug or metabolite thereof) employed may vary depending on the particular compound, salt, prodrug or metabolite used, the mode of administration, age, weight, sex and medical condition of the patient, and the severity of the disease, disorder, condition, and/or system being treated. The selection of the appropriate administration and dosage form for an individual mammal will be apparent to those skilled in the art. Such determinations are routine to a physician, veterinarian or clinician of ordinary skill in the art (*see e.g.*, *Harrison's Principles of Internal Medicine*, Anthony Fauci *et al.* (eds.) 14th ed. New York: McGraw Hill (1998)). Further, the dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the needs of the therapeutic situation.

Solid carriers, *e.g.*, starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, liquid carriers, *e.g.*, sterile water, polyethylene glycols, glycerol, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, may be employed as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included. Non-limiting examples of adjuvants include flavoring agents, coloring agents, preserving agents, and antioxidants, such as vitamin E, ascorbic acid, BHT and BHA.

An active compound also may be administered parenterally or intraperitoneally. Solutions or suspensions of the active compound as a free base, neutral compound or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions also can be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. These preparations may contain a preservative to prevent the growth of microorganisms under ordinary conditions of storage and use.

The pharmaceutical forms suitable for injectable or infusing use include sterile aqueous solutions, suspensions or dispersions, and sterile powders for the extemporaneous preparation of sterile injectable or infusing solutions, suspension or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy injectability and infusing exists. It must be stable under conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, and polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

Furthermore, active compounds of the present invention can be administered intranasally or transdermally using vehicles suitable for intranasal or transdermal delivery known to those ordinarily skilled in the art. Transdermal administration includes all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues, using carrier systems such as lotions, creams, foams, pastes, patches, suspensions, solutions, and suppositories (rectal and vaginal). Creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing

the active ingredient also may be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature. When using a transdermal delivery system, the dosage administration will be continuous rather than a single or divided daily dose.

A compound of the present invention can also be administered in the form of a liposome delivery system where the liposomal lipid bilayer is formed from a variety of phospholipids. A compound of the present invention also may be delivered by the use of a carrier such as monoclonal antibodies to which the compound is coupled. Other carriers to which a compound of the present invention also may be coupled are a soluble polymer or a biodegradable polymer useful in achieving controlled release of an active ingredient.

It is understood by those practicing the art that some of the compounds of the present invention may contain one or more asymmetric centers, and thus may give rise to enantiomers and diastereomers. The present invention includes all stereoisomers including individual diastereomers and resolved, enantiomerically pure stereoisomers, as well as racemates, and all other variations of stereoisomers, and mixtures and pharmaceutically acceptable salts thereof, which possess the indicated activity. Optical isomers may be obtained in pure form by customary procedures known to those skilled in the art, and include, but are not limited to, chiral chromatographic separations, diastereomeric salt formation, kinetic resolution, and asymmetric synthesis. It is also understood that this invention encompasses all possible regioisomers, endo-exo isomers, and mixtures thereof that possess the indicated activity. Such isomers can be obtained in pure form by customary procedures known to those skilled in the art, and include, but are not limited to, column chromatography, thin-layer chromatography, and high-performance liquid chromatography. It is understood by those practicing the art that some of the compounds of the present invention may be chiral due to hindered rotation, and give rise to atropisomers, which can be resolved and obtained in pure form by customary procedures known to those skilled in the art. It is further understood by those practicing the art that some of the compounds of the present invention include structural isomers, including tautomers.

Included also in this invention are all polymorphs and hydrates of the compounds of the present invention.

Another aspect of the present invention is a method for using the compounds of the invention. The invention is to be understood as embracing all simultaneous, sequential or separate use of any combination of the compounds of the invention with any pharmaceutical composition useful in the methods described herein.

In some embodiments, the method includes administering an effective amount of a combination of two or more of the compounds described herein, or salts thereof. It is specifically intended that the phrases "combination of two or more of the compounds described herein, or salts thereof," or "at least one compound as described herein, or a pharmaceutically acceptable salt thereof," or similar language describing specific compounds, includes the administration of such compounds in any proportion and combination of salt, neutral or free base forms; *i.e.*, includes the administration of such compounds each in the base form, each in the neutral form or each in the salt form, or one or more in the base form and one or more in the neutral form, or one or more in the base form and one or more in the salt form, or one or more in the neutral form and one or more in the salt form, in any proportion of the neutral and/or basic compounds and/or salts.

As used herein, the phrase "effective amount" when applied to a compound of the invention, is intended to denote an amount sufficient to cause an intended biological effect. The phrase "therapeutically effective amount" when applied to a compound of the invention is intended to denote an amount of the compound that is sufficient to ameliorate, palliate, stabilize, reverse, slow or delay the progression of a disorder or disease state, or of a symptom of the disorder or disease. In some embodiments, the method of the present invention provides for administration of combinations of compounds. In such instances, the "effective amount" is the amount of the combination sufficient to cause the intended biological effect.

The term "treatment" or "treating" as used herein means curing, ameliorating or reversing the progress of a disease or disorder, or ameliorating or reversing one or more symptoms or side effects of such disease or disorder. "Treatment" or "treating", as used herein, also means to inhibit or block, as in retard, arrest, restrain, impede or obstruct, the progress of a system,

condition or state of a disease or disorder. For purposes of this invention, "treatment" or "treating" further means an approach for obtaining beneficial or desired clinical results, where "beneficial or desired clinical results" include, without limitation, alleviation of a symptom, diminishment of the extent of a disorder or disease, stabilized (i.e., not worsening) disease or disorder state, delay or slowing of a disease or disorder state, amelioration or palliation of a disease or disorder state, and remission of a disease or disorder, whether partial or total, detectable or undetectable.

The term "prevent" or "preventing" as used herein means to keep from happening or existing. The term "administering" as used herein refers to either directly administering a compound of the present invention, or administering a prodrug, derivative, or analog of same, that will form an effective amount of the compound within a mammal.

The present invention also provides a method of treating a disease or disorder, the method comprises administering a therapeutically effective amount of at least one compound of the present invention or a pharmaceutically acceptable salt thereof to a mammal in need thereof, wherein the disease or disorder is a central nervous system disease or disorder.

A compound of the present invention can allosterically modulate the mGlu5 receptor. An allosteric modulator that enhances or potentiates the affinity of an orthosteric ligand for the mGluR5 receptor and/or enhances or potentiates an orthosteric agonist's efficacy is an allosteric enhancer (or potentiator) or positive allosteric modulator (PAM). *See e.g.*, May, L.T. *Annu. Rev. Pharmacol. Toxicol.* **2007**, *47*, 1-51. An allosteric modulator that reduces or diminishes the affinity of an orthosteric ligand for the mGluR5 receptor and/or reduces or diminishes an orthosteric agonist's efficacy is an allosteric antagonist (or inhibitor) or negative allosteric modulator (NAM). *Id.*

In some embodiments, the mammal of the method of the invention is a human.

In some embodiments of the method of the invention, the central nervous system disease or disorder is a cognitive, neurodegenerative, psychiatric or neurological disease or disorder. In some such embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is selected from a group consisting of a mood disorder, an anxiety, a schizophrenia (including schizoaffective disorders), Alzheimer's disease, Parkinson's

disease, multiple sclerosis, Huntington's chorea, amyotrophic lateral sclerosis, Creutzfeld-Jakob disease, a trauma-induced neurodegeneration, AIDS-induced encephalopathy, another infection-related encephalopathy (*i.e.*, a non-AIDS-induced encephalopathy), Fragile X syndrome, an autism spectrum disorder, and a combination thereof.

As used herein, the phrase "mood disorder" refers to any of several psychological disorders characterized by abnormalities of emotional state, such as, without limitation, bipolar disorders, depressive disorders, cyclothymic disorders, dysthymic disorders, mood disorders due to a general medical condition, mood disorders not otherwise specified and substance-induced mood disorders; and as characterized by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) (American Psychiatric Association: Arlington, VA, 1994).

As used herein, the phrase "autism spectrum disorder" (ASD) refers to a disorder that causes severe and pervasive impairment in thinking, feeling, language, and the ability to relate to others, which is often first diagnosed in early childhood and range from a severe form, called autistic disorder ("classic" autism), through pervasive development disorder not otherwise specified (PDD-NOS), to a much milder form, Asperger syndrome. The phrase, as used herein, also includes Rett syndrome and childhood disintegrative disorder, and as used herein, is synonymous with the phrase, "pervasive developmental disorders" (PDDs).

In some such embodiments, the mood disorder is a depression (*i.e.*, a depressive disorder). In some such embodiments, the depression is selected from the group consisting of atypical depression, bipolar depression, unipolar depression, major depression, endogenous depression (*i.e.*, acute depression with no obvious cause), involutional depression (*i.e.*, depression that occurs in mid-life or the elderly), reactive depression (*i.e.*, depression caused by an obvious traumatic life episode), postpartum depression, primary depression (*i.e.*, depression that has no obvious physical or psychological cause such as a medical illness or disorder), psychotic depression, and secondary depression (*i.e.*, depression that seems to be caused by some other underlying condition such another medical illness or disorder).

In some such embodiments, the anxiety disease or disorder is selected from a group comprising generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social

phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, an adjustment disorder, a hypochondriacal disorder, separation anxiety disorder, agoraphobia, a specific phobia, anxiety disorder due to general medical condition, substance-induced anxiety disorder, alcohol withdrawal-induced anxiety, and a combination thereof.

In some embodiments, the central nervous system disease or disorder of the method of the invention is a seizure disease or disorder. In some embodiments, the seizure disease or disorder is selected from the group consisting of a convulsion, epilepsy, status epilepticus, and a combination thereof.

In some embodiments, the central nervous system disease or disorder of the method of the invention is a pain disease or disorder selected from the group consisting of inflammatory pain, neuropathic pain and migraine pain. In some embodiments, the neuropathic pain or migraine pain disease or disorder is selected from the group consisting of allodynia, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathy, neuropathic pain related to migraine, and a combination thereof.

In some embodiments, the central nervous system disease or disorder of the method of the invention is a neuronal hyperexcitation state disease or disorder. In some embodiments, the neuronal hyperexcitation state disease or disorder is a neuronal hyperexcitation state in medicament withdrawal, a neuronal hyperexcitation state in intoxication, or a combination thereof.

In some embodiments of the method of the invention, at least one symptom of the cognitive neurodegenerative, psychiatric or neurological disease or disorder is treated.

In some embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is a depression. In some such embodiments, the at least one symptom of the depression is depressed feeling, depressed mood, loss of interest or pleasure in some or all activities, changes in appetite, changes in weight, changes in sleep patterns, lack of energy, fatigue, low self esteem, diminished capacity for thinking, concentration, or decisiveness, feelings of hopelessness or worthlessness, psychomotor agitation or retardation, self-reproach, inappropriate guilt, frequent thoughts of death or suicide, plans or attempts to commit suicide, or a combination thereof.

In some embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is an anxiety. In some such embodiments, the at least one symptom of anxiety is apprehension, fear, trembling, muscle aches, insomnia, abdominal upsets, dizziness, irritability, persistent, recurring thoughts, compulsions, heart palpitations, chest pain, chest discomfort, sweating, tingling sensations, feeling of choking, fear of losing control, flashbacks, nightmares, intrusive thoughts, intrusive recollections, avoidance behaviors, emotional numbing, an inability to sleep, anxious feelings, overactive startle response, hypervigilance, outbursts of anger, faintness, blushing, profuse sweating, or a combination thereof.

In some embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is schizophrenia. In some such embodiments, the at least one symptom of schizophrenia is a positive symptom selected from the group consisting of hallucination, delusion, paranoia, and a combination thereof. In some such embodiments, the symptom of schizophrenia is a negative symptom selected from the group consisting of social withdrawal, flat affect, anhedonia, decreased motivation, and a combination thereof. In some such embodiments, the symptom of schizophrenia is a cognitive symptom selected from the group consisting of severe deficit in attention, severe deficit in object naming, severe deficit in working memory, severe deficit in long-term memory storage, severe deficit in executive functioning, a slowing of information processing, a slowing of neural activity, long term depression, and a combination thereof.

In some embodiments of the method of the invention, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is Parkinson's disease. In some such embodiments, the at least one symptom of Parkinson's disease is levodopa-induced dyskinesia, poor balance, Parkinsonian gait, bradykinesia, rigidity, tremor, change in speech, loss of facial expression, micrographia, difficulty swallowing, drooling, pain, dementia, confusion, a sleep disturbance, constipation, a skin problem, depression, fear, anxiety, difficulty with memory, slowed thinking, sexual dysfunction, an urinary problem, fatigue, aching, loss of energy, or a combination thereof.

In some embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is Alzheimer's disease. In some such embodiments, the at least one symptom of

Alzheimer's disease is impairment in memory, impairment in attention, impairment in judgment, impairment in decision-making, impairment in orientation to physical surroundings, language impairment, impairment in speed-dependent activities, impairment in abstract reasoning, impairment in visuospatial abilities, impairment in executive functioning, impairment in behavioral disturbances, disinterest and passivity, apathy, inappropriate dressing, poor self care, agitation, violent outburst, aggression, depression, anxiety, hallucination, delusion, change in personality, change in mood, dementia, or a combination thereof.

In some embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is multiple sclerosis. In some such embodiments, the at least one symptom of multiple sclerosis is optic neuritis blurred vision, eye pain, loss of color vision, blindness, diplopia double vision, nystagmus jerky eye movements, ocular dysmetria, constant under- or overshooting eye movements, internuclear ophthalmoplegia, nystagmus, diplopia, movement and sound phosphenes, diplopia, afferent pupillary defect, motor paresis, monoparesis, paraparesis, hemiparesis, quadraparesis plegia, paraplegia, hemiplegia, tetraplegia, quadraplegia, spasticity, dysarthria, muscle atrophy, spasms, cramps, hypotonia, clonus, myoclonus, myokymia, restless leg syndrome, footdrop dysfunctional reflexes (MRSs, Babinski's, Hoffman's, Chaddock's), paraesthesia, anaesthesia, neuralgia, neuropathic pain, neurogenic pain, l'hermitte's, proprioceptive dysfunction, trigeminal neuralgia, ataxia, intention tremor, dysmetria, vestibular ataxia, vertigo, speech ataxia, dystonia, dysdiadochokinesia, frequent micturation, bladder spasticity, flaccid bladder, detrusor-sphincter dyssynergia, erectile dysfunction, anorgasmy, retrograde ejaculation, frigidity, constipation, fecal urgency, depression, cognitive dysfunction, dementia, mood swings, emotional lability, euphoria, bipolar syndrome, anxiety, aphasia, dysphasia, fatigue, uhthoffs symptom, gastroesophageal reflux, a sleeping disorder, or a combination thereof.

The present invention further provides a method of treating gastroesophageal reflux, the method comprises administering a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt thereof to a mammal in need thereof.

The present invention further provides a method of treating alcohol dependence, the method comprises administering a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt thereof to a mammal in need thereof.

In some embodiments, the compound of the present invention is used in the preparation of a medicament for treatment of a central nervous system disease or disorder. In some embodiments, the central nervous disease or disorder is as previously disclosed herein.

Another aspect of the present invention is a process for producing the compounds of the present invention.

PREPARATION OF THE COMPOUNDS OF THE PRESENT INVENTION

The compounds of the present invention may be prepared, without limitation, according to one of the general methods outlined below. For example, Schemes 1-11 that follow are intended as an illustration of some embodiments of the invention and no limitation of the present invention is implied because of them.

The following defines acronyms as used herein unless specified otherwise in a particular instance.

BOP = benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate, CAS No. 56602-33-6

DCM = dichloromethane or methylene chloride

DIEA = *N,N*-diisopropylethylamine, CAS No. 7087-68-5

DMA = *N,N*-dimethylacetamide, CAS No. 127-19-5

DMC = dimethylimidazolinium chloride

DMF = *N,N*-dimethylformamide, CAS No. 68-12-2

DPPA = Diphenylphosphoryl azide, CAS No. 26386-88-9

EDCI = *N*-Ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride, CAS No. 93128-40-6

HBTU = 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-Tetramethyluronium hexafluorophosphate, CAS No. 94790-37-1

NMP = *N*-Methyl-Pyrrolidone, CAS No. 872-50-4

PyBOP = benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, CAS No. 128625-52-5

RT or rt = room temperature

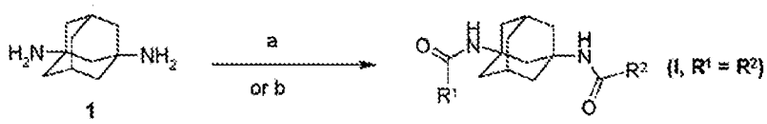
TBTU = O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, CAS No. 125700-67-6

TEA = triethanolamine, CAS No. 102-71-6

THF = tetrahydrofuran, CAS No. 109-99-9

Symmetrical amides of the formula (I) ($R^1 = R^2$) can be prepared *via* the process outlined in **Scheme 1** using customary amidation procedures from commercially available compound **1**, adamantane-1,3-diamine, where R^1 is equal to R^2, and R^1 and R^2 are as previously defined herein.

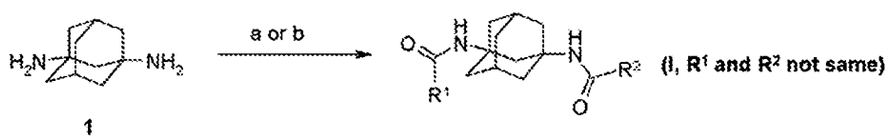
Scheme 1



a) R^1CO_2H, PyBOP (or BOP or EDCI), *N,N*-diisopropylethylamine (DIEA) or Et_3N, CH_2Cl_2 (or THF or DMF)
b) R^1COCl, DIEA or Et_3N, CH_2Cl_2

Unsymmetrical amides of formula (I) ($R^1 \neq R^2$) also can be prepared *via* the processes outlined in **Schemes 2** and **3**, where R^1 and R^2 are as previously defined herein.

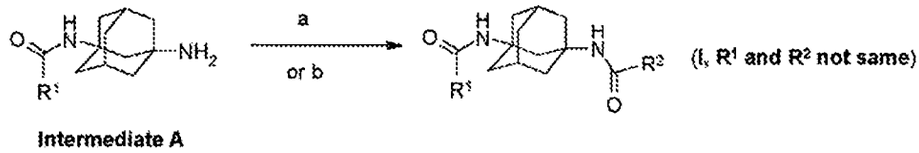
Scheme 2



a) 1.1 eq. R^1CO_2H, 1.1 eq. R^2CO_2H, DIEA, PyBOP (or BOP, DMC, EDCI), CH_2Cl_2
b) 1.1 eq. R^1COCl, 1.1 eq. R^2COCl, DIEA, CH_2Cl_2

Amidation of compound **1** with a mixture of R^1COCl and R^2COCl, or a mixture of R^1CO_2H and R^2CO_2H using customary amidation procedures affords unsymmetrical amides of formula (I).

Scheme 3

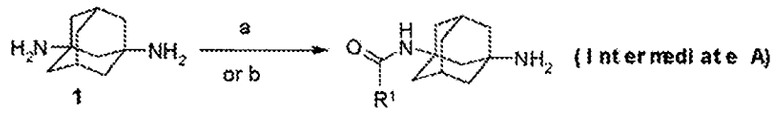


a) R^2CO_2H, PyBOP (or BOP or DMC or EDCI or HBTU etc.), DIEA or TEA, CH_2Cl_2 (or THF or DMF or CH_3CN etc);
b) R^2COCl, DIEA or TEA, CH_2Cl_2; or R^2COCl, aq. NaOH, THF/CH_2Cl_2

Amidation of Intermediate A with R^2CO_2H or R^2COCl using customary amidation procedures affords unsymmetrical amides of formula (I).

Intermediate A can be prepared *via* the processes outlined in Schemes 4-6.

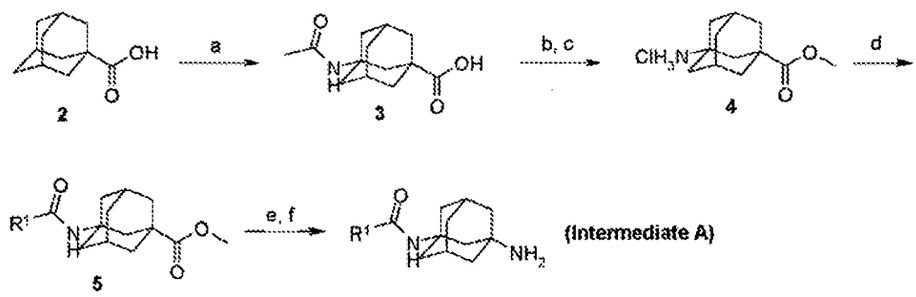
Scheme 4



a) R^1CO_2H, PyBOP (or BOP, DMC, EDCI), DIEA or TEA, CH_2Cl_2 (or THF, DMF, CH_3CN)
b) R^1COCl, DIEA , CH_2Cl_2 or R^1COCl, aq. NaOH, THF/CH_2Cl_2

Amidation of compound **1** with R^1CO_2H or R^1COCl using customary amidation procedures yields Intermediate A. The yield of this route is low due to the formation of bis-amides.

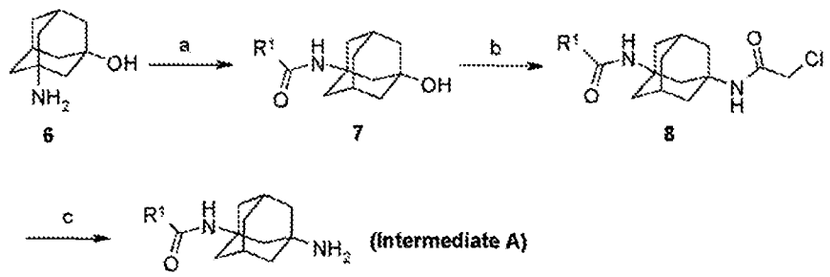
Scheme 5



a) H_2SO_4, HNO_3, MeCN; b) HCl, H_2O; c) $SOCl_2$, MeOH; d) R^1COCl, NEt_3, DCM; or R^1CO_2H, PyBOP, NEt_3, DCM;
e) LiOH, H_2O, THF; f) DPPA, NEt_3, Toluene then HCl, H_2O

Commercially available 1-adamantanecarboxylic acid (compound **2**) can be converted to acetamide **3** *via* a Ritter reaction. Hydrolysis of compound **3** under acidic conditions affords the corresponding amine salt, which is then converted to methyl ester **4.** Customary amidation of compound **4** affords compound **5**. Hydrolysis of ester **5** followed by a standard Curtius rearrangement yields Intermediate A.

Scheme 6

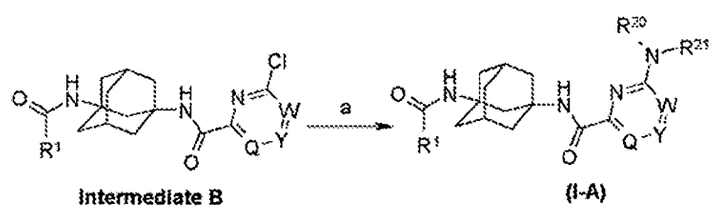


a) R^1CO_2H, HBTU, Et_3N, DMF; b) $ClCH_2CN$, H_2SO_4; c) Thiourea, EtOH, HOAc, 80°C

Customary amidation of commercially available 3-amino-adamantan-1-ol (compound **6**) affords monoamide **7**, which is then converted to compound **8** *via* a Ritter reaction. Hydrolysis of compound **8** affords Intermediate A.

Amides with solubilizing groups (formula I-A, I-B and I-C) can be prepared *via* the processes outlined in Schemes 7-9.

Scheme 7

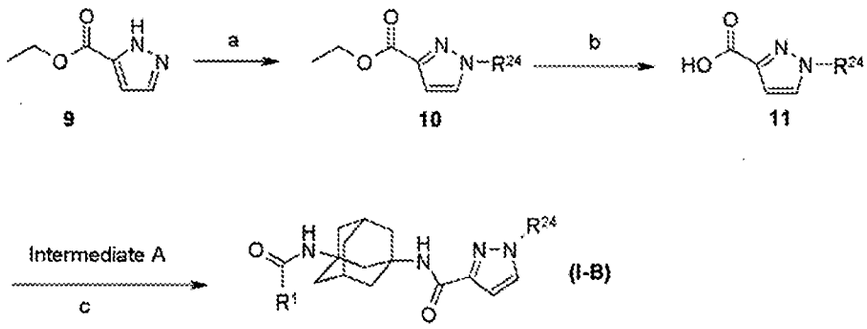


a) $(R^{20})NH(R^{21})$, K_2CO_3 or Cs_2CO_3, DMA or NMP, microwave, 180°C

Displacement of chloride of Intermediate B with amines $(R^{20})NH(R^{21})$ under basic conditions with microwave irradiation yields compounds of formula (I-A), where R^{20} and R^{21} are alkyl

or linked together to form a heterocycle that is optionally substituted by hydroxyl, alkoxy, amine, alkylamine, dialkylamine, -C(O)NH-alkyl, -C(O)N(dialkyl), -NHC(O)-alkyl, -N(alkyl)-C(O)-alkyl; or one of R^{20} and R^{21} is H and the other is alkyl, cycloalkyl or heterocycle that is optionally substituted by hydroxyl, cyano, alkoxy, amine, alkylamine, dialkylamine, -C(O)-NH_2, -C(O)NH-alkyl, -C(O)N(dialkyl), -NHC(O)-alkyl, -N(alkyl)-C(O)-alkyl; Q, Y and W are CR^{23}, where R^{23} is H, alkyl or cycloalkyl; or one of Q, Y and W is nitrogen.

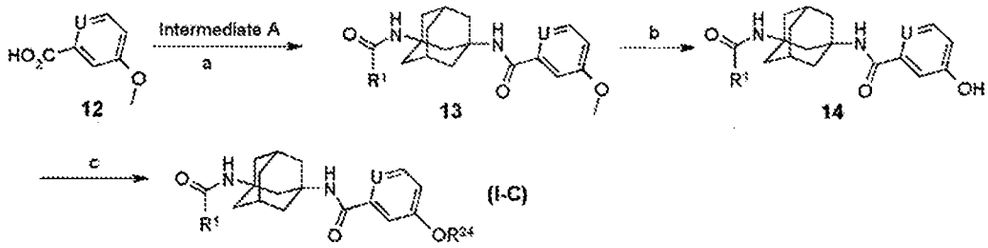
Scheme 8



a) $R^{24}Br$ or $R^{24}OMs$ or $R^{24}OTs$, base, DMF; b) aq. NaOH, EtOH; c) Et_3N, PyBOP, DCM

Alkylation of commercially available compound **9** with $R^{24}Br$, $R^{24}OMs$ or $R^{24}OTs$ under basic conditions such as K_2CO_3 or Cs_2CO_3 in DMF affords compound **10**. $R^{24}OMs$ or $R^{24}OTs$ could be easily made from corresponding $R^{24}OH$ and $MeSO_2Cl$ or 4-methylbenzenesulfonyl chloride. Saponification of ester **10** gives carboxylic acid **11**. Amidation of compound **11** with Intermediate A using customary procedures could yield compounds of formula (I-B), where R^{24} is alkyl, cycloalkyl or heterocycle that is optionally substituted by hydroxyl, alkoxy, amine, alkylamine, dialkylamine, -C(O)NH-alkyl, -C(O)N(dialkyl), -NHC(O)-alkyl, -N(alkyl)-C(O)-alkyl.

Scheme 9

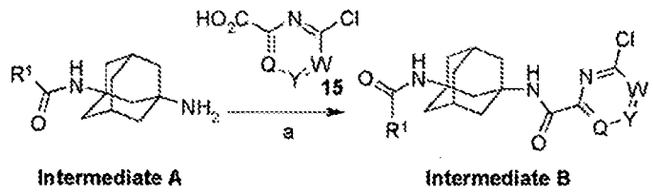


a) PyBOP, Et_3N, DCM; b) BBr_3, DCM;
c) $R^{24}OH$, Mitsunobu reaction; or $R^{24}Br$ ($R^{24}OMs$ or $R^{24}OTs$), base, DMF (or THF), 60-100°C

Customary amidation of commercially available carboxylic acid **12** with Intermediate A affords compound **13**, which upon demethylation gives compound **14**. Mitsunobu reaction of compound **14** with $R^{24}OH$, or alkylation of compound **14** with $R^{24}Br$, $R^{24}OMs$ or $R^{24}OTs$ under basic conditions, such as K_2CO_3 or Cs_2CO_3 in DMF, THF or CH_3CN, yields compounds of formula of (I-C), where U is CH or N, and R^{24} is as previously defined herein.

Intermediate B can be made *via* the process outlined in Scheme 10.

Scheme 10

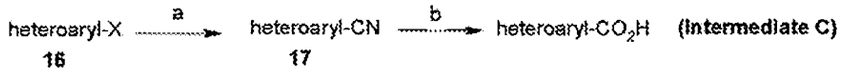


a) R^1CO_2H, PyBOP (or BOP or HBTU or EDCI or DMC), DIEA or Et_3N, DCM (or DMF or CH_3CN)

Customary amidation of Intermediate A with carboxylic acid **15** affords Intermediate B.

Non-commercially available carboxylic acids can be made *via* the process outlined in Scheme 11.

Scheme 11



a) $Zn(CN)_2$, Ph_2-pentedienone Pd and $(Ph_3P)_2$-ferrocene, DMF, 100°C
b) HCl, water, reflux; or 1) NaOH, water, 90°C; 2) HCl and water

Displacement of halogen X (X= F, Cl, Br or I) of compound **16** with cyano using customary procedures, such as $Zn(CN)_2$, and catalyst Ph_2-pentedienone Pd with ligand $(Ph_2P)_2$-ferrocene in DMF at 100 °C to afford compound **17**, which upon hydrolysis under acidic or basic conditions yields Intermediate C.

EXPERIMENTAL SECTION

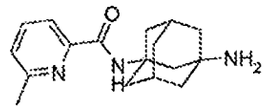
1. General Methods

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. All operations were carried out at room temperature (about 18 °C to about 25 °C) under nitrogen atmosphere. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure or in a high performance solvent evaporation system HT-4X (Genevac Inc., Gardiner, NY, USA). The course of the reaction was followed by thin layer chromatography (TLC) or liquid chromatography-mass spectrometry (LC-MS), and reaction times are given for illustration only. Silica gel chromatography was carried out on a Combi*Flash*® system (Teledyne Isco, Inc., Lincoln, NE, USA) with pre-packed silica gel cartridge or performed on Merck silica gel 60 (230-400 mesh). The structure and purity of all final products was assured by at least one of the following analytical methods: nuclear magnetic resonance (NMR) and LC-MS. NMR spectra was recorded on a Bruker Avance™ 300 spectrometer (Bruker BioSpin Corp., Billerica, MA, USA) or a Varian UNITY *INOVA*® 400 (Varian, Inc., Palo Alto, CA, USA) using the indicated solvent. Chemical shift (δ) is given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are expressed in hertz (Hz), and conventional abbreviations used for signal shape are: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad; etc. Unless stated otherwise, mass spectra were obtained using electrospray ionization (ESMS) *via* either a Micromass® Platform II system or a Quattro micro™ system (both from Waters Corp., Milford, MA, USA) and $(M+H)^+$ is reported.

2. Preparation of Intermediates of the Invention

Unless specified otherwise, the reagents used in the preparation of compounds, including intermediates, of the present invention were purchased from Sigma-Aldrich Corporation (St. Louis, MO, USA).

Intermediate 1: 6-Methyl-pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide

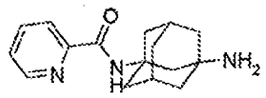


Intermediate 1 was prepared *via* the process of **Scheme 4**, *supra*, as follows:

To a flask containing 6-methyl-pyridine-2-carboxylic acid and (3-amino-adamantan-1-yl)-amide (1.0 g, 7 mmol) in DCM (75 mL), was added DIEA (2 mL, 10 mmol), and benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (3.2 g, 7.3 mmol), followed by a solution of adamantane-1,3-diamine (1.3 g, 8 mmol, Zerenex Molecular Ltd., Greater Manchester, UK) in DCM (25 mL) dropwise. After stirring at rt for 16 h, the reaction mixture was washed with saturated sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on a reversed phase liquid chromatography/mass spectrometry (RP-HPLC/MS) purification system (Gradient: acetonitrile in water, 18-95%, in 3.9 min with a cycle time of 5 min. A shallow gradient between 19-30% of acetonitrile was used between 0.7-2.5 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium formate. Column: Inertsil® C18, 30 x 50 mm, 5 μm particle size (GL Sciences, Tokyo, Japan)) to afford 0.5 g (20%) of the title compound, 6-methyl-pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide, as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.89-7.81 (m, 2H), 7.46-7.42 (m, 1H), 2.59 (s, 3H), 2.44-2.06 (m, 6H), 2.09-1.67 (m, 8H). ESI-MS m/z: 286.1 $(M+H)^+$.

Intermediate 1 was also made *via* the same synthetic procedures for Intermediate 2 (see below). Starting from 3-amino-adamantane-1-carboxylic acid methyl ester hydrochloride (14.9 g, 60.8 mmol), coupling with 6-methyl-pyridine-2-carboxylic acid afforded 3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantane-1-carboxylic acid methyl ester (14.9 g, 75%). The methyl ester was then hydrolyzed to give 3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantane-1-carboxylic acid (12.2 g, 86%). Finally, the Curtius rearrangement of 3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantane-1-carboxylic acid (10.0 g, 31.8 mmol) yielded Intermediate 1 (8.48 g, 93%).

Intermediate 2: Pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide



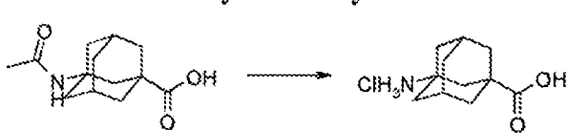
Intermediate 2 was synthesized *via* the process of **Scheme 5**, *supra*, as follows:

Step1: 3-Acetylamino-adamantane-1-carboxylic acid



To a 10-L reactor was added 1-adamantanecarboxylic acid (503 g, 2.79 mol; TCI America, Wellesley Hills, MA, USA) and 70% nitric acid (400 mL, 6.72 mol), and the resulting suspension was cooled at 0 °C with a recirculating chiller. To the mixture was slowly added 98% sulfuric acid (3.00 L, 55.5 mol) at such a rate that the temperature was kept below 10 °C. Once the addition completed, acetonitrile (2.00 L, 38.5 mol) was added at such a rate that the temperature was kept below 10 °C. After all the acetonitrile was added, the reaction was stirred at 0 °C for 1 hour. The crude reaction was then added to a 20-L reactor filled with about 10-L of ice mixed with a small amount of water and the resulting mixture was stirred and allowed to warm to room temperature. The solids were then filtered and washed with water. More solids precipitated from the acidic aqueous layer and these were filtered as well and washed with water. The combined solid material was then dried under high vacuum at 50 °C for 2 days to afford 432 g (73%) of the title compound, 3-acetylamino-adamantane-1-carboxylic acid, as a white solid.

Step 2: 3-Amino-adamantane-1-carboxylic acid hydrochloride



To a 3-neck 5-L flask equipped with a reflux condenser, a mechanical stirrer and a temperature probe was added 3-acetylamino-adamantane-1-carboxylic acid (432 g, 1.82 mol), water (1.00 L) and concentrated hydrochloric acid (2.44 L), and the resulting mixture was heated at 95 °C for 6 days. During this time, solid material precipitated from the solution. After cooling at 0 °C, the solids were filtered and washed with acetone. The solid

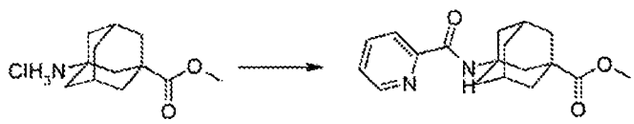
was then dried under high vacuum at 50 °C for about 2 hours to afford 328 g (78%) of the title compound, 3-amino-adamantane-1-carboxylic acid hydrochloride, as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.35 (br s, 1H), 8.27 (br s, 3H), 2.22-2.12 (m, 2H), 1.92-1.85 (m, 2H), 1.83-1.71 (m, 6H), 1.69-1.48 (m, 4H).

Step 3: 3-Amino-adamantane-1-carboxylic acid methyl ester hydrochloride



To a 3-neck 2-L flask equipped with a reflux condenser and a temperature probe was added 3-amino-adamantane-1-carboxylic acid hydrochloride (100 g, 432 mmol) and methanol (1.0 L). To this solution was slowly added thionyl chloride (15.7 mL, 216 mmol) and the reaction was heated at 60 °C for 4 hours. Once cooled to room temperature, the crude reaction mixture was concentrated under reduced pressure to remove most of the methanol. Heptane (about 1-L) was then added and the mixture was once again concentrated under reduced pressure at which point a solid began to precipitate. This process was repeated three more times, then the solids were filtered off, washed with heptane and allowed to dry in open air to afford 97.2 g (92%) of the title compound, 3-amino-adamantane-1-carboxylic acid methyl ester hydrochloride, as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (br s, 3H), 3.65 (s, 3H), 2.33-2.24 (m, 2H), 2.23-2.16 (m, 2H), 2.11-1.95 (m, 4H), 1.94-1.78 (m, 4H), 1.75-1.62 (m, 2H).

Step 4: 3-[(Pyridine-2-carbonyl)-amino]-adamantane-1-carboxylic acid methyl ester



To a round bottom flask was added 3-amino-adamantane-1-carboxylic acid methyl ester hydrochloride (20.0 g, 81.4 mmol) and methylene chloride (500 mL) and the solution was cooled at 0 °C. To this solution was then added triethylamine (57 mL, 0.41 mol) followed by

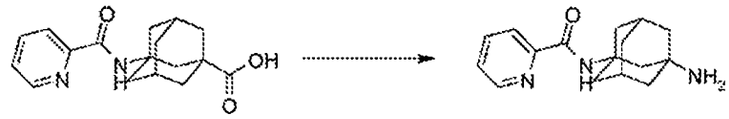
picolinoyl chloride hydrochloride (15.2 g, 85.4 mmol; TCI America, Wellesley Hills, MA, USA) and the reaction was stirred at 0 °C for 30 minutes, then at room temperature for 6 hours. To the reaction was added saturated aqueous sodium bicarbonate (500 mL) and the biphasic mixture was stirred vigorously for a few minutes, then transferred to a 2-L separatory funnel. The mixture was extracted, the layers separated and the aqueous layer was extracted again with methylene chloride (2 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 24.8 g (97%) of the title compound, 3-[(pyridine-2-carbonyl)-amino]-adamantane-1-carboxylic acid methyl ester, as a pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54-8.49 (m, 1H), 8.16 (dt, J = 7.8, 1.0 Hz, 1H), 7.96 (br s, 1H), 7.83 (td, J = 7.8, 1.8 Hz, 1H), 7.40 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 3.66 (s, 3H), 2.34-2.30 (m, 2H), 2.29-2.23 (m, 2H), 2.17-2.13 (m, 4H), 1.97-1.80 (m, 4H), 1.78-1.62 (m, 2H). ESI-MS m/z: 315.0 $(M+H)^+$.

Step 5: 3-[(Pyridine-2-carbonyl)-amino]-adamantane-1-carboxylic acid



To a round bottom flask was added 3-[(pyridine-2-carbonyl)-amino]-adamantane-1-carboxylic acid methyl ester (24.8 g, 78.9 mmol), tetrahydrofuran (250 mL), water (250 mL) and lithium hydroxide monohydrate (14.9 g, 355 mmol) and the mixture was stirred vigorously at room temperature for 25 hours. The crude mixture was concentrated under reduced pressure to remove most of the tetrahydrofuran, then the aqueous solution was diluted with water (200 mL) and the pH was adjusted to about 3-4 by adding solid citric acid monohydrate. A voluminous white precipitate appeared which was filtered, washed with water and dried under high vacuum at 50 °C to afford 22.1 g (93%) of the title compound, 3-[(pyridine-2-carbonyl)-amino]-adamantane-1-carboxylic acid, as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55-8.50 (m, 1H), 8.18 (d, J = 7.7 Hz, 1H), 7.97 (br s, 1H), 7.85 (td, J = 7.8, 1.8 Hz, 1H), 7.42 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 2.35-2.31 (m, 2H), 2.31-2.25 (m, 2H), 2.25-2.09 (m, 4H), 2.00-1.86 (m, 4H), 1.80-1.64 (m, 2H). ESI-MS m/z: 301.0 $(M+H)^+$.

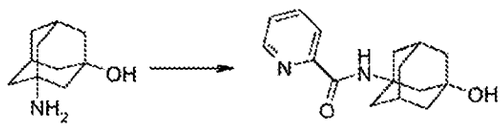
Step 6: Pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide



To a round bottom flask was added 3-[(pyridine-2-carbonyl)-amino]-adamantane-1-carboxylic acid (10.0 g, 33.3 mmol) and toluene (100 mL). To the suspension was added triethylamine (5.6 mL, 40 mmol) and the mixture was stirred for a few minutes until most of the solids were dissolved. To the mixture was then added diphenylphosphonic azide (7.9 mL, 37 mmol) and the reaction was stirred at room temperature for 1 hour. The reaction mixture was transferred to an addition funnel and added dropwise to a 3-neck round bottom flask equipped with a reflux condenser containing toluene (70 mL) heated at 90 °C. After the addition, the reaction was stirred at 90 °C for two more hours, then allowed to cool down to room temperature. The reaction mixture was then slowly added to a flask containing 6.0 N aqueous hydrochloric acid (55 mL, 330 mmol) and stirred vigorously for 1 hour. The biphasic mixture was transferred to a separatory funnel and the toluene layer was discarded. The aqueous acidic layer was then slowly treated with solid sodium carbonate until a pH of 10 was obtained. The aqueous layer was transferred to a 500-mL separatory funnel and extracted with methylene chloride (3 x 100 mL). The combined organic layers were then washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 8.38 g (93%) of the title compound, pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide, as a gummy foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55-8.50 (m, 1H), 8.16 (d, J = 7.9 Hz, 1H), 7.94 (br s, 1H), 7.84 (td, J = 7.7, 1.7 Hz, 1H), 7.40 (ddd, J = 7.6, 4.7, 1.3 Hz, 1H), 2.31-2.21 (m, 2H), 2.13-1.97 (m, 6H), 1.71-1.51 (m, 6H). ESI-MS m/z: 272 $(M+H)^+$.

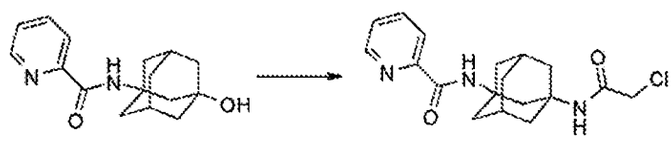
Intermediate 2 was also made *via* the process of **Scheme 6**, *supra*, as follows:

Step1: Pyridine-2-carboxylic acid (3-hydroxy-adamantan-1-yl)-amide



To a 40 ml vial was added picolinic acid (0.68 g, 5.5 mmol), DMF (15 ml), triethylamine (0.90 mL, 6.4 mmol), and *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU, 2.3 g, 6.0 mmol). The mixture was stirred at rt for 5 minutes to get a clear solution. 3-Amino-adamantanol (0.84 g, 5.0 mmol; AK Scientific, 897-4G Independence Ave., Mountain View, CA 94043) was added to the above solution and stirred at rt for 2 hours. DMF was removed in Genevac and the residue was dissolved in DCM (20 mL), washed with 1N aqueous NaOH, water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford 1.32 g (97%) of crude title compound, pyridine-2-carboxylic acid (3-hydroxy-adamantan-1-yl)-amide, as an oil, which became a colorless solid upon standing at room temperature. LC/MS (Gradient: acetonitrile in water, 20-85%, in 1.7 minutes with a cycle time of 2 min. Flow rate: 5.0 mL/min. Mobile phase additive: 30 mM of ammonium formate. Column: Inertsil® ODS-3, 50 x 4.6 mm, 3 μm particle size (GL Sciences, Tokyo, Japan)): Retention time: 0.79 min; purity (UV_{254}): 100%; ESI-MS m/z: 273 $(M+H)^+$. It was used in the next step without further purification.

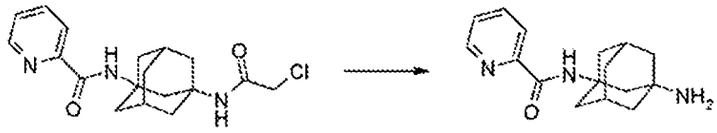
Step 2: Pyridine-2-carboxylic acid [3-(2-chloro-acetylamino)-adamantan-1-yl]-amide



Chloroacetonitrile (2.0 mL, 32 mmol) was cooled to 0 °C. Sulfuric acid (1.0 mL, 19 mmol) was added slowly at 0 °C. After addition completed, the mixture was stirred at 0 °C for 5 minutes. Pyridine-2-carboxylic acid (3-hydroxy-adamantan-1-yl)-amide (0.42 g, 1.56 mmol, from step 1) was added in one portion and the mixture was stirred at rt overnight. The thick solution was poured into ice-water (10 mL). DCM (10 mL) was added. While the mixture was cooled with an ice-bath, the pH of the aqueous phase (top) was adjusted to 10-13 with 10 N aq. NaOH. The aqueous layer was extracted with DCM. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford 0.53 g (96.9%) of crude title compound, pyridine-2-carboxylic acid [3-(2-chloro-acetylamino)-adamantan-1-yl]-amide, as an oil, which became a colorless solid upon standing at room temperature. LC-MS (Gradient: acetonitrile in water, 20-85%, in 1.7 minutes with a cycle time of 2 min. Flow rate: 5.0 mL/min. Mobile phase additive: 30 mM of

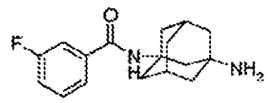
ammonium formate. Column: Inertsil® ODS, 50 x 4.6 mm, 3 μm particle size (GL Sciences, Tokyo, Japan)): Retention time: 1.08 min; purity (UV_{254}): 100%; ESI-MS m/z: 348 $(M+H)^+$. It was used in the next step without further purification.

Step 3: Pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide



To a 40 ml vial containing pyridine-2-carboxylic acid [3-(2-chloro-acetylamino) adamantan-1-yl]-amide (1.69 g, 4.85 mmol, from step 2) and thiourea (0.56g, 7.4 mmol), was added ethanol (20.0 mL), and acetic acid (4.0 mL). The mixture was stirred at 78 °C overnight. The reaction solution was cooled to rt, poured into water (100 mL), and the pH of the solution was adjusted to 10-13 using 10 N aq. NaOH. The mixture was transferred into a separation funnel, extracted with DCM (3 x 150 mL). Combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford 1.35 g (95.4%) of crude title compound, pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide, as an oil, which became a colorless solid upon standing at room temperature. LC-MS (Gradient: acetonitrile in water, 10-85%, in 1.7 minutes with a cycle time of 2 min. Flow rate: 5.0 mL/min. Mobile phase additive: 30 mM of ammonium formate. Column: Inertsil® C8, 50 x 4.6 mm, 3 μm particle size (GL Sciences, Tokyo, Japan)): Retention time: 0.63 min; purity (UV_{254}): 93%; ESI-MS m/z: 272 $(M+H)^+$. It was used in the next step, amidation, without further purification.

Intermediate 3: N-(3-Amino-adamantan-1-yl)-3-fluoro-benzamide



Using the same procedures as in the synthesis of Intermediate 2, Intermediate 3 was made at 4.33 mmol reaction scale, and 1.26 g (95.6%) of crude product was obtained. LC-MS (Gradient: acetonitrile in water, 10-85%, in 1.7 minutes with a cycle time of 2 min. Flow rate: 5.0 mL/min. Mobile phase additive: 30 mM of ammonium formate. Column: Inertsil® C8, 50 x 4.6 mm, 3 μm particle size (GL Sciences, Tokyo, Japan)): Retention time: 0.70 min;

purity (UV_{254}): 95%. ESI-MS m/z: 289 $(M+H)^+$. It was used in the next step without further purification.

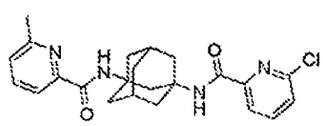
Intermediate 4: 6-Chloro-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide



Intermediate 4 was prepared from Intermediate 2 *via* the process of **Scheme 10**, *supra*, as follows:

To a 40 ml vial was added 6-chloropyridine-2-carboxylic acid (0.79 g, 5.0 mmol), DMF (15 ml), triethylamine (0.90 mL, 6.4 mmol), and O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (2.3 g, 6.0 mmol). The mixture was stirred at room temperature for 5 minutes to get a clear solution. Pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide (Intermediate 2, 1.38 g, 4.73 mmol) was added to the solution, and the reaction mixture was stirred at room temperature for 2 hours. DMF was removed in Genevac. The residue was dissolved in DCM (20 mL), washed with aq. 1 N NaOH (15 mL), water (15 mL) and brine (15 mL), and dried over Na_2SO_4. Solvent was removed under reduced pressure to afford 1.85 g (95.2%) of crude title compound, 6-chloro-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide. LC-MS (Gradient: acetonitrile in water, 30-90%, in 1.7 minutes with a cycle time of 2 min. Flow rate: 5.0 mL/min. Mobile phase additive: 30 mM of ammonium formate. Column: Inertsil® C8, 50 x 4.6 mm, 3 μm particle size (GL Sciences, Tokyo, Japan)): Retention time: 1.17 min; purity (UV_{254}): 100%. ESI-MS m/z: 411 $(M+H)^+$. It was used in the next step without further purification.

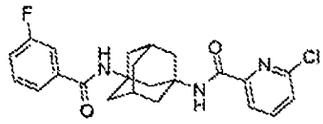
Intermediate 5: 6-Chloro-pyridine-2-carboxylic acid {3-[(6-methylpyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide



In a similar manner to Intermediate 4, Intermediate 5 was prepared from Intermediate 1 (2.00 g, 7.01 mmol). After purification by silica gel chromatography, Intermediate 5 (1.94 g, 65%)

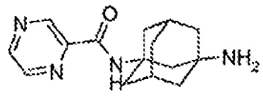
was obtained as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 8.09 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.84-7.69 (m, 3H), 7.44 (d, J = 7.7 Hz, 1H), 7.26 (d, 1H), 2.60-2.55 (m, 5H), 2.40-2.32 (m, 2H), 2.31-2.12 (m, 8H), 1.76-1.70 (m, 2H). ESI-MS m/z: 425.0 $(M+H)^+$.

Intermediate 6: 6-Chloro-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide



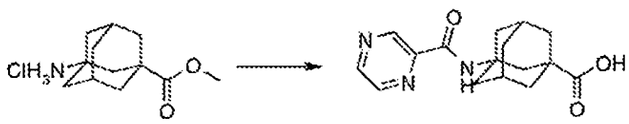
In a similar manner to Intermediate 4, Intermediate 6 was prepared from Intermediate 3 at a 4.6 mmol reaction scale. Crude product (1.99 g, 97%) was obtained. LC-MS (Gradient: acetonitrile in water, 30-90%, in 1.7 minutes with a cycle time of 2 min. Flow rate: 5.0 mL/min. Mobile phase additive: 30 mM of ammonium formate. Column: Inertsil® C8, 50 x 4.6 mm, 3 μm particle size (GL Sciences, Tokyo, Japan)): Retention time: 1.21 min; purity (UV_{254}):100%. ESI-MS m/z: 428 $(M+H)^+$. It was used in the next step without further purification.

Intermediate 7: Pyrazine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide



Intermediate 7 was synthesized *via* the process of **Scheme 5** from compound 4, *supra*, as follows:

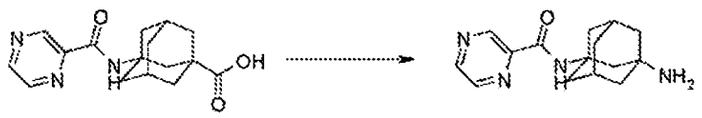
Step 1: 3-[(Pyrazine-2-carbonyl)-amino]-adamantane-1-carboxylic acid



To a round bottom flask was added 3-amino-adamantane-1-carboxylic acid methyl ester hydrochloride (7.00 g, 28.5 mmol), 2-pyrazinecarboxylic acid (3.71 g, 29.9 mmol) and methylene chloride (200 mL). The mixture was stirred vigorously and treated with PyBOP® (15.6 g, 29.9 mmol) followed by triethylamine (9.9 mL, 71 mmol), and then stirred at room

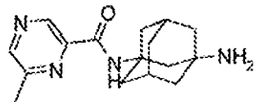
temperature for 16 hours. To the reaction was added saturated aqueous sodium bicarbonate (200 mL) and the biphasic mixture was stirred vigorously for a few minutes, then transferred to a 1-L separatory funnel. The mixture was extracted, the layers separated and the aqueous layer was extracted again with methylene chloride (200 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was then dissolved in tetrahydrofuran (200 mL) and water (200 mL) was added. To the biphasic mixture was added lithium hydroxide monohydrate (5.38 g, 128 mmol), and the resultant mixture stirred vigorously at room temperature for 22 hours. Most of the volatiles were removed under reduced pressure and the resulting aqueous solution was transferred to a 500-mL separatory funnel and washed with methylene chloride (3 x 150 mL). The aqueous layer was diluted with water (200 mL) and the pH was adjusted to about 3-4 by adding solid citric acid monohydrate. A voluminous white precipitate appeared that was filtered, washed with water and dried under high vacuum at 50 °C to afford 8.11 g (95%) of the title compound, 3-[(pyrazine-2-carbonyl)-amino]-adamantane-1-carboxylic acid, as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.14-10.07 (br s, 1H), 9.38 (d, J = 1.5 Hz, 1H), 8.74 (d, J = 2.5 Hz, 1H), 8.50 (dd, J = 2.4, 1.5 Hz, 1H), 7.68 (br s, 1H), 2.35-2.25 (m, 4H), 2.23-2.08 (m, 4H), 2.00-1.86 (m, 4H), 1.81-1.64 (m, 2H). ESI-MS m/z: 301.9 $(M+H)^+$.

Step 2: Pyrazine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide



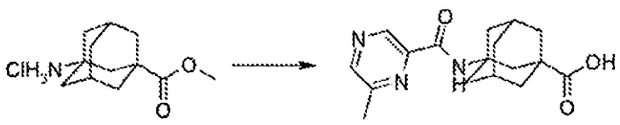
Using the same procedure as that used to prepare Intermediate 2 in step 6, from 3-[(pyrazine-2-carbonyl)-amino]-adamantane-1-carboxylic acid (4.00 g, 13.3 mmol), the Curtius rearrangement afforded 3.56 g (99%) of the title compound, pyrazine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide, as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (d, J = 1.4 Hz, 1H), 8.73 (d, J = 2.5 Hz, 1H), 8.49 (dd, J = 2.4, 1.5 Hz, 1H), 7.64 (br s, 1H), 2.31-2.21 (m, 2H), 2.14-1.95 (m, 6H), 1.71-1.51 (m, 6H) (Note: the -NH_2 is hidden between 2.52-1.78 ppm). ESI-MS m/z: 273.0 $(M+H)^+$.

Intermediate 8: 6-Methyl-pyrazine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide



Intermediate 8 was synthesized *via* the process of **Scheme 5** from compound 4, *supra*, as follows:

Step 1: 3-[(6-Methyl-pyrazine-2-carbonyl)-amino]-adamantane-1-carboxylic acid



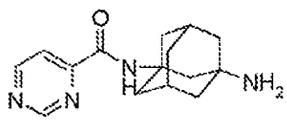
Using the same procedure as that used to prepare Intermediate 7 in step 1, from 3-amino-adamantane-1-carboxylic acid methyl ester hydrochloride (7.00 g, 28.5 mmol) and 6-methylpyrazine-2-carboxylic acid (4.13 g, 29.9 mmol, RihaChem, Kostalov Czech Republic), the coupling reaction with PyBOP®, followed by basic hydrolysis of the methyl ester group, afforded 8.01 g (89%) of the title compound, 3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantane-1-carboxylic acid, as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.03-10.32 (br s, 1H), 9.17 (s, 1H), 8.60 (s, 1H), 7.72 (br s, 1H), 2.60 (s, 3H), 2.35-2.26 (m, 4H), 2.26-2.18 (m, 2H), 2.16-2.07 (m, 2H), 2.00-1.86 (m, 4H), 1.80-1.65 (m, 2H). ESI-MS m/z: 316.0 $(M+H)^+$.

Step 2: 6-Methyl-pyrazine-2-carboxylic acid (3-amino-adamantan-1-yl) amide



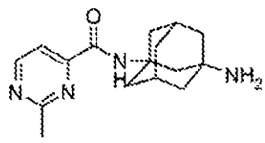
Using the same procedure as that used to prepare Intermediate 2 in step 6, from 3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantane-1-carboxylic acid (3.00 g, 9.51 mmol), the Curtius rearrangement afforded 2.65 g (97%) of the title compound, 6-methyl-pyrazine-2-carboxylic acid (3-amino-adamantan-1-yl) amide, as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.59 (s, 1H), 7.69 (br s, 1H), 2.60 (s, 3H), 2.32-2.21 (m, 2H), 2.13-1.97 (m, 6H), 1.70-1.52 (m, 6H) (Note: the -NH_2 is hidden between 2.41-1.29 ppm). ESI-MS m/z: 287.0 $(M+H)^+$.

Intermediate 9: Pyrimidine-4-carboxylic acid (3-amino-adamantan-1-yl)-amide



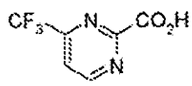
Using the same procedures as in the synthesis of Intermediate 7, Intermediate 9 was made at 16.8 mmol reaction scale from 3-amino-adamantane-1-carboxylic acid methyl ester hydrochloride and pyrimidine-4-carboxylic acid (Ark Pharm Inc., Libertyville, IL, USA), and 4.00 g (88%) of crude product was obtained. LC-MS (Gradient: acetonitrile in water, 20-85%, in 1.7 minutes with a cycle time of 2 min. Flow rate: 5.0 mL/min. Mobile phase additive: 30 mM of ammonium formate. Column: Inertsil® ODS, 50 x 4.6 mm, 3 µm particle size (GL Sciences)): Retention time: 0.24 min; purity (UV_{254}): 95%. ESI-MS m/z: 273 $(M+H)^+$. It was used in the next step without further purification.

Intermediate 10: 2-Methyl-pyrimidine-4-carboxylic acid (3-amino-adamantan-1-yl)-amide



Using the same procedures as in the synthesis of Intermediate 7, Intermediate 10 was made at 15.8 mmol reaction scale from 3-amino-adamantane-1-carboxylic acid methyl ester hydrochloride and 2-methyl-pyrimidine-4-carboxylic acid (Ark Pharm Inc.), and 4.6 g (100%) of crude product was obtained. LC-MS (Gradient: acetonitrile in water, 20-85%, in 1.7 minutes with a cycle time of 2 min. Flow rate: 5.0 mL/min. Mobile phase additive: 30 mM of ammonium formate. Column: Inertsil® ODS, 50 x 4.6 mm, 3 µm particle size (GL Sciences)): Retention time: 0.30 min; purity (UV_{254}): 82%. ESI-MS m/z: 287 $(M+H)^+$. It was used in the next step without further purification.

Intermediate 11: 4-Trifluoromethyl-pyrimidine-2-carboxylic acid



Intermediate 11 was made *via* the process of **Scheme 11**, supra, as follows:

Step 1: 4-Trifluoromethyl-pyrimidine-2-carbonitrile



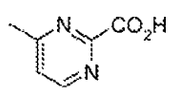
To a solution 2-chloro-4-(trifluoromethyl)pyrimidine (5.00 g, 27.4 mmol) in dimethyl sulfoxide (25 mL) was added sodium cyanide (1.68 g, 34.2 mmol). The reaction was stirred at room temperature for 30 minutes and poured into cold saturated aqueous $NaHCO_3$ solution. The mixture was transferred to a 100 mL separatory funnel and extracted with ethyl ether (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound, 4-trifluoromethyl-pyrimidine-2-carbonitrile, as a brown oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, *J*=5.1 Hz, 1H), 7.88 (d, J=5.1 Hz, 1H).

Step 2: 4-Trifluoromethyl-pyrimidine-2-carboxylic acid



The crude 4-trifluoromethyl-pyrimidine-2-carbonitrile from Step 1 was dissolved in a solution of hydrogen chloride in water (6 M, 20.0 mL) and heated at reflux temperature overnight. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. Toluene (20 mL) was then added and the mixture was concentrated under reduced pressure. This process was repeated with 1,4-dioxane and ethyl ether, then the solids were filtered off. The filtrate was concentrated under reduced pressure to afford 4.80 g (82.1%) of the title compound, 4-trifluoromethyl-pyridine-2-carboxylic acid, as brown solid, which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.35 (d, J=5.0 Hz, 1H), 8.25 (d, J=5.1 Hz, 1H).

Intermediate 12: 4-Methyl-pyrimidine-2-carboxylic acid



Step 1: 4-Methyl-pyrimidine-2-carbonitrile



To a solution of 2-chloro-4-methylpyrimidine (3.00 g, 23.3 mmol; 3B Pharmachem International, China) in ethyl ether (24 mL) was added a solution of sodium cyanide (2.86 g, 58.3 mmol) in trimethylamine solution (1:3, trimethylamine:water, 24.0 mL). The reaction mixture was stirred at room temperature overnight. The aqueous layer was extracted with ethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the title compound, 4-methyl-pyrimidine-2-carbonitrile (1.80 g; 64.8%), which was used in the next step without further purification. ^1H NMR (400 MHz, D_2O) δ 8.64 (d, J=5.4 Hz, 1H), 7.59 (d, J=5.5 Hz, 1H).

Step 2: 4-Methyl-pyrimidine-2-carboxylic acid

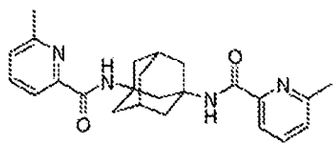


The solution of 4-methyl-pyrimidine-2-carbonitrile (500 mg, 4.20 mmol) and sodium hydroxide (504 mg, 12.6 mmol) in water (12.5 mL) was stirred at 60 °C for 1 hour. The reaction mixture was cooled to room temperature, acidified to pH ~2 with citric acid and extracted with $CHCl_3$:*i*-PrOH (3:1, 2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford 0.294 g of the title compound, 4-methyl-2-pyrimidinecarboxylic acid (51%), which was used in the next step without further purification. ^1H NMR (300 MHz, D_2O) δ 8.50 (d, J=5.2 Hz, 1H), 7.31 (d, J=5.3 Hz, 1H).

3. Preparation of Compounds of the Invention

Unless specified otherwise, the reagents used in the preparation of compounds, including intermediates, of the present invention were purchased from Sigma-Aldrich Corporation (St. Louis, MO, USA).

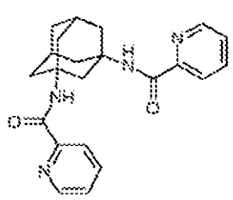
Example 1: *N,N'*-(1,3-adamantylene)bis(6-methyl-pyridine-2-carboxamide)



Example 1 was prepared *via* the process of **Scheme 1**, *supra*, as follows:

To a vial containing 6-methyl picolinic acid (40 mg, 0.3 mmol), methylene chloride (10 mL) and *N,N*-diisopropylethylamine (60 mg, 0.5 mmol), was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (60 mg, 0.3 mmol). The mixture was stirred for 5 minutes. Adamantane-1,3-diamine hydrochloride salt (20 mg, 0.1 mmol; Zerenex™ Molecular Ltd., Greater Manchester, UK) was added and the reaction was allowed to proceed for 16 h. The reaction mixture was washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on a reversed phase liquid chromatography/mass spectrometry (RP-HPLC/MS) purification system (Gradient: acetonitrile in water, 25-95%, in 3.9 min with a cycle time of 5 min. A shallow gradient between 28-58% of acetonitrile was used between 0.75-3.5 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium acetate. Column: Inertsil® C8, 30 x 50 mm, 5 um particle size) to afford the title compound (33 mg, 80%) as an off white oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s,br, 2H), 7.96 (d, J = 7.76 Hz, 2H), 7.70 (t, J =7.70 Hz, 2 H), 7.27-7.22 (m, 2H), 2.58-2.55 (m, 2H), 2.38-2.13 (m, 10H). 1.75-1.71 (m, 2H). ESI-MS m/z: 405.0 $(M+H)^+$.

Example 2: *N,N'*-(1,3-adamantylene)bis(2-pyridinecarboxamide)

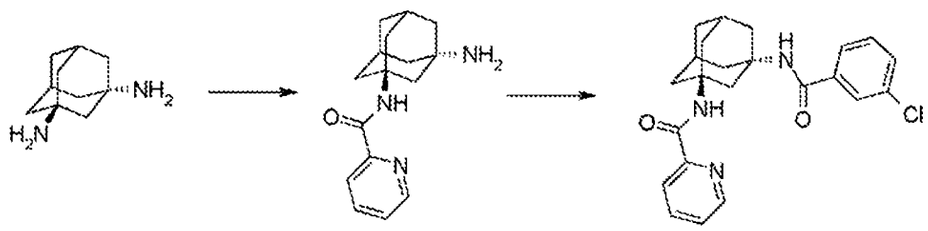


Example 2 was prepared *via* the process of **Scheme 1**, *supra*, as follows:

Into a vial containing adamantane-1,3-diamine (50 mg, 0.3 mmol; Zerenex™ Molecular Ltd., Greater Manchester, UK) and methylene chloride (10 mL) at 0 °C was added *N,N*-diisopropylethylamine (200 mg, 2 mmol; Alfa Aesar®, Ward Hill, MA, USA). Into the reaction was added pyridine-2-carbonyl chloride (60 mg, 0.4 mmol; TCI America, Wellesley Hills, MA, USA). After stirring at room temperature for 16 h, the reaction mixture was washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on a reversed phase liquid chromatography/mass spectrometry (RP-HPLC/MS) purification system (Gradient: acetonitrile in water, 30-95%, in 3.9 min with a cycle time of 5 min. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium formate. Column: Inertsil® C8, 30 x 50 mm, 5 um particle size) to obtain the title compound as a brownish oil. (58 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J=4.86 Hz, 2H), 8.15 (d, J=7.85 Hz, 2H), 8.03 (s, br 2H), 7.83 (d, J=7.70 Hz, 2H), 7.43-7.37 (m, 2H), 2.58 (s, br, 2H), 2.38-2.31 (m, 2H). 2.20-2.13 (m, 8H), 1.76-1.71 (m, 2H). ESI-MS m/z: 377.0 $(M+H)^+$.

In an analogous manner to Example 2, Examples 3-5 of Table 1 (below) were made from commercially available aryl or heteroaryl carbonyl chloride on 0.1 to 0.3 mmol reaction scales.

Example 6: Pyridine-2-carboxylic acid [3-(3-chloro-benzoylamino)-adamantan-1-yl]-amide



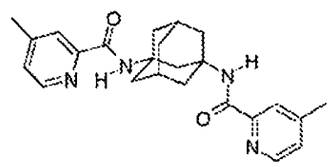
Example 6 was prepared *via* the process of **Schemes 4** and **3**, *supra*, as follows:

To a vial containing adamantane-1,3-diamine (50 mg, 0.3 mmol) and tetrahydrofuran (5 mL) was added dropwise, 5M aq NaOH (0.6 mL, 3 mmol). With vigorous stirring, picolinoyl chloride hydrochloride (50 mg, 0.3 mmol) was added in portions. After stirring at room temperature for 16 h, the reaction mixture was partitioned into dichloromethane and saturated

sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was retaken into 5 mL of DCM (dichloromethane). To the suspension was added DIEA (*N,N*-diisopropyl-ethylamine) (160 mg, 1.2 mmol) and 3-chloro-benzoyl chloride (79 mg, 0.45 mmol). The reaction mixture was stirred at room temperature for 16 h, washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on a reversed phase liquid chromatography/mass spectrometry (RP-HPLC/MS) purification system (Gradient: acetonitrile in water, 25-95%, in 3.9 min with a cycle time of 5 min. A shallow gradient between 35-65% of acetonitrile was used between 0.75-3.5 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium acetate. Column: Inertsil® C8, 30 x 50 mm, 5 um particle size) to afford the title compound (28 mg, 22%) as an off white oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J=4.75 Hz, 1H), 8.15 (d, J=7.84 Hz, 1H), 8.03 (s, br 1H), 7.83 (t, J=7.72 Hz, 1H), 7.69 (t, J=1.82 Hz, 1H), 7.57 (d, J=7.60 Hz, 1H), 7.46-7.31 (m, 3H), 5.87 (s,br 1H), 2.56 (s, br, 2H), 2.38-2.31 (m, 2H). 2.24-2.12 (m, 8H), 1.76-1.69 (m, 2H). ESI-MS m/z: 410.0 $(M+H)^+$.

In an analogous manner to Example 6, Examples 7-10 in Table 1 (below) were made from commercially available aryl or heteroaryl carbonyl chloride on a 0.3 mmol reaction scale.

Example 11: *N,N'*-(1,3-Adamantylene)bis(4-methyl-pyridine-2-carboxamide)



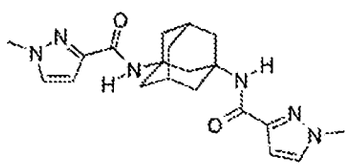
Example 11 was synthesized *via* the process of **Scheme 1**, *supra*, as follows:

To a vial containing 4-methyl-pyridine-2-carboxylic acid (30 mg, 0.22 mmol) in DMF (1 mL), was added benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (97 mg, 0.22 mmol), DIEA (40 mg, 0.3 mmol; Alfa Aesar, Ward Hill, MA, USA), followed by adamantane-1,3-diamine (20 mg, 0.1 mmol in 1 mL of THF; Zerenex Molecular Ltd., Greater Manchester, UK). After stirring for 16 h at rt, the reaction mixture was partitioned into dichloromethane and saturated sodium bicarbonate. The organic

layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified on a reversed phase liquid chromatography/mass spectrometry (RP-HPLC/MS) purification system (Gradient: acetonitrile in water, 30-95%, in 3.7 minutes with a cycle time of 5 min. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium formate. Column: Inertsil® C8, 30 x 50 mm, 5 μm particle size (GL Sciences, Tokyo, Japan)) to afford 18 mg (40%) of the title compound, *N,N'*-(1,3-adamantylene)bis(4-methyl-pyridine-2-carboxamide, as an off-white oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 4.9 Hz, 2H), 8.02 (s, br, 2H), 7.98-7.96 (m, 2H), 7.21-7.19 (m, 2H), 2.57-2.55 (m, 2H), 2.41 (s, 6H), 2.36-2.31 (m, 2H), 2.25-2.13 (m, 8H), 1.74-1.70 (m, 2H). ESI-MS m/z: 405.0 $(M+H)^+$.

In an analogous manner to Example 11, Examples 12-16 in Table 1 (below) were made from commercially available aryl or heteroaryl carboxylic acids on 0.1 to 0.3 mmol reaction scales.

Example 17: *N,N'*-(1,3-Adamantylene)bis(1-methyl-1*H*-pyrazole-3-carboxamide)

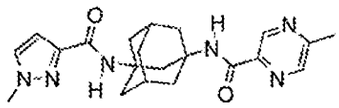


Example 17 was synthesized from heteroaryl carbonyl chloride *via* the process of **Scheme 1**, *supra*, as follows:

To a solution of adamantane-1,3-diamine (20 mg, 0.1 mmol; Zerenex Molecular Ltd., Greater Manchester, UK) in THF (4 mL), was added 1-methyl-1*H*-pyrazole-3-carbonyl chloride (40 mg, 0.3 mmol) and DIEA (40 mg, 0.3 mmol). After stirring for 16 h at rt, the reaction mixture was partitioned into dichloromethane and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified on a RP-HPLC/MS purification system (Gradient: acetonitrile in water, 18-95%, in 3.9 minutes with a cycle time of 5 min. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium acetate. Column: Inertsil® C8, 30 x 50 mm, 5 μm particle size (GL Sciences, Tokyo, Japan)) to afford 19 mg (50%) of the title compound, *N,N'*-(1,3-adamantylene)bis(1-methyl-1*H*-pyrazole-3-carboxamide, as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 2.3 Hz, 2H), 6.74-6.71 (m, 4H), 3.89 (s, 6H),

2.49 (s, br, 2H), 2.33-2.26 (m, 2H), 2.23-2.06 (m, 8H), 1.72-1.64 (m, 2H). ESI-MS m/z: 383.1 $(M+H)^+$.

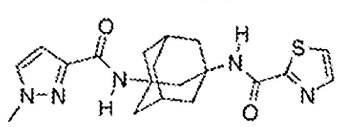
Example 18: 5-Methyl-pyrazine-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide



Example 18 was synthesized *via* the process of **Scheme 2** using commercially available carboxylic acids, *supra*, as follows:

To a solution of adamantane-1,3-diamine (20 mg, 0.1 mmol; Zerenex Molecular Ltd., Greater Manchester, UK) in DCM (2 mL) was added DIEA (26 mg, 0.15 mmol), 1-methyl-1*H*-pyrazole-3-carboxylic acid (14 mg, 0.11 mmol), 5-methyl-pyrazine-2-carboxylic acid (15 mg, 0.11 mmol) and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (110 mg, 0.20 mmol). After stirring for 3 hours at rt, the reaction mixture was partitioned into dichloromethane and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified on a RP-HPLC/MS purification system (Gradient: acetonitrile in water, 25-95%, in 3.4 minutes with a cycle time of 5 min. A shallow gradient between 25-50% of acetonitrile was used between 0.75-3.3 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium formate. Column: Inertsil® C8, 30 x 50 mm, 5 μm particle size (GL Sciences, Tokyo, Japan)) to afford 15 mg (37%) of the title compound, 5-methyl-pyrazine-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide, as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.34-8.33 (m, 1H), 7.67 (s, br, 1H), 7.33 (d, J = 2.3 Hz, 1H), 6.76-6.72 (m, 2H), 3.89 (s, 3H), 2.64 (s, 3H), 2.54 (s, br, 2H), 2.37-2.09 (m, 10H), 1.73-1.68 (m, 2H). ESI-MS m/z: 395.0 $(M+H)^+$.

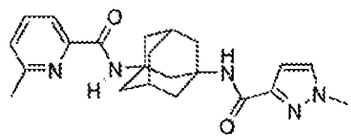
Example 19: Thiazole-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide



Example 19 was synthesized *via* the process of **Scheme 2** using commercially available carboxylic acid chlorides, *supra*, as follows:

To a solution of adamantane-1,3-diamine (17 mg, 0.1 mmol, Zerenex Molecular Ltd., Greater Manchester, UK) in DCM (2 mL) was added DIEA (20 mg, 0.15 mmol), 1-methyl-1*H*-pyrazole-3-carbonyl chloride (16 mg, 0.11 mmol; Maybridge Chemical Co., Cornwall, UK) and thiazole-2-carbonyl chloride (16 mg, 0.11 mmol; Maybridge Chemical Co., Cornwall, UK). After stirring at room temperature for 3 h, the reaction mixture was partitioned into dichloromethane and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on a RP-HPLC/MS purification system (Gradient: acetonitrile in water, 25-95%, in 3.9 minutes with a cycle time of 5 min. A shallow gradient between 27-53% of acetonitrile was used between 0.75-3.3 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium formate. Column: Inertsil® C8, 30 x 50 mm, 5 μm particle size (GL Sciences, Tokyo, Japan)) to afford 15 mg (38%) of the title compound, thiazole-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide, as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 3.2 Hz, 1H), 7.53 (d, J = 3.2 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.74-6.71 (m, 2H), 3.89 (s, 3H), 2.55-2.51 (m, 2H), 2.35-2.29 (m, 2H), 2.19-2.11 (m, 8H), 1.71-1.67 (m, 2H), ESI-MS m/z: 386.0 $(M+H)^+$.

Example 20: 6-Methyl-pyridine-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide



Example 20 was synthesized from Intermediate 1 *via* the process of **Scheme 3**, *supra*, as follows:

To a solution of 6-methyl-pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide (Intermediate 1, 20 mg, 0.07 mmol) in DCM (5 mL) was added DIEA (30 mg, 0.2 mmol) and 1-methyl-1*H*-pyrazole-3-carbonyl chloride (20 mg, 0.1 mmol, Maybridge Chemical Co., Cornwall, UK). After stirring at room temperature for 16 h, the reaction mixture was

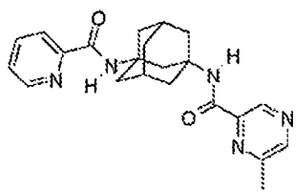
partitioned into dichloromethane and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on a RP-HPLC/MS purification system (Gradient: acetonitrile in water, 25-95%, in 3.9 minutes with a cycle time of 5 min. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium formate. Column: Inertsil® C8, 30 x 50 mm, 5 µm particle size (GL Sciences, Tokyo, Japan)) to afford 10 mg (30%) of the title compound, 6-methyl-pyridine-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide, as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, br, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.26-7.21 (m, 1H), 6.76-6.72 (m, 2H), 3.89 (s, 3H), 2.55 (s, 3H), 2.54-2.52 (m, 2H), 2.35-2.08 (m, 10H), 1.72-1.69 (m, 2H). ESI-MS m/z: 394.1 $(M+H)^+$.

In an analogous manner to Example 20, Examples 21-57 in Table 1 (below) were made from commercially available aryl, heteroaryl or aliphatic carboxylic acids, or aryl, heteroaryl or aliphatic carbonyl chlorides on 0.05-7.0 mmol reaction scales.

In an analogous manner to Example 20, Examples 114-130, 132-139 and 142 in Table 1 (below) were made from commercially available aryl, heteroaryl or aliphatic carboxylic acids, or aryl, heteroaryl or aliphatic carbonyl chlorides.

In an analogous manner to Example 20, Examples 131 and 141 in Table 1 (below) were made from 4-trifluoromethyl-pyrimidine-2-carboxylic acid (Intermediate 11) and 4-methyl-pyrimidine-2-carboxylic acid (Intermediate 12).

Example 58: 6-Methyl-pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide



Example 58 was synthesized from Intermediate 2 *via* the process of **Scheme 3**, *supra*, as follows:

To a round bottom flask was added pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide (3.10 g, 11.0 mmol, Intermediate 2), 6-methylpyrazine-2-carboxylic acid (1.83 g, 13.3 mmol; RihaChem, Kostalov, Czech Republic) and methylene chloride (120 mL). To the solution was then added PyBOP® (6.90 g, 13.3 mmol) followed by triethylamine (3.85 mL, 27.6 mmol) and the reaction was stirred for two hours at room temperature. The reaction was transferred to a 500-mL separatory funnel with methylene chloride (50 mL) and saturated aqueous sodium bicarbonate (150 mL), and extracted with methylene chloride. The organic layer was separated and the aqueous layer was extracted again with methylene chloride (2 x 75 mL). The combined organic layers were washed with brine (150 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified on a RP-HPLC/MS purification system (Gradient: acetonitrile in water, 27-95%, in 3.5 min with a shallow gradient from 30-60% between 0.75-3.4 min and a cycle time of 5 min. Flow rate: 100 mL/min. Mobile phase additive: 38 mM of ammonium acetate. Column: Inertsil® C8, 30 x 50 mm, 5 μm particle size (GL Sciences, Tokyo, Japan). Mobile phase and column temperature: 50 °C). Fractions were then concentrated under reduced pressure to remove most of the acetonitrile, the resulting aqueous layer was made basic with solid sodium carbonate (pH > 10) and the aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 3.21 g (74%) of the title compound, 6-methyl-pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide, as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.58 (s, 1H), 8.54-8.50 (m, 1H), 8.17 (dt, J = 7.8, 1.0 Hz, 1H), 8.06 (br s, 1H), 7.85 (td, J = 7.7, 1.7 Hz, 1H), 7.77 (br s, 1H), 7.42 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 2.61-2.57 (m, 5H), 2.40-2.28 (m, 4H), 2.27-2.19 (m, 2H), 2.18-2.08 (m, 4H), 1.78-1.68 (m, 2H). ESI-MS m/z: 392.0 $(M+H)^+$.

In an analogous manner to Example 58, Examples 59-92 in Table 1 (below) were made from commercially available aryl, heteroaryl or aliphatic carboxylic acids, or aryl, heteroaryl or aliphatic carbonyl chlorides on 0.05-0.5 mmol reaction scales.

In an analogous manner to Example 58, Examples 105-111 in Table 1 (below) were made from commercially available aryl, heteroaryl or aliphatic carboxylic acids, or aryl, heteroaryl or aliphatic carbonyl chlorides.

In an analogous manner to Example 58, Example 113 in Table 1 (below) was made from 4-trifluoromethyl-pyrimidine-2-carboxylic acid (Intermediate 11).

In a similar manner to Example 58, Example 93-104 in Table 1 (below) were made from Intermediate 3, N-(3-amino-adamantan-1-yl)-3-fluoro-benzamide, and commercially available heteroaryl carboxylic acids on 0.05-0.5 mmol reaction scales.

In a similar manner to Example 58, Example 182 and 184 were made from Intermediate 3, N-(3-amino-adamantan-1-yl)-3-fluoro-benzamide, and 4-methyl-pyrimidine-2-carboxylic acid (Intermediate 12) and 4-trifluoromethyl-pyrimidine-2-carboxylic acid (Intermediate 11), respectively.

In a similar manner to Example 58, Example 183 in Table 1 (below) was made from Intermediate 3, N-(3-amino-adamantan-1-yl)-3-fluoro-benzamide, and a commercially available heteroaryl carboxylic acid.

In a similar manner to Example 58, Examples 145-179 in Table 1 (below) were made from Intermediate 8, 6-methyl-pyrazine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide, and commercially available aryl or heteroaryl carboxylic acids, while Example 181 in Table 1 (below) was made from Intermediate 8 and 4-trifluoromethyl-pyrimidine-2-carboxylic acid (Intermediate 11).

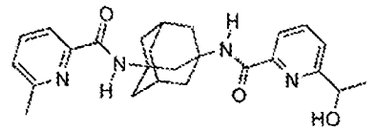
In a similar manner to Example 58, Examples 185-188 in Table 1 (below) was made from Intermediate 7, pyrazine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide, and commercially available heteroaryl carboxylic acids; Example 189 and was made from the Intermediate 7 and 4-methyl-pyrimidine-2-carboxylic acid (Intermediate 12).

In a similar manner to Example 58, Examples 191-193 in Table 1 (below) were made from Intermediate 10, 2-methyl-pyrimidine-4-carboxylic acid (3-amino-adamantan-1-yl)-amide, and commercially available 5-fluoro-pyridine-2-carboxylic acid (Beta Pharm, Inc., New Haven, CT, USA), 4-trifluoromethyl-pyrimidine-2-carboxylic acid (Intermediate 11) or 4-methyl-pyrimidine-2-carboxylic acid (Intermediate 12).

In a similar manner to Example 58, Examples 194-196 in Table 1 (below) were made from Intermediate 9, pyrimidine-4-carboxylic acid (3-amino-adamantan-1-yl)-amide, and 4-methyl-pyrimidine-2-carboxylic acid (Intermediate 12), commercially available 5-fluoro-

pyridine-2-carboxylic acid or 4-trifluoromethyl-pyrimidine-2-carboxylic acid (Intermediate 11).

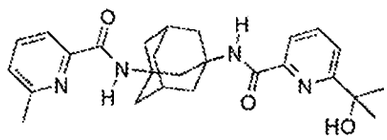
Example 143: 6-Methyl-pyridine-2-carboxylic acid {3-[(6-(1-hydroxy-ethyl)-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide



Example 143 in Table 1 (below) was made from Example 142 *via* $NaBH_4$ reduction, *supra*, as follows:

Into a vial containing 6-methyl-pyridine-2-carboxylic acid {3-[(6-acetyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide (50 mg, 0.1 mmol, Example 142) in MeOH (2 mL) was added sodium borohydride (6 mg, 0.17 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was concentrated and partitioned into dichloromethane and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on a RP-HPLC/MS purification system (Gradient: acetonitrile in water, 25-95%, in 3.6 min with a shallow gradient from 33-63% of acetonitrile between 0.75-3.3 min and a cycle time of 5 min. Flow rate: 100 mL/min. Mobile phase additive: 48 mM of ammonium formate. Column: Inertsil® C18, 30 x 50 mm, 5 um particle size) to afford 45 mg (90%) of the title compound, 6-methyl-pyridine-2-carboxylic acid {3-[(6-(1-hydroxy-ethyl)-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.00 (m, 2H), 7.90-(d, J = 7.9 Hz, 1H), 7.78 (t, J = 7.9 Hz, 1H), 7.74 (s, b, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8, Hz 1H), 7.20-7.06 (m, 1H), 4.91-4.85 (m, 1H), 2.50 (s, b, 5H), 2.31-2.26 (m, 2H), 2.21-2.06 (m, 8H), 1.69-1.64 (m, 2H), 1.48 (s, 3H). ESI-MS m/z: 435.0 $(M+H)^+$.

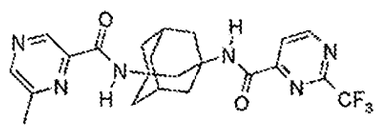
Example 144: 6-Methyl-pyridine-2-carboxylic acid (3-{[6-(1-hydroxy-1-methyl-ethyl)-pyridine-2-carbonyl]-amino}-adamantan-1-yl)-amide



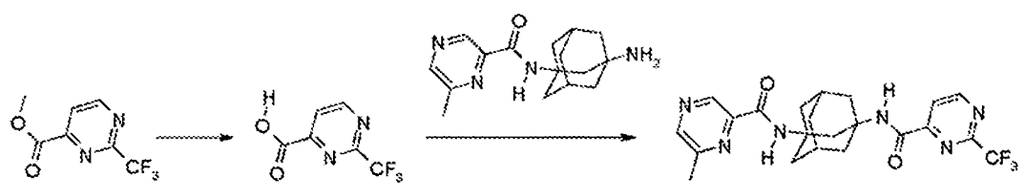
Example 144 in Table 1 (below) was made from Example 142 *via* Grignard reaction, *supra*, as follows:

Into a vial containing 6-methyl-pyridine-2-carboxylic acid {3-[(6-acetyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide (35 mg, 0.08 mmol, Example 142) in THF (2 mL) was added 1M methyl lithium (0.4 mL) at -40°C. After stirring for 2 h, the reaction mixture was quenched with cold water, concentrated and partitioned into dichloromethane and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on a RP-HPLC/MS purification system (Gradient: acetonitrile in water, 28-95%, in 3.6 min with a shallow gradient from 33-60% of acetonitrile between 0.75-3.4 min and a cycle time of 5 min. Flow rate: 100 mL/min. Mobile phase additive: 48 mM of ammonium formate. Column: Inertsil® C8, 30 x 50 mm, 5 um particle size) to afford 25 mg (69%) of the title compound, 6-methyl-pyridine-2-carboxylic acid (3-{[6-(1-hydroxy-1-methyl-ethyl)-pyridine-2-carbonyl]-amino}-adamantan-1-yl)-amide. ^{1}H NMR (400 MHz, CDCl3) δ 8.10-8.06 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H), 7.86 (t, J = 7.8 Hz, 1H), 7.75 (s, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.26-7.22 (m, 1H), 2.58-2.55 (m, 5H), 2.39-2.13 (m, 10H), 1.76-1.71 (m, 2H), 1.59 (s, 6H). ESI-MS m/z: 449.0 (M+H)+.

Example 180: 2-Trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide



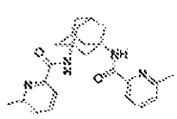
Example 180 in Table 1 (below) was made *via* the process of **Scheme 3** from Intermediate 8 and 2-trifluoromethyl-pyrimidine-4-carboxylic acid, which was prepared from the corresponding ester, *supra*, as follows:

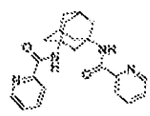
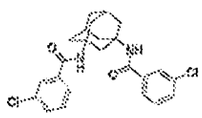
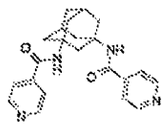
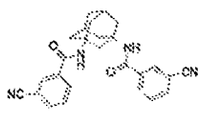
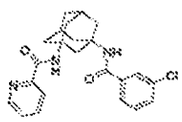
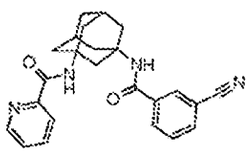
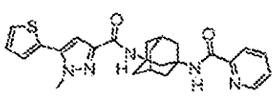


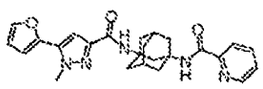
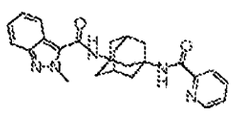
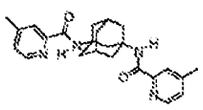
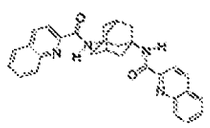
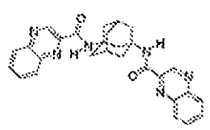
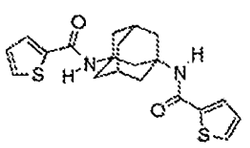
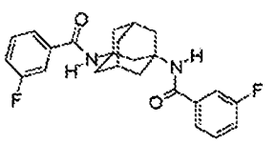
To a microwave vial was added 2-trifluoromethyl-pyrimidine-4-carboxylic acid methyl ester (110 mg, 0.52 mmol, CNH Tech, MA), THF (2 mL), and lithium hydroxide (18 mg, 0.75 mmol) in 200 µL of water. The mixture was heated in a microwave oven for 5 min at 100 °C, and then concentrated to dryness under reduced pressure. To the residue was added Intermediate 8, 6-methyl-pyrazine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide (100 mg, 0.4 mmol), THF (5 mL), DIEA (90 mg, 0.7 mmol) and TBTU (140 mg, 0.42 mmol, AKSCI, CA). After stirring at rt for 16 h, the reaction mixture was concentrated and partitioned into DCM and saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. The crude product was purified on a RP-HPLC/MS system (Gradient: acetonitrile in water, 30-95%, in 3.6 min with a cycle time of 5 min. with a shallow gradient from 40-68% of acetonitrile between 0.75-3.4 min. Flow rate: 100 mL/min. Mobile phase additive: 48 mM of ammonium formate . Column: Inertsil® C8, 30 x 50 mm, 5 um particle size) to give 60 mg (40%) of the title compound, 2-trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 9.12 (d, J=5.0, 1H), 8.6 (s, 1H), 8.28 (d, J=5.0, 1H), 7.80-7.75 (m, 2H), 2.6 (s, b, 5H), 2.42-2.36 (m, 2H), 2.23-2.17 (m, 8H), 1.77-1.73(m, 2H). ESI-MS m/z: 460.9 $(M+H)^+$.

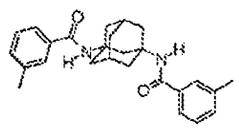
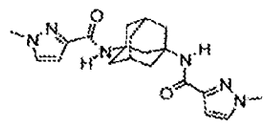
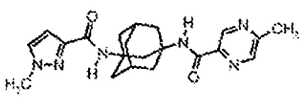
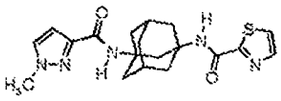
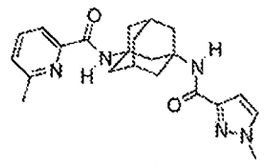
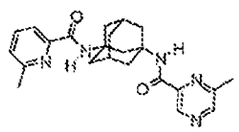
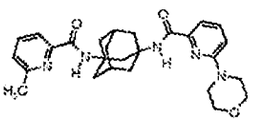
In a similar manner to Example 180, Examples 112, 140 and 190 in Table 1 (below) were made from Intermediate 2, pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide, Intermediate 1, 6-methyl- pyridine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide, and Intermediate 7, pyrazine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide, respectively.

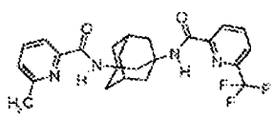
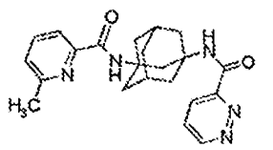
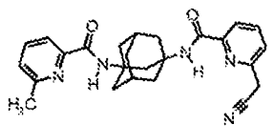
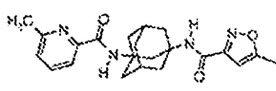
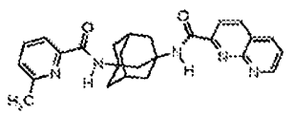
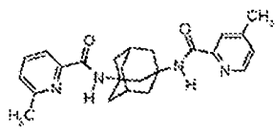
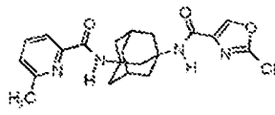
Table 1

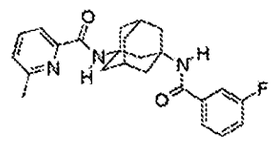
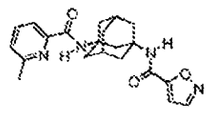
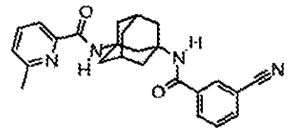
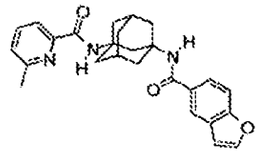
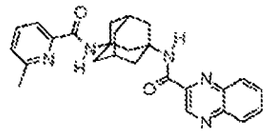
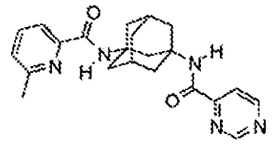
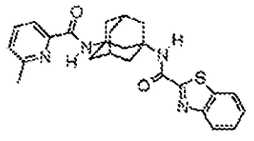
EXAMPLE	STRUCTURE	CHEMICAL NAME
1		*N,N'*-(1,3-adamantylene)bis(6-methyl-pyridine-2-carboxamide)

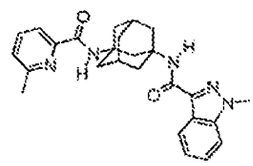
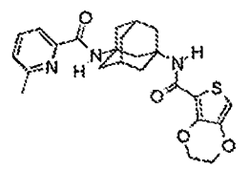
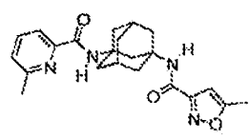
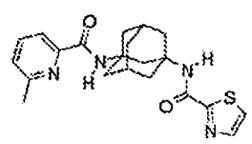
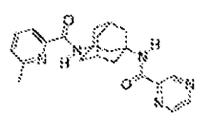
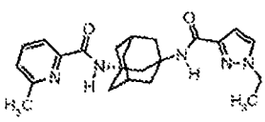
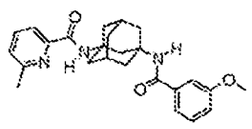
EXAMPLE	STRUCTURE	CHEMICAL NAME
2		*N,N'*-(1,3-adamantylene)bis(2-pyridinecarboxamide)
3		*N,N'*-(1,3-adamantylene)bis(3-chloro-benzamide)
4		*N,N'*-(1,3-adamantylene)bis(4-pyridinecarboxamide)
5		*N,N'*-(1,3-adamantylene)bis(3-cyano-benzamide)
6		Pyridine-2-carboxylic acid[3-(3-chloro-benzoylamino)-adamantan-1-yl]-amide
7		Pyridine-2-carboxylic acid[3-(3-cyano-benzoylamino)-adamantan-1-yl]-amid
8		Pyridine-2-carboxylic acid {3-[(1-methyl-5-thiophen-2-yl-1H-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide

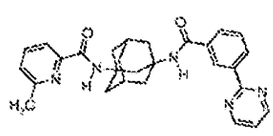
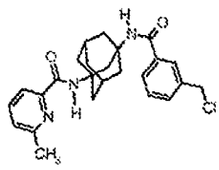
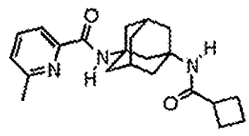
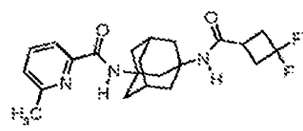
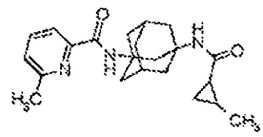
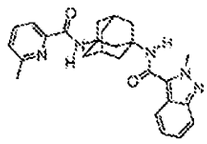
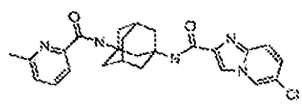
EXAMPLE	STRUCTURE	CHEMICAL NAME
9		Pyridine-2-carboxylic acid {3-[(5-furan-2-yl-1-methyl-1H-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide
10		2-Methyl-2H-indazole-3-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
11		*N,N'*-(1,3-adamantylene)bis(4-methyl-pyridine-2-carboxamide)
12		*N,N'*-(1,3-adamantylene)bis(quinoline-2-carboxamide)
13		*N,N'*-(1,3-adamantylene)bis(quinoxaline-2-carboxamide)
14		*N,N'*-(1,3-adamantylene)bis(thiophene-2-carboxamide)
15		*N,N'*-(1,3-adamantylene)bis(3-fluorobenzamide)

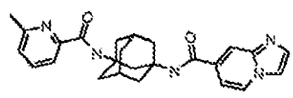
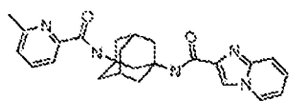
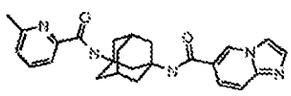
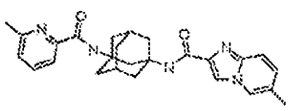
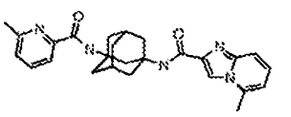
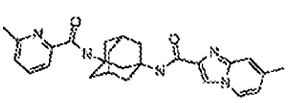
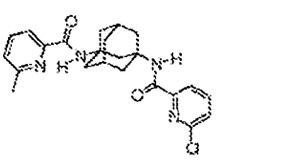
EXAMPLE	STRUCTURE	CHEMICAL NAME
16		*N,N'*-(1,3-adamantylene)bis(3-methylbenzamide)
17		*N,N'*-(1,3-adamantylene)bis(1-methyl-1*H*-pyrazole-3-carboxamide)
18		5-Methyl-pyrazine-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide
19		Thiazole-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide
20		6-Methyl-pyridine-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide
21		6-Methyl-pyrazine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
22		6-Morpholin-4-yl-pyridine-2-carboxylic acid-{3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

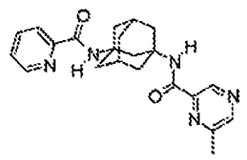
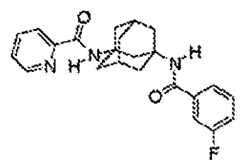
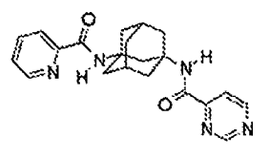
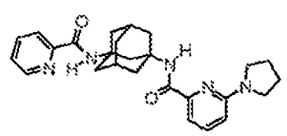
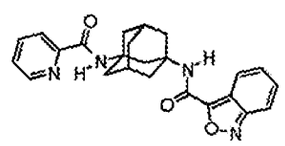
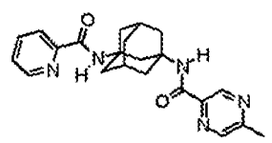
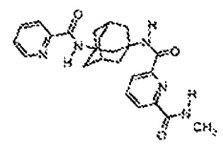
EXAMPLE	STRUCTURE	CHEMICAL NAME
23		6-Trifluoromethyl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino] -adamantan-1-yl}-amide
24		Pyridazine-3-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
25		6-Cyanomethyl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino] -adamantan-1-yl}-amide
26		6-Methyl-pyridine-2-carboxylic acid {3-[(5-cyclopropyl-isoxazole-3-carbonyl)-amino}-adamantan-1-yl}-amide
27		[1,8]Naphthyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino}-adamantan-1-yl}-amide
28		4-Methyl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino}-adamantan-1-yl}-amide
29		6-Methyl-pyridine-2-carboxylic acid {3-[(2-methyl-oxazole-4-carbonyl)-amino}-adamantan-1-yl}-amide

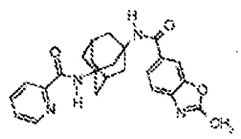
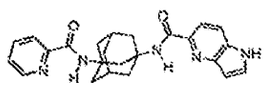
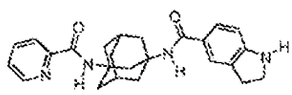
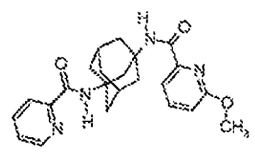
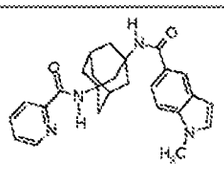
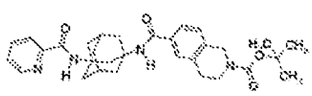
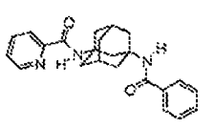
EXAMPLE	STRUCTURE	CHEMICAL NAME
30		6-Methyl-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
31		6-Methyl-pyridine-2-carboxylic acid {3-[(isoxazole-5-carbonyl)-amino]-adamantan-1-yl}-amide
32		6-Methyl-pyridine-2-carboxylic acid [3-(3-cyano-benzoylamino)-adamantan-1-yl]-amide
33		6-Methyl-pyridine-2-carboxylic acid {3-[(benzofuran-5-carbonyl)-amino]-adamantan-1-yl}-amide
34		Quinoxaline-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
35		Pyrimidine-4-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
36		Benzothiazole-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

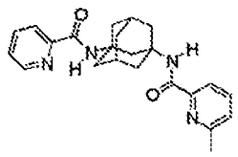
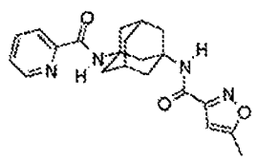
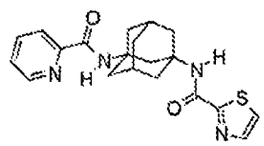
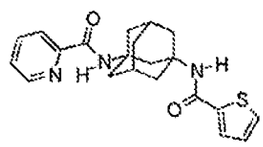
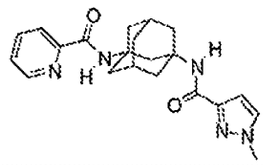
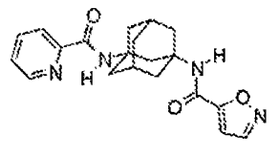
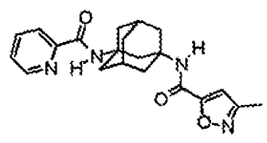
EXAMPLE	STRUCTURE	CHEMICAL NAME
37		1-Methyl-1*H*-indazole-3-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
38		6-Methyl-pyridine-2-carboxylic acid {3-[(2,3-dihydro-thieno[3,4-b][1,4]dioxine-5-carbonyl)-amino]-adamantan-1-yl}-amide
39		6-Methyl-pyridine-2-carboxylic acid {3-[(5-methyl-isoxazole-3-carbonyl)-amino]-adamantan-1-yl}-amide
40		6-Methyl-pyridine-2-carboxylic acid {3-[(thiazole-2-carbonyl)-amino]-adamantan-1-yl}-amide
41		Pyrazine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
42		6-Methyl-pyridine-2-carboxylic acid {3-[(1-ethyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide
43		6-Methyl-pyridine-2-carboxylic acid [3-(3-methoxy-benzoylamino)-adamantan-1-yl]-amide

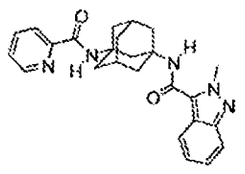
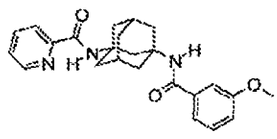
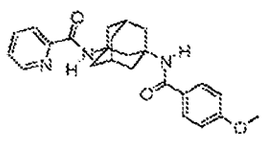
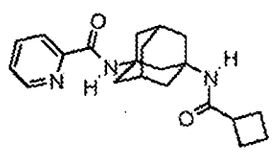
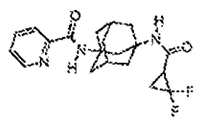
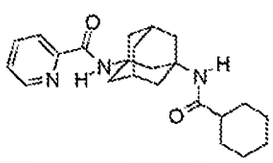
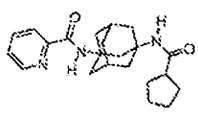
EXAMPLE	STRUCTURE	CHEMICAL NAME
44		6-Methyl-pyridine-2-carboxylic acid [3-(3-pyrimidin-2-yl-benzoylamino)-adamantan-1-yl]-amide
45		6-Methyl-pyridine-2-carboxylic acid [3-(3-chloromethyl-benzoylamino)-adamantan-1-yl]-amide
46		6-Methyl-pyridine-2-carboxylic acid [3-(cyclobutanecarbonyl-amino)-adamantan-1-yl]-amide
47		6-Methyl-pyridine-2-carboxylic acid {3-[(3,3-difluoro-cyclobutanecarbonyl)-amino]-adamantan-1-yl}-amide
48		6-Methyl-pyridine-2-carboxylic acid {3-[(2-methyl-cyclopropanecarbonyl)-amino]-adamantan-1-yl}-amide
49		2-Methyl-2*H*-indazole-3-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
50		6-Chloro-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

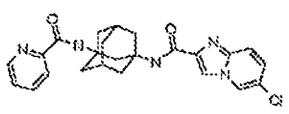
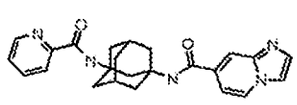
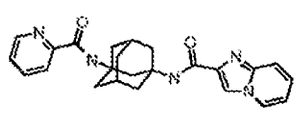
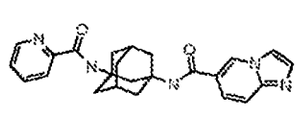
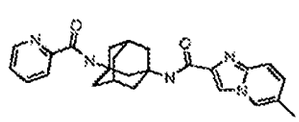
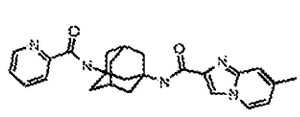
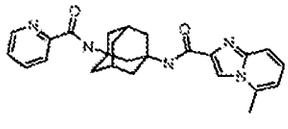
EXAMPLE	STRUCTURE	CHEMICAL NAME
51		Imidazo[1,2-a]pyridine-7-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
52		Imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
53		Imidazo[1,2-a]pyridine-6-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
54		6-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
55		5-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
56		7-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
57		6-Chloro-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

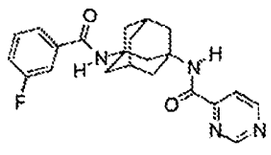
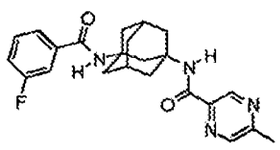
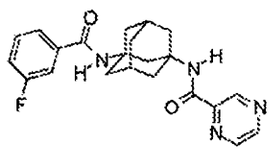
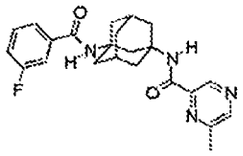
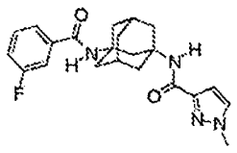
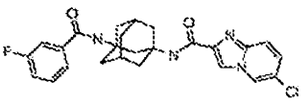
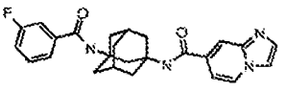
EXAMPLE	STRUCTURE	CHEMICAL NAME
58		6-Methyl-pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
59		Pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
60		Pyrimidine-4-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
61		6-Pyrrolidin-1-yl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
62		Benzo[c]isoxazole-3-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
63		5-Methyl-pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
64		Pyridine-2,6-dicarboxylic acid 2-methylamide 6-({3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide)

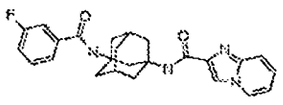
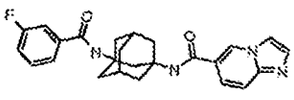
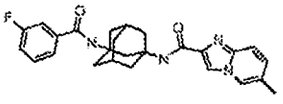
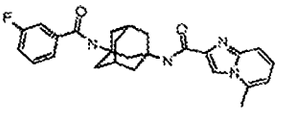
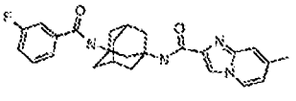
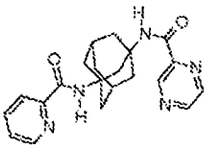
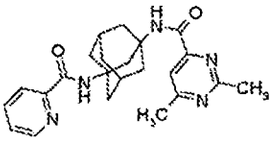
EXAMPLE	STRUCTURE	CHEMICAL NAME
65		2-Methyl-benzoxazole-6-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
66		1*H*-Pyrrolo[3,2-b]pyridine-5-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
67		2,3-Dihydro-1*H*-indole-5-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
68		6-Methoxy-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
69		1-Methyl-1*H*-indole-5-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
70		6-{3-[(Pyridine-2-carbonyl)-amino]-adamantan-1-yl-carbamoyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester
71		Pyridine-2-carboxylic acid (3-benzoylamino-adamantan-1-yl)-amide

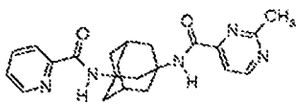
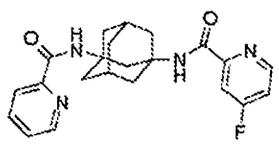
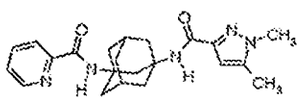
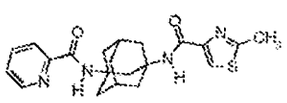
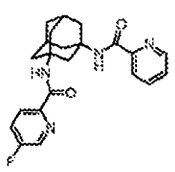
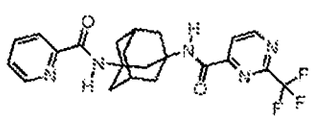
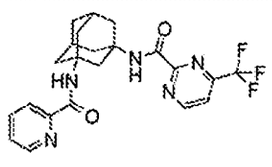
EXAMPLE	STRUCTURE	CHEMICAL NAME
72		6-Methyl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
73		Pyridine-2-carboxylic acid {3-[(5-methyl-isoxazole-3-carbonyl)-amino]-adamantan-1-yl}-amide
74		Pyridine-2-carboxylic acid {3-[(thiazole-2-carbonyl)-amino]-adamantan-1-yl}-amide
75		Pyridine-2-carboxylic acid {3-[(thiophene-2-carbonyl)-amino]-adamantan-1-yl}-amide
76		Pyridine-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide
77		Pyridine-2-carboxylic acid {3-[(isoxazole-5-carbonyl)-amino]-adamantan-1-yl}-amide
78		Pyridine-2-carboxylic acid {3-[(3-methyl-isoxazole-5-carbonyl)-amino]-adamantan-1-yl}-amide

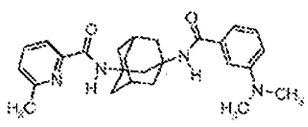
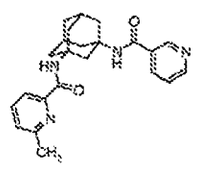
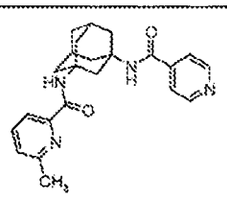
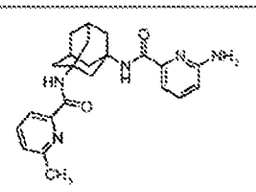
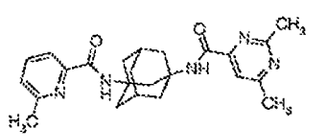
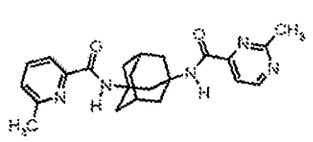
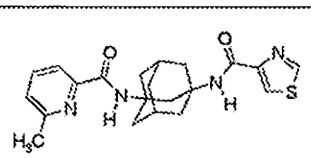
EXAMPLE	STRUCTURE	CHEMICAL NAME
79		2-Methyl-2*H*-indazole-3-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
80		Pyridine-2-carboxylic acid [3-(3-methoxy-benzoylamino)-adamantan-1-yl]-amide
81		Pyridine-2-carboxylic acid [3-(4-methoxy-benzoylamino)-adamantan-1-yl]-amide
82		Pyridine-2-carboxylic acid [3-(cyclobutanecarbonyl-amino)-adamantan-1-yl]-amide
83		Pyridine-2-carboxylic acid {3-[(2,2-difluoro-cyclopropanecarbonyl)-amino]-adamantan-1-yl}-amide
84		Pyridine-2-carboxylic acid [3-(cyclohexanecarbonyl-amino)-adamantan-1-yl]-amide
85		Pyridine-2-carboxylic acid [3-(cyclopentanecarbonyl-amino)-adamantan-1-yl]-amide

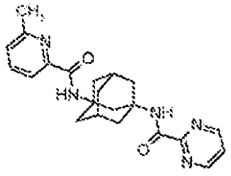
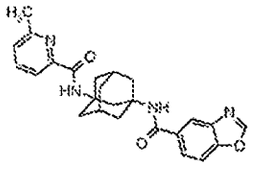
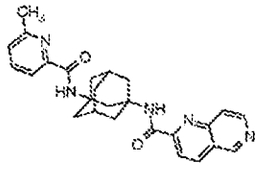
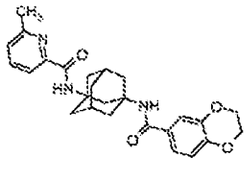
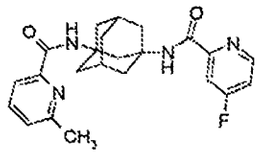
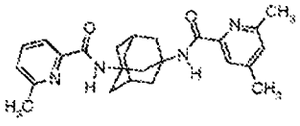
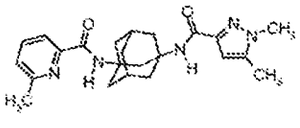
EXAMPLE	STRUCTURE	CHEMICAL NAME
86		6-Chloro-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
87		Imidazo[1,2-a]pyridine-7-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
88		Imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
89		Imidazo[1,2-a]pyridine-6-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
90		6-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
91		7-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
92		5-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

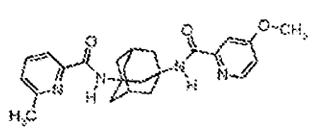
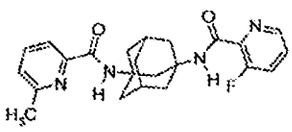
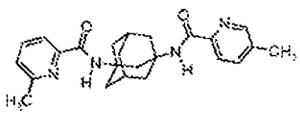
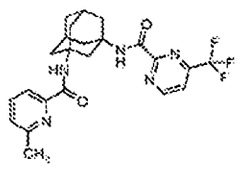
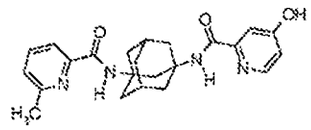
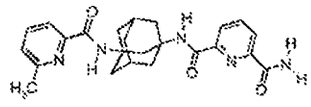
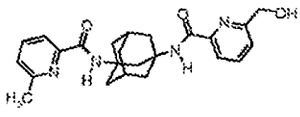
EXAMPLE	STRUCTURE	CHEMICAL NAME
93		Pyrimidine-4-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
94		5-Methyl-pyrazine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
95		Pyrazine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
96		6-Methyl-pyrazine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
97		1-Methyl-1*H*-pyrazole-3-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
98		6-Chloro-imidazo[1,2-a]pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
99		Imidazo[1,2-a]pyridine-7-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide

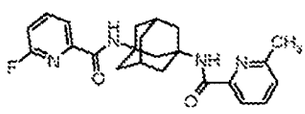
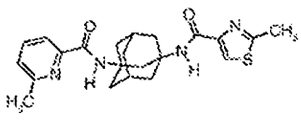
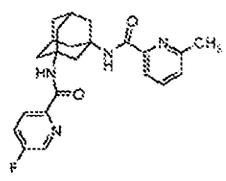
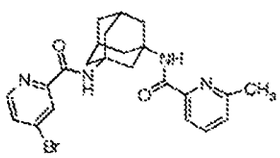
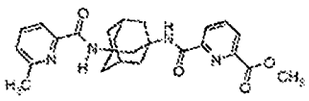
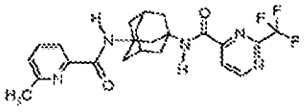
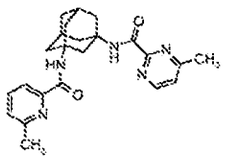
EXAMPLE	STRUCTURE	CHEMICAL NAME
100		Imidazo[1,2-a]pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
101		Imidazo[1,2-a]pyridine-6-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
102		6-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
103		5-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
104		7-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
105		Pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
106		2,6-Dimethyl-pyrimidine-4-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

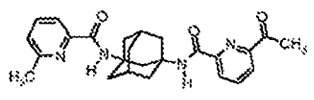
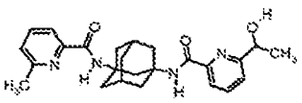
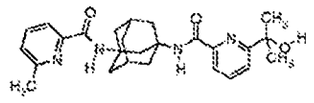
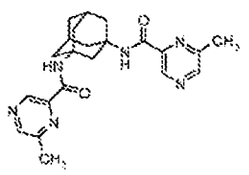
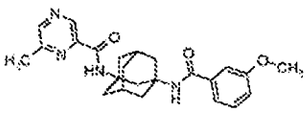
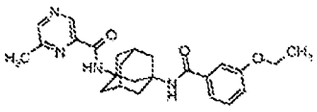
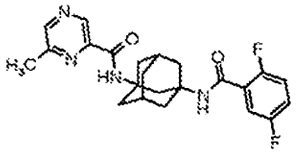
EXAMPLE	STRUCTURE	CHEMICAL NAME
107		2-Methyl-pyrimidine-4-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
108		4-Fluoro-pyridine-2-carboxylic acid{3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
109		Pyridine-2-carboxylic acid {3-[(1,5-dimethyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide
110		Pyridine-2-carboxylic acid {3-[(2-methyl-thiazole-4-carbonyl)-amino]-adamantan-1-yl}-amide
111		5-Fluoro-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
112		2-Trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
113		4-Trifluoromethyl-pyrimidine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

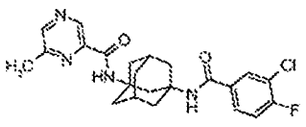
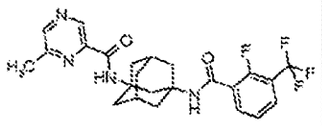
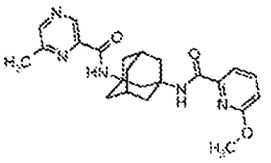
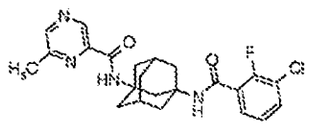
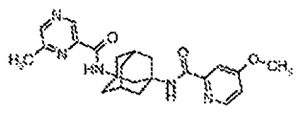
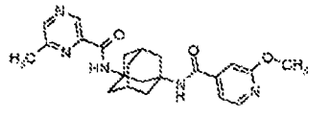
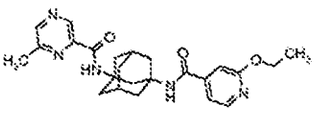
EXAMPLE	STRUCTURE	CHEMICAL NAME
114		6-Methyl-pyridine-2-carboxylic acid [3-(3-dimethylamino-benzoylamino)-adamantan-1-yl]-amide
115		6-Methyl-pyridine-2-carboxylic acid {3-[(pyridine-3-carbonyl)-amino]-adamantan-1-yl}-amide
116		6-Methyl-pyridine-2-carboxylic acid {3-[(pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide
117		6-Methyl-pyridine-2-carboxylic acid {3-[(6-aminopyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
118		2,6-Dimethyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
119		2-Methyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
120		6-Methyl-pyridine-2-carboxylic acid {3-[(thiazole-4-carbonyl)-amino]-adamantan-1-yl}-amide

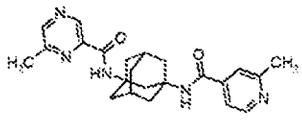
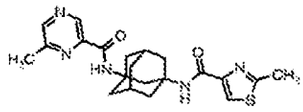
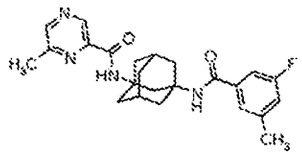
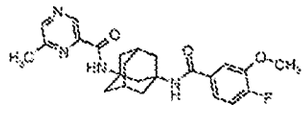
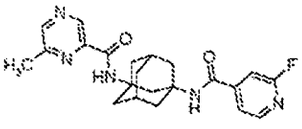
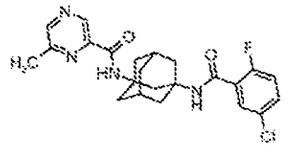
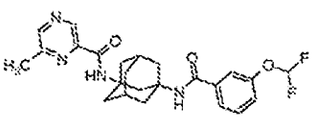
EXAMPLE	STRUCTURE	CHEMICAL NAME
121		Pyrimidine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
122		Benzoxazole-5-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
123		[1,6]Naphthyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
124		6-Methyl-pyridine-2-carboxylic acid {3-[(2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-amino]-adamantan-1-yl}-amide
125		6-Methyl-pyridine-2-carboxylic acid {3-[(4-fluoropyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
126		4,6-Dimethyl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
127		6-Methyl-pyridine-2-carboxylic acid {3-[(1,5-dimethyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide

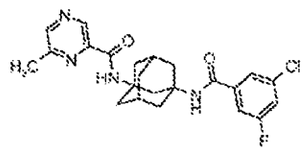
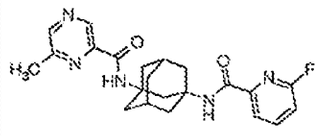
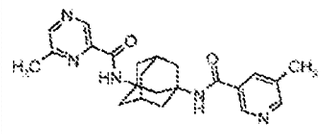
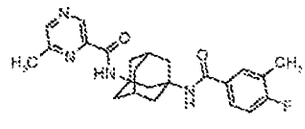
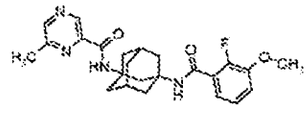
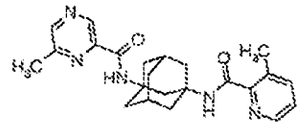
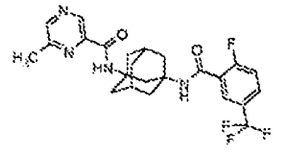
EXAMPLE	STRUCTURE	CHEMICAL NAME
128		6-Methyl-pyridine-2-carboxylic acid {3-[(4-methoxypyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
129		6-Methyl-pyridine-2-carboxylic acid {3-[(3-fluoropyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
130		6-Methyl-pyridine-2-carboxylic acid {3-[(5-methylpyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
131		4-Trifluoromethyl-pyrimidine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
132		6-Methyl-pyridine-2-carboxylic acid {3-[(4-hydroxypyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
133		Pyridine-2,6-dicarboxylic acid 2-amide 6-({3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide)
134		6-Methyl-pyridine-2-carboxylic acid {3-[(6-hydroxymethylpyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

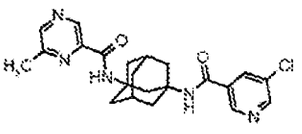
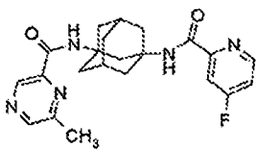
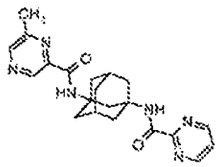
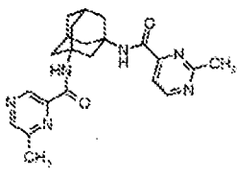
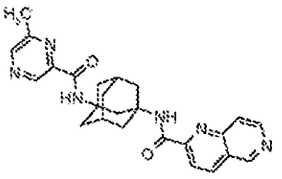
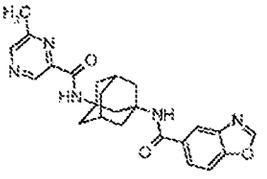
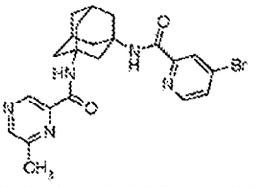
EXAMPLE	STRUCTURE	CHEMICAL NAME
135		6-Methyl-pyridine-2-carboxylic acid {3-[(6-fluoropyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
136		6-Methyl-pyridine-2-carboxylic acid {3-[(2-methyl-thiazole-4-carbonyl)-amino]-adamantan-1-yl}-amide
137		5-Fluoro-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
138		6-Methyl-pyridine-2-carboxylic acid {3-[(4-bromopyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
139		6-{3-[(6-Methyl-pyridine-2-carbonyl)-amino]-adamantan-1-ylcarbamoyl}-pyridine-2-carboxylic acid methyl ester
140		2-Trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
141		4-Methyl-pyrimidine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

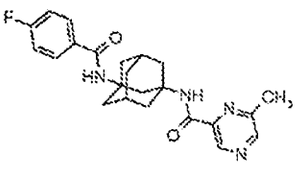
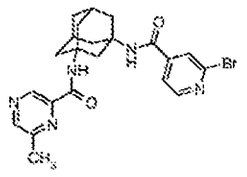
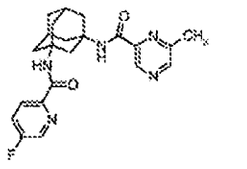
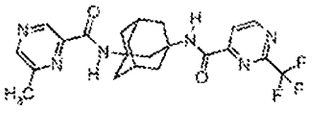
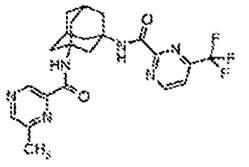
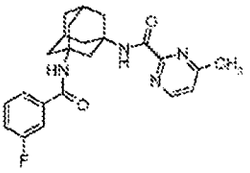
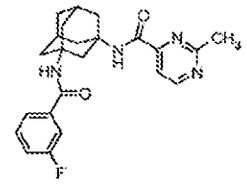
EXAMPLE	STRUCTURE	CHEMICAL NAME
142		6-Methyl-pyridine-2-carboxylic acid {3-[(6-acetylpyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
143		6-Methyl-pyridine-2-carboxylic acid {3-[(6-(1-hydroxy-ethyl)-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
144		6-Methyl-pyridine-2-carboxylic acid {3-[(6-(1-hydroxy-1-methyl-ethyl)-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
145		*N,N'*-(1,3-adamantylene)bis(6-methyl-pyrazine-2-carboxamide)
146		6-Methyl-pyrazine-2-carboxylic acid [3-(3-methoxy-benzoylamino)-adamantan-1-yl]-amide
147		6-Methyl-pyrazine-2-carboxylic acid [3-(3-ethoxy-benzoylamino)-adamantan-1-yl]-amide
148		6-Methyl-pyrazine-2-carboxylic acid [3-(2,5-difluoro-benzoylamino)-adamantan-1-yl]-amide

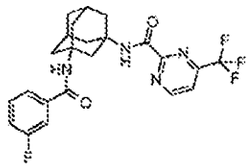
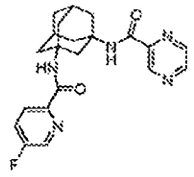
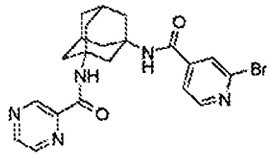
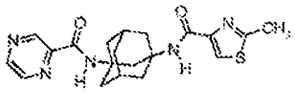
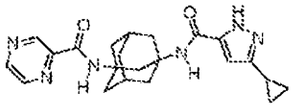
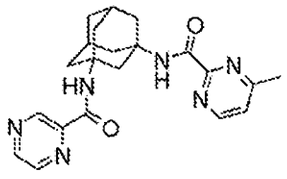
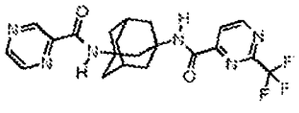
EXAMPLE	STRUCTURE	CHEMICAL NAME
149		6-Methyl-pyrazine-2-carboxylic acid [3-(3-chloro-4-fluoro-benzoylamino)-adamantan-1-yl]-amide
150		6-Methyl-pyrazine-2-carboxylic acid [3-(2-fluoro-3-trifluoromethyl-benzoylamino)-adamantan-1-yl]-amide
151		6-Methyl-pyrazine-2-carboxylic acid {3-[(6-methoxy-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
152		6-Methyl-pyrazine-2-carboxylic acid [3-(3-chloro-2-fluoro-benzoylamino)-adamantan-1-yl]-amide
153		6-Methyl-pyrazine-2-carboxylic acid {3-[(4-methoxy-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
154		6-Methyl-pyrazine-2-carboxylic acid {3-[(2-methoxy-pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide
155		6-Methyl-pyrazine-2-carboxylic acid {3-[(2-ethoxy-pyridine-4-carbonyl)-amino}-adamantan-1-yl}-amide

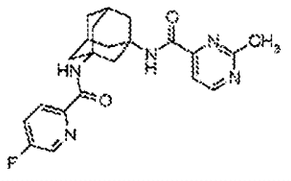
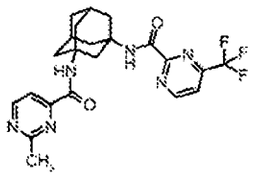
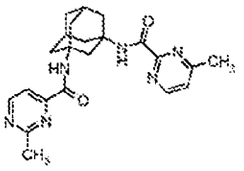
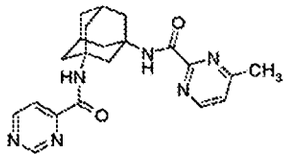
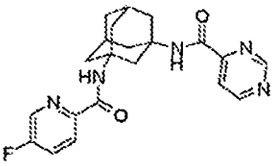
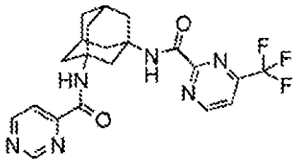
EXAMPLE	STRUCTURE	CHEMICAL NAME
156		6-Methyl-pyrazine-2-carboxylic acid {3-[(2-methyl-pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide
157		6-Methyl-pyrazine-2-carboxylic acid {3-[(2-methyl-thiazole-4-carbonyl)-amino]-adamantan-1-yl}-amide
158		6-Methyl-pyrazine-2-carboxylic acid [3-(3-fluoro-5-methyl-benzoylamino)-adamantan-1-yl]-amide
159		6-Methyl-pyrazine-2-carboxylic acid [3-(4-fluoro-3-methoxy-benzoylamino)-adamantan-1-yl]-amide
160		6-Methyl-pyrazine-2-carboxylic acid {3-[(2-fluoro-pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide
161		6-Methyl-pyrazine-2-carboxylic acid [3-(5-chloro-2-fluoro-benzoylamino)-adamantan-1-yl]-amide
162		6-Methyl-pyrazine-2-carboxylic acid [3-(3-difluoromethoxy-benzoylamino)-adamantan-1-yl]-amide

EXAMPLE	STRUCTURE	CHEMICAL NAME
163		6-Methyl-pyrazine-2-carboxylic acid [3-(3-chloro-5-fluoro-benzoylamino)-adamantan-1-yl]-amide
164		6-Methyl-pyrazine-2-carboxylic acid {3-[(6-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
165		6-Methyl-pyrazine-2-carboxylic acid {3-[(5-methyl-pyridine-3-carbonyl)-amino]-adamantan-1-yl}-amide
166		6-Methyl-pyrazine-2-carboxylic acid [3-(4-fluoro-3-methyl-benzoylamino)-adamantan-1-yl]-amide
167		6-Methyl-pyrazine-2-carboxylic acid [3-(2-fluoro-3-methoxy-benzoylamino)-adamantan-1-yl]-amide
168		6-Methyl-pyrazine-2-carboxylic acid {3-[(3-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
169		6-Methyl-pyrazine-2-carboxylic acid [3-(2-fluoro-5 trifluoromethyl-benzoylamino)-adamantan-1-yl]-amide

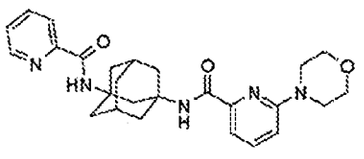
EXAMPLE	STRUCTURE	CHEMICAL NAME
170		6-Methyl-pyrazine-2-carboxylic acid {3-[(5-chloro-pyridine-3-carbonyl)-amino]-adamantan-1-yl}-amide
171		6-Methyl-pyrazine-2-carboxylic acid {3-[(4-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
172		Pyrimidine-2-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide
173		2-Methyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide
174		[1,6]Naphthyridine-2-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide
175		Benzoxazole-5-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide
176		6-Methyl-pyrazine-2-carboxylic acid {3-[(4-bromo-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

EXAMPLE	STRUCTURE	CHEMICAL NAME
177		6-Methyl-pyrazine-2-carboxylic acid [3-(4-fluoro-benzoylamino)-adamantan-1-yl]-amide
178		6-Methyl-pyrazine-2-carboxylic acid {3-[(2-bromo-pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide
179		6-Methyl-pyrazine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
180		2-Trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide
181		4-Trifluoromethyl-pyrimidine-2-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide
182		4-Methyl-pyrimidine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
183		2-Methyl-pyrimidine-4-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide

EXAMPLE	STRUCTURE	CHEMICAL NAME
184		4-Trifluoromethyl-pyrimidine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
185		Pyrazine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
186		Pyrazine-2-carboxylic acid {3-[(2-bromo-pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide
187		Pyrazine-2-carboxylic acid {3-[(2-methyl-thiazole-4-carbonyl)-amino]-adamantan-1-yl}-amide
188		Pyrazine-2-carboxylic acid {3-[(5-cyclopropyl-2H-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide
189		4-Methyl-pyrimidine-2-carboxylic acid {3-[(pyrazine-2-carbonyl)-amino] -adamantan-1-yl}-amide
190		2-Trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide

EXAMPLE	STRUCTURE	CHEMICAL NAME
191		2-Methyl-pyrimidine-4-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
192		4-Trifluoromethyl-pyrimidine-2-carboxylic acid {3-[(2-methyl-pyrimidine-4-carbonyl)-amino]-adamantan-1-yl}-amide
193		2-Methyl-pyrimidine-4-carboxylic acid {3-[(4-methyl-pyrimidine-2-carbonyl)-amino]-adamantan-1-yl}-amide
194		4-Methyl-pyrimidine-2-carboxylic acid {3-[(pyrimidine-4-carbonyl)-amino]-adamantan-1-yl}-amide
195		Pyrimidine-4-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
196		4-Trifluoromethyl-pyrimidine-2-carboxylic acid {3-[(pyrimidine-4-carbonyl)-amino]-adamantan-1-yl}-amide

Example 197: 6-Morpholin-4-yl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide



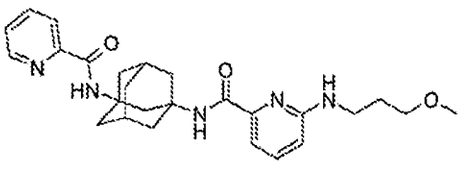
Example 197 in Table 2 (below) was synthesized from Intermediate 4 *via* the process of **Scheme 7**, *supra*, as follows:

To a microwave vial was added a stir bar, 6-chloro-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide (Intermediate 4, 20 mg, 0.05 mmol), DMA (1.0 mL), morpholine (0.05 mL) and cesium carbonate (60 mg, 0.15 mmol). The mixture was heated at 180 °C under microwave irradiation for 15 minutes.

The reaction mixture was cooled to room temperature. Solvent was removed in a high performance solvent evaporation system HT-4X (Genevac Inc., *supra*). The residue was dissolved in DCM (2 mL), washed with aq. 1 N NaOH (2 mL) and water (2 x 2 mL). After removing the solvent, the residue was purified on a RP-HPLC/MS purification system (Gradient: acetonitrile in water with a cycle time of 5 min. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium acetate. Column: Inertsil® C8, 30 x 50 mm, 5 μm particle size (GL Sciences, Tokyo, Japan)) to afford 1.3 mg of the title compound, 6-morpholin-4-yl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide. The product was quality checked (QC) by LC-MS (Gradient: acetonitrile in water, 30-90%, in 1.7 minutes with a cycle time of 2 min. Flow rate: 5.0 mL/min. Mobile phase additive: 30 mM of ammonium formate. Column: Inertsil® C8, 50 x 4.6 mm, 3 μm particle size (GL Sciences, Tokyo, Japan)): Retention time: 1.26 min; purity (UV_{254}): 95%; ESI-MS m/z: 462.1 $(M+H)^+$.

In an analogous manner to Example 197, Examples 198-203 in Table 2 (below) were synthesized from Intermediate 4 and commercially available amines on 0.05-0.3 mmol scales; Examples 204-211 in Table 2 (below) were synthesized from Intermediate 5 and commercially available amines on a 0.05 mmol scale; and Examples 212-219 in Table 2 (below) were synthesized from Intermediate 6 and commercially available amines on a 0.05 mmol scale.

Example 220: 6-(3-Methoxy-propylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

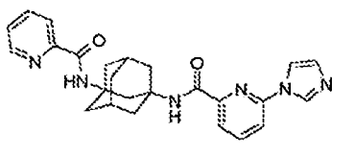


Example 220 in Table 2 (below) was synthesized from Intermediate 4 *via* the process of **Scheme** 7, *supra*, as follows:

To a microwave vial was added a stir bar, 6-chloro-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide (Intermediate 4, 20 mg, 0.05 mmol), copper (II) oxide (20 mg, 0.2 mmole), DMA (1 mL), 3-methoxy-propylamine (0.05 mL) and cesium carbonate (120 mg, 0.3 mmol). The mixture was heated at 230 °C under microwave irradiation for 30 min. Solvent was removed in Genevac. The residue was dissolved in DCM (2 mL), washed with aq. 1 N NaOH (2 mL), and water (2 x 2 mL). After removing the solvent, the crude product was purified on a RP-HPLC/MS system (Gradient: acetonitrile in water with a cycle time of 5 min. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium acetate. Column: Inertsil® C8, 30 x 50 mm, 5 µm particle size (GL Sciences, Tokyo, Japan)) to afford 3.9 mg of the title compound, 6-(3-methoxy-propylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide. The product was quality checked (QC) by LC-MS (Gradient: acetonitrile in water, 30-90%, in 1.7 minutes with a cycle time of 2 min. Flow rate: 5.0 mL/min. Mobile phase additive: 30 mM of ammonium formate. Column: Inertsil® C8, 50 x 4.6 mm, 3 µm particle size (GL Sciences, Tokyo, Japan)): Retention time: 1.29 min; purity (UV_{254}): 94%; ESI-MS m/z: 464.6 $(M+H)^+$.

In an analogous manner to Example 220, Examples 219-230 in Table 2 (below) were synthesized from Intermediate 4 and commercially available amines on 0.05-0.3 mmol scales; Examples 231-240 in Table 2 (below) were synthesized from Intermediate 5 and commercially available amines on a 0.05 mmol scale; and Examples 241-252 in Table 2 (below) were synthesized from Intermediate 6 and commercially available amines on a 0.05 mmol scale.

Example 253: 6-Imidazol-1-yl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

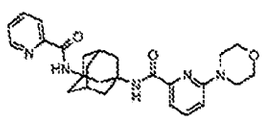
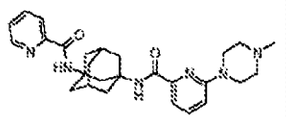
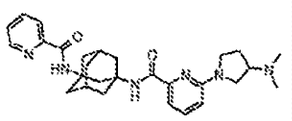


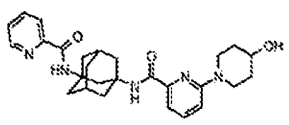
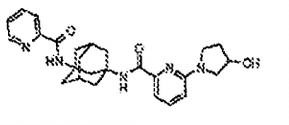
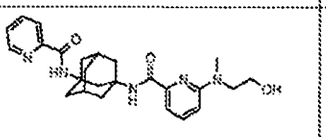
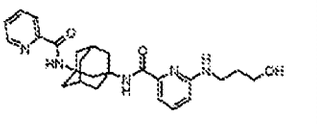
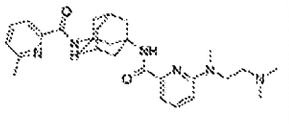
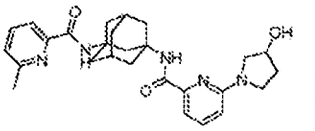
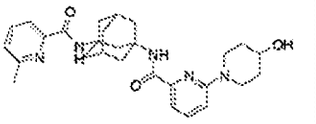
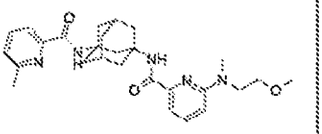
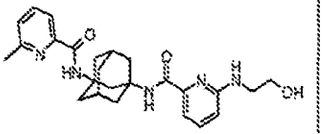
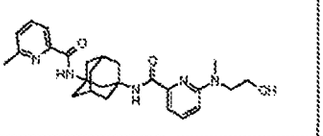
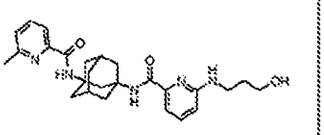
Example 253 in Table 2 (below) was synthesized from Intermediate 4 *via* the process of **Scheme** 7, *supra*, as follows:

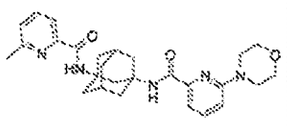
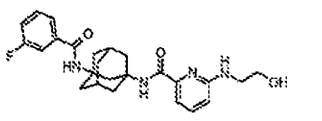
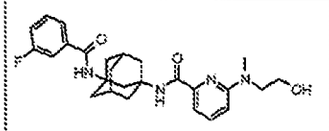
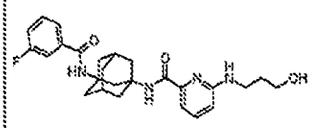
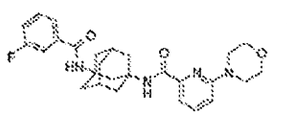
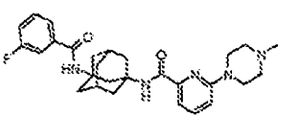
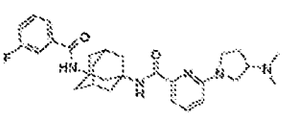
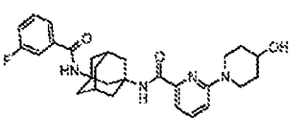
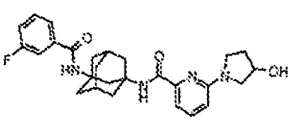
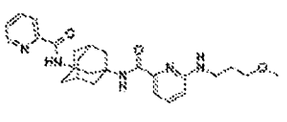
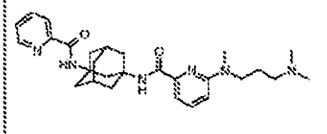
To a microwave vial was added a stir bar, 6-chloro-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide (Intermediate 4, 20 mg, 0.05 mmol), copper (II) acetoacetonate (20 mg), DMA (1 mL), imidazole (50 mg, 0.73 mmol) and cesium carbonate (60 mg, 0.15 mmol). The mixture was heated at 180 °C under microwave irradiation for 15 minutes. Solvent was removed in a high performance solvent evaporation system HT-4X (Genevac, Inc., *supra*). The residue was dissolved in DCM (2 mL), washed with aq. 1 N NaOH (2 mL), and water (2 x 2 mL). After removing the solvent, the residue was purified on a RP-HPLC/MS system (Gradient: acetonitrile in water with a cycle time of 5 min. Flow rate: 100 mL/min. Mobile phase additive: 25 mM of ammonium acetate. Column: Inertsil® C8, 30 x 50 mm, 5 μm particle size (GL Sciences, Tokyo, Japan) to afford 4.5 mg of the title compound, 6-imidazol-1-yl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide. ESI-MS m/z: 443.5 $(M+H)^+$.

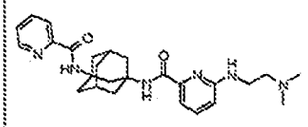
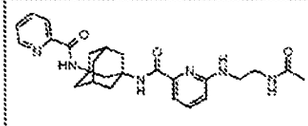
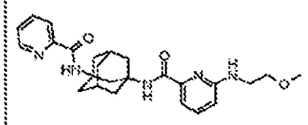
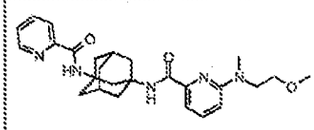
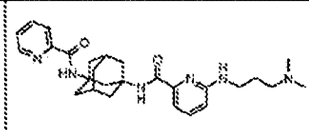
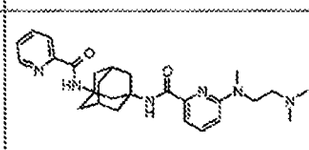
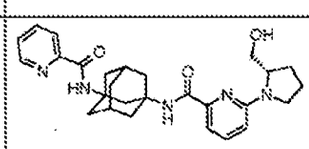
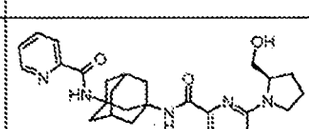
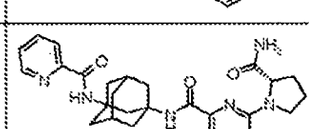
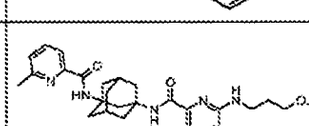
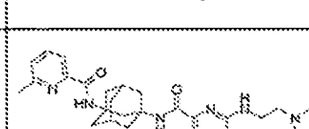
In an analogous manner to Example 253, Examples 254-255 in Table 2 (below) were synthesized on a 0.05 mmol reaction scale from Intermediates 5 and 6, respectively.

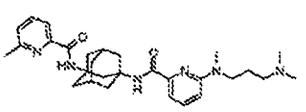
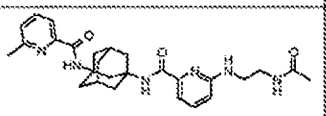
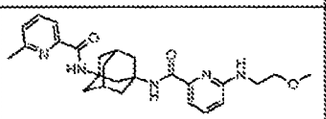
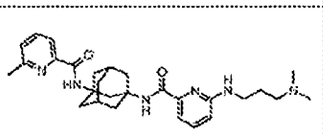
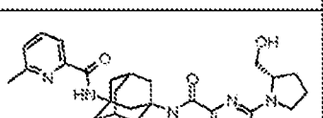
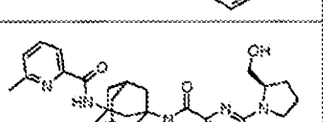
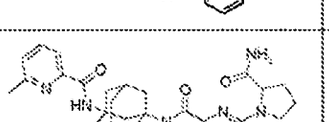
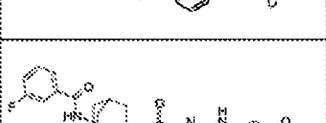
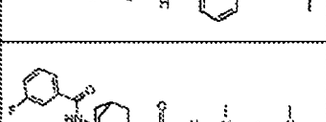
Table 2

EXAMPLE	STRUCTURE	CHEMICAL NAME
197		6-Morpholin-4-yl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
198		6-(4-Methyl-piperazin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
199		6-(3-Dimethylamino-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

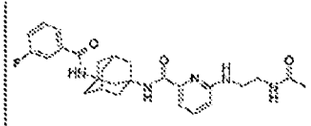
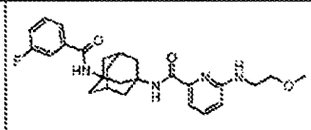
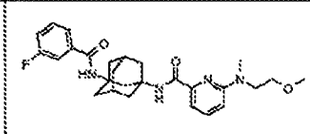
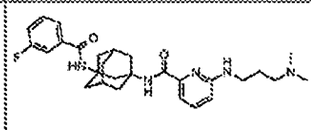
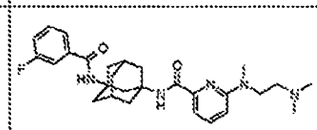
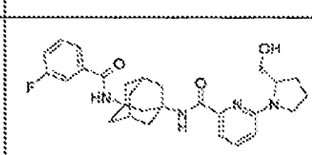
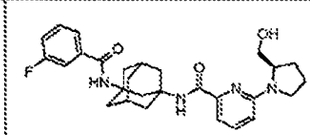
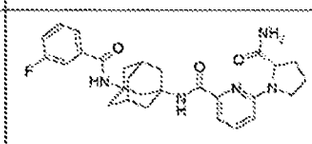
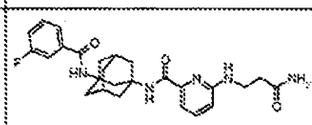
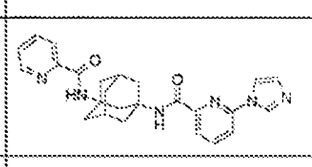
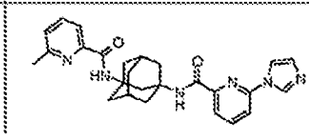
200		4-Hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
201		6-(3-Hydroxy-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
202		6-[(2-Hydroxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
203		6-(3-Hydroxy-propylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
204		6-[(2-Dimethylamino-ethyl)-methyl-amino]-pyridine-2-carboxylic acid{3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
205		6-(3-Hydroxy-pyrrolidin-1-yl)-pyridine-2-carboxylic acid{3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
206		4-Hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-carboxylic acid{3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
207		6-[(2-Methoxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid{3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
208		6-(2-Hydroxy-ethylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
209		6-[(2-Hydroxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
210		6-(3-Hydroxy-propylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

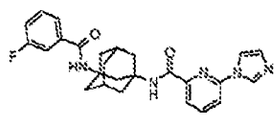
211		6-Morpholin-4-yl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
212		6-(2-Hydroxy-ethylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
213		6-[(2-Hydroxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
214		6-(3-Hydroxy-propylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
215		6-Morpholin-4-yl-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
216		6-(4-Methyl-piperazin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
217		6-(3-Dimethylamino-pyrrolidin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
218		4-Hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
219		6-(3-Hydroxy-pyrrolidin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
220		6-(3-Methoxy-propylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
221		6-[(3-Dimethylamino-propyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

222		6-(2-Dimethylamino-ethylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
223		6-(2-Acetylamino-ethylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
224		6-(2-Methoxy-ethylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
225		6-[(2-Methoxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
226		6-(3-Dimethylamino-propylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
227		6-[(2-Dimethylamino-ethyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
228		6-((S)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
229		6-((R)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
230		6-((S)-2-Carbamoyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
231		6-(3-Methoxy-propylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
232		6-(2-Dimethylamino-ethylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

233		6-[(3-Dimethylamino-propyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
234		6-(2-Acetylamino-ethylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
235		6-(2-Methoxy-ethylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
236		6-(3-Dimethylamino-propylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
237		6-((S)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
238		6-((R)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
239		6-((S)-2-Carbamoyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
240		6-(2-Carbamoyl-ethylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
241		6-(3-Methoxy-propylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
242		6-(2-Dimethylamino-ethylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
243		6-[(3-Dimethylamino-propyl)-methyl-amino]-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide

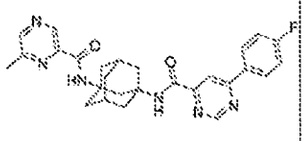
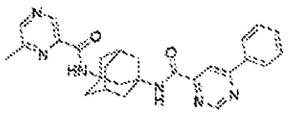
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244		6-(2-Acetylamino-ethylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
245		6-(2-Methoxy-ethylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
246		6-[(2-Methoxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
247		6-(3-Dimethylamino-propylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
248		6-[(2-Dimethylamino-ethyl)-methyl-amino]-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
249		6-((S)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
250		6-((R)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
251		6-((S)-2-Carbamoyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
252		6-(2-Carbamoyl-ethylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
253		6-Imidazol-1-yl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
254		6-Imidazol-1-yl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

255		6-Imidazol-1-yl-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide

Examples 256 and 257 in Table 3 (below) were made *via* **Scheme 3** from Intermediate 8 and commercially available 6-(4-fluoro-phenyl)-pyrimidine-4-carboxylic acid and 6-phenyl-pyrimidine-4-carboxylic acid, respectively, on a 0.05 mmol scale.

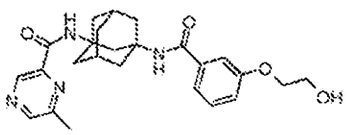
Table 3

Example	STRUCTURE	CHEMICAL NAME
256		6-(4-Fluoro-phenyl)-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide
257		6-Phenyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide

4. Hypothetical Compounds of the Invention

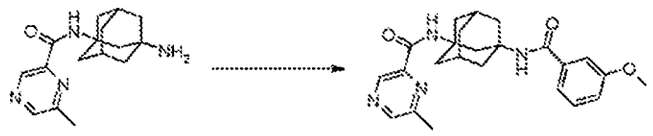
In a similar manner to Example 58, Examples 258-279 in Table 4 (below) can be made from aryl or heteroaryl carboxylic acids *via* the process of **Schemes 3** and **5**. Non-commercially available carboxylic acids, such as 4-methyl-pyrimidine-2-carboxylic acid, 2-methyl-pyrimidine-4-carboxylic acid, 4-trifluoromethyl-pyrimidine-2-carboxylic acid, 2-trifluoromethyl-pyrimidine-4-carboxylic acid, 6-trifluromethyl-pyrazine-2-carboxylic acid, and 5-trifluoromethyl-pyrazine-2-carboxylic acid, can be readily made from commercially available heteroaryl-chlorides, such as 2-chloro-4-methyl-pyrimidine, 4-chloro-2-methyl-pyrimidine, 2-chloro-4-trifluoromethyl-pyrimidine, 4-chloro-2-trifluoromethyl-pyrimidine, 2-chloro-6-trifluromethyl-pyrazine, and 2-chloro-5-trifluoromethyl-pyrazine, *via* the process of **Scheme 11**, in a similar manner to the synthesis of Intermediate 11, 4-trifluoromethyl-pyrimidine-2-carboxylic acid, and of Intermediate 12, 4-methyl-pyrimidine-2-carboxylic acid.

Example 280: 6-Methyl-pyrazine-2-carboxylic acid {3-[3-(2-hydroxy-ethoxy)-benzoylamino]-adamantan-1-yl}-amide



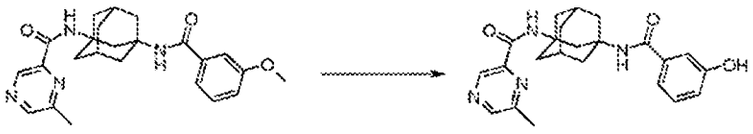
Example 280 can be made *via* the process of **Scheme 9**, *supra*, as follows:

Step 1: 6-Methyl-pyrazine-2-carboxylic acid [3-(3-methoxy-benzoylamino)-adamantan-1-yl]-amide



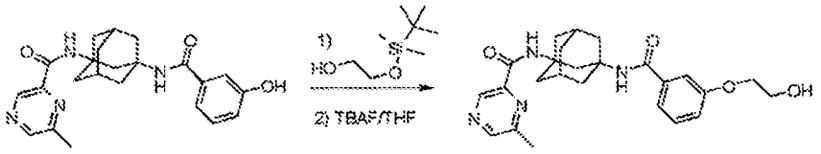
6-Methyl-pyrazine-2-carboxylic acid [3-(3-methoxy-benzoylamino)-adamantan-1-yl]-amide can be made from customary amidation of commercially available 3-methoxybenzoic acid and Intermediate 8, 6-methyl-pyrazine-2-carboxylic acid (3-amino-adamantan-1-yl)-amide.

Step 2: 6-Methyl-pyrazine-2-carboxylic acid [3-(3-hydroxy-benzoylamino)-adamantan-1-yl]-amide



6-Methyl-pyrazine-2-carboxylic acid [3-(3-hydroxy-benzoylamino)-adamantan-1-yl]-amide can be readily made by treatment of 6-methyl-pyrazine-2-carboxylic acid [3-(3-methoxy-benzoylamino)-adamantan-1-yl]-amide with BBr_3 in DCM.

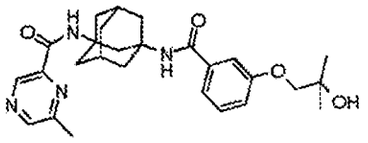
Step 3: 6-Methyl-pyrazine-2-carboxylic acid {3-[3-(2-hydroxy-ethoxy)-benzoylamino]-adamantan-1-yl}-amide



Customary Mitsunobu reaction of 6-Methyl-pyrazine-2-carboxylic acid [3-(3-hydroxy-benzoylamino)-adamantan-1-yl]-amide and 2-(*t*-butyldimethylsiloxy)-ethanol, followed by deprotection of the *t*-butyldimethylsiloxy group by treatment with tetrabutylammonium fluoride (TBAF) could afford the title compound, 6-methyl-pyrazine-2-carboxylic acid {3-[3-(2-hydroxy-ethoxy)-benzoylamino]-adamantan-1-yl}-amide.

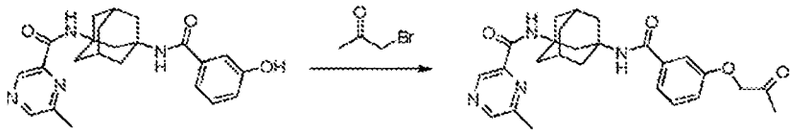
Example 281 in Table 4 (below) can be made in a similar manner to Example 280.

Example 282: 6-Methyl-pyrazine-2-carboxylic acid {3-[3-(2-hydroxy-2-methyl-propoxy)-benzoylamino]-adamantan-1-yl}-amide



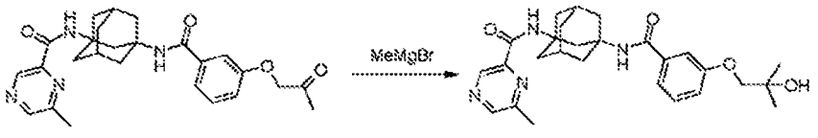
Example 282 can be made from 6-methyl-pyrazine-2-carboxylic acid [3-(3-hydroxy-benzoylamino)-adamantan-1-yl]-amide (step 2, Example 280):

Step 1: 6-Methyl-pyrazine-2-carboxylic acid {3-[3-(2-oxo-propoxy)-benzoylamino]-adamantan-1-yl}-amide



Alkylation of 6-methyl-pyrazine-2-carboxylic acid [3-(3-hydroxy-benzoylamino)-adamantan-1-yl]-amide (step 2, Example 280) with 1-bromo-propan-2-one in DMF under basic conditions, such as Cs_2CO_3 at 60 °C, could afford the title compound, 6-methyl-pyrazine-2-carboxylic acid {3-[3-(2-oxo-propoxy)-benzoyl-amino]-adamantan-1-yl}-amide.

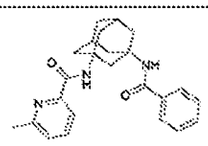
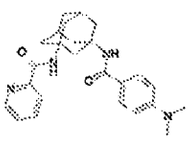
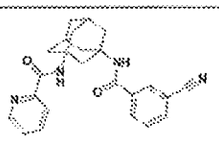
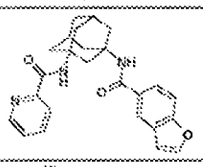
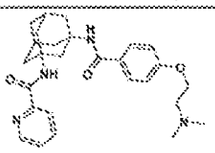
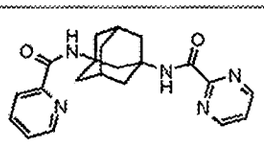
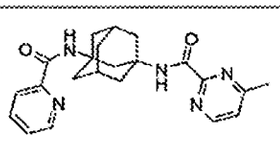
Step 2: 6-Methyl-pyrazine-2-carboxylic acid {3-[3-(2-hydroxy-2-methylpropoxy)-benzoylamino]-adamantan-1-yl}-amide

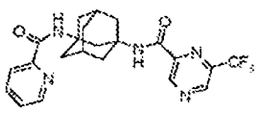
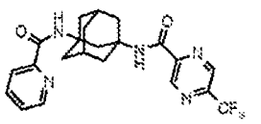
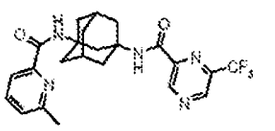
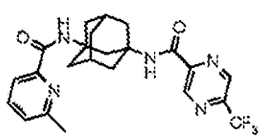
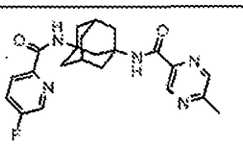
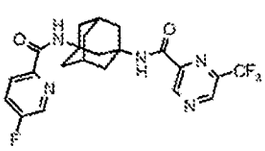
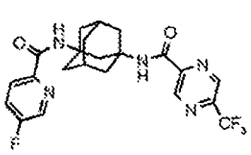
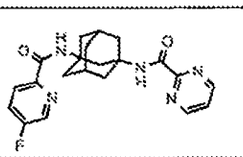
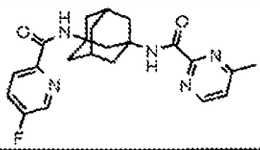


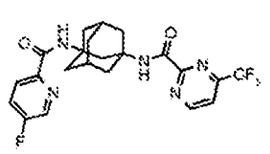
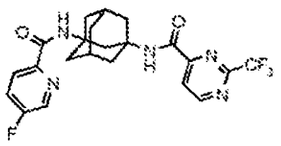
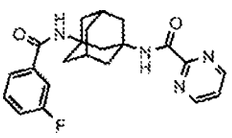
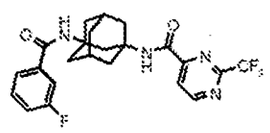
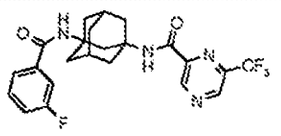
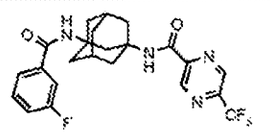
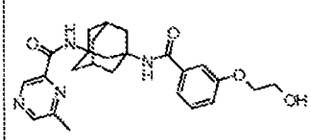
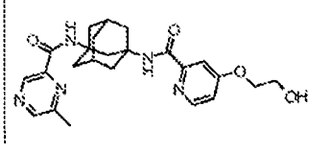
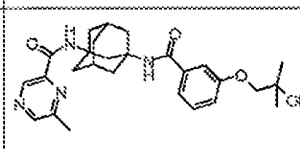
Reaction of 6-methyl-pyrazine-2-carboxylic acid {3-[3-(2-oxo-propoxy)-benzoyl-amino]-adamantan-1-yl}-amide with MeMgBr in THF or ether at 0 °C could yield the title compound, 6-methyl-pyrazine-2-carboxylic acid {3-[3-(2-hydroxy-2-methylpropoxy)-benzoylamino]-adamantan-1-yl}-amide.

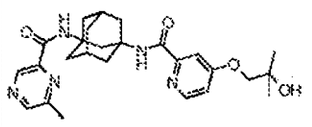
Example 283 in Table 4 (below) can be made in a similar manner to Example 282.

Table 4: Hypothetical Compounds

EXAMPLE	STRUCTURE	CHEMICAL NAME
258		6-Methyl-pyridine-2-carboxylic acid (3-benzoylamino-adamantan-1-yl)-amide
259		Pyridine-2-carboxylic acid [3-(4-dimethylamino-benzoylamino)-adamantan-1-yl]-amide
260		Pyridine-2-carboxylic acid [3-(3-cyano-benzoylamino)-adamantan-1-yl]-amide
261		Pyridine-2-carboxylic acid {3-[(benzofuran-5-carbonyl)-amino]-adamantan-1-yl}-amide
262		Pyridine-2-carboxylic acid {3-[4-(2-dimethylamino-ethoxy)-benzoylamino]-adamantan-1-yl}-amide
263		Pyrimidine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
264		4-Methyl-pyrimidine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

EXAMPLE	STRUCTURE	CHEMICAL NAME
265		6-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
266		5-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
267		6-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
268		5-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
269		5-Methyl-pyrazine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
270		6-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
271		5-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
272		Pyrimidine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
273		4-Methyl-pyrimidine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide

EXAMPLE	STRUCTURE	CHEMICAL NAME
274		4-Trifluoromethyl-pyrimidine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
275		2-Trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide
276		Pyrimidine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
277		2-Trifluoromethyl-pyrimidine-4-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
278		6-Trifluoromethyl-pyrazine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
279		5-Trifluoromethyl-pyrazine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide
280		6-Methyl-pyrazine-2-carboxylic acid {3-[3-(2-hydroxy-ethoxy)-benzoylamino]-adamantan-1-yl}-amide
281		6-Methyl-pyrazine-2-carboxylic acid (3-{[4-(2-hydroxy-ethoxy)-pyridine-2-carbonyl]-amino}-adamantan-1-yl)-amide
282		6-Methyl-pyrazine-2-carboxylic acid {3-[3-(2-hydroxy-2-methyl-propoxy)-benzoylamino]-adamantan-1-yl}-amide

EXAMPLE	STRUCTURE	CHEMICAL NAME
283		6-Methyl-pyrazine-2-carboxylic acid (3-{[4-(2-hydroxy-2-methyl-propoxy)-pyridine-2-carbonyl]-amino}-adamantan-1-yl)-amide

5. Pharmacological Evaluation of Compounds of the Invention

Compounds of the present invention have been tested *in vitro* and *in vivo*, and can be tested *in vitro* and *in vivo*, in the assays as described below.

***In vitro* Assays**

Radioligand binding assays

Binding assays were performed as described in [J. A. O'Brien *et al. Mol Pharmacol.*, **2003**, *64*, 731-740] with slight modifications. Briefly, after thawing, the membrane homogenates were resuspended in 50 mM Tris-HCl, 0.9% NaCl binding buffer at pH 7.4 to a final assay concentration of 40 µg protein/well for [^{3}H] methoxy-5-(2-pyridinylethynyl)pyridine ([^{3}H] MPEP) (American Radiolabeled Chemicals, Inc., St. Louis, MO) filtration binding. Incubations included 5 nM [^{3}H] MPEP, membranes and either buffer or varying concentrations of compound. Samples were incubated for 60 min at room temperature with shaking. Non-specific binding was defined with 10 µM MPEP. After incubation, samples were filtered over a GF/C filter (presoaked in 0.25% polyethyleneimine (PEI)) and then washed 4 times using a Tomtec® Harvester 96® Mach III cell harvester (Tomtec, Hamden, CT) with 0.5 mL ice-cold 50 mM Tris-HCl (pH 7.4).

IC_{50} values were derived from the inhibition curve and K_i values were calculated according to the Cheng and Prusoff equation of $K_i = IC_{50}/(1+[L]/K_d)$ described in [Y. Cheng and W.H. Prusoff *Biochem. Pharmacol.* **1973**, *22*, 3099-3108] where [L] is the concentration of radioligand and K_d is its dissociation constant at the receptor, derived from the saturation isotherm. The K_i value for Examples 1 and 2 were 6.7 and 40 nM, respectively. Examples 19, 42, 44, 58, 65, 67, 69, 72, 74, 79, 93, 94, 95, 96, 105, 107, 119 and 120, have Ki values ranging from 6 to 700 nM.

Calcium mobilization assay to test for negative or positive allosteric activity

The cDNA for rat metabotropic glutamate receptor 5 (rmGluR5) was a generous gift from S. Nakanishi (Kyoto University, Kyoto, Japan). The rmGluR5 was stably expressed in a HEK 293 cell line and grown in Dulbecco's Modified Eagle Medium (DMEM) (Invitrogen, Carlsbad, CA) with supplements (10% bovine calf serum, 4 mM glutamine, 100 units/mL penicillin, 100 μg/mL streptomycin and 0.75mM G1418) at 37 °C, 5% CO_2. Twenty-four hours prior to assay, cells were seeded into 384-well black wall microtiter plates coated with poly-D-lysine. Just prior to assay, media was aspirated and cells dye-loaded (25 μL/well) with 3 μM Fluo-4/ 0.01% pluronic acid in assay buffer (Hank's Balanced Saline Solution (HBSS)): 150 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, plus 20 mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES), pH 7.4, 0.1% bovine serum albumin (BSA) and 2.5 mM probenicid) for 1 hour in 5% CO_2 at 37 °C. After excess dye was discarded, cells were washed in assay buffer and layered with a final volume equal to 30 μL/well. Basal fluorescence is monitored in a fluorometric imaging plate reader (FLIPR) (Molecular Devices, Sunnyvale, CA) with an excitation wavelength of 488 nm and an emission range of 500 to 560 nm. Laser excitation energy was adjusted so that basal fluorescence readings were approximately 10,000 relative fluorescent units. Cells were stimulated with an EC_{20} or an EC_{80} concentration of glutamate in the presence of a compound to be tested, both diluted in assay buffer, and relative fluorescent units were measured at defined intervals (exposure = 0.6 sec) over a 3 min period at room temperature. Basal readings derived from negative controls were subtracted from all samples. Maximum change in fluorescence was calculated for each well. Concentration-response curves derived from the maximum change in fluorescence were analyzed by nonlinear regression (Hill equation). A negative modulator can be identified from these concentration-response curves if a compound produces a concentration dependent inhibition of the EC_{80} glutamate response. Exemplified compounds Examples 1-10 were tested in the above assay for negative allosteric modulation: FLIPR maximum inhibition ranged 90% to 99% while FLIPR IC_{50} ranged from 0.9 nM to 1300 nM. Examples 11-163 also were tested in the above assay. For Examples 11-104, FLIPR maximum inhibition ranged from 63% to 99%, while FLIPR IC_{50} ranged from 0.7 nM to 600 nM; and for Examples 105-163, FLIPR maximum inhibition ranged from 70% to 99%, while FLIPR IC_{50} ranged from 0.7 nM to 1800 nM. Examples 164-178, 181-182, 184-187, 189-

194, 196, 197-255 were tested in the above assay for negative allosteric modulation: FLIPR maximum inhibition ranged 63% to 99% while FLIPR IC_{50} ranged from 0.4 nM to 1300 nM.

A positive modulator can be identified from these concentration-response curves if a compound produces a concentration dependent increase in the EC_{20} glutamate response. Examples 256-257 exhibited positive modulation, having FLIPR EC_{50} of 300 nM and 830 nM, and maximum modulation of 170 % and 120%, respectively.

***In vivo* Assays**

Examples 1, 2 and 58 were evaluated *in vivo* for anxiolytic effects using (1) mouse marble burying (mMB) methods similar to those described in [K. Njung'e, K. and S.L. Handley, *Pharmacology, Biochemistry and Behavior*, **1991**, *38*, 63– 67] and (2) a modified Geller-Seifter conflict test described in [N.A. Moore *et al. Behavioural Pharmacology*. **1994**, *5*, 196-202].

More specifically for the mMB testing, adult, male CD1 mice (Charles River Laboratories (Kingston, NY)), weighing 25 to 30 g, were used. All animals were group-housed in a standard colony room with a 12:12 light/dark cycle (lights on at 6:00 am) for at least one week prior to testing. Food and water were provided *ad libitum*. Animals were weighed, tail marked, and randomly assigned to treatment groups before testing.

For each test, sixty minutes after the injection of vehicle or test compound, or 30 min after injection of the positive control, buspirone, mice were individually placed into test cages containing 1.5 in of Aspen bedding (PWI brand) and two rows of 10 marbles (20 marbles per test cage total). Filter tops were used to cover each test cage. Thirty minutes later, mice were removed from test cages and returned to their home cages. The number of fully visible marbles (less than 2/3 covered with bedding) were counted and subtracted from 20 to arrive at the number of marbles buried. Twelve mice were tested per group.

Testing included multiple tests with each test performed to evaluate buspirone hydrochloride (BUS; Sigma Aldrich) (positive control) and/or a compound of the present invention. Each compound was dissolved immediately prior to testing in 20% beta-cyclodextrin (compound of the present invention) or distilled water (BUS) and administered at one or more doses (such as 3, 10, and/or 30 mg/kg) via subcutaneous (SC) or intraperitoneal (IP) injection at the indicated pretreatment times (i.e., 30, 60, or 120 min pretreatment). Doses were measured in mg drug (salt

form) per kg body weight. Data was analyzed using one-way ANOVA with post-hoc Dunnett's test.

More specifically for the Geller-Seifter Conflict testing, rodent operant chambers (ENV-007CT, Med Associates Inc. (Georgia, VT)) and sound-attenuating chambers (ENV-018MD, Med Associates Inc.) were used. Each chamber was equipped with a house light, cue lights, grid floor to deliver foot shocks via a programmable shocker, (ENV-414, Med Associates, Inc.) and food hopper. Two levers were located on either side of the food hopper. Rats were trained to only respond on the left lever. Food reinforcement was used (Dustless Precision Pellets, 45 mg, BioServ, (Frenchtown, NJ)). MED-PCIV software (Med Associates) was used to run experimental sessions and collect data.

Prior to beginning the Conflict procedure, animals were initially trained to lever press on fixed ratio schedules (FR 1, 2, 5, and 10). Once animals obtained 25 rewards on a FR 10 schedule for 2 consecutive days, animals began training on a three component Conflict schedule. The three components were as follows: (1) an unpunished, variable interval 30 s (VI30) schedule of food reinforcement to reinforce lever pressing on a variable time schedule that averaged 30 s; this period had a duration of 9 minutes and was signaled by illumination of the rear house light only; (2) immediately following was a 3 minute time out period (TO) that was signaled by total darkness; responding was recorded but was neither rewarded nor punished; (3) a punished, fixed ratio 10 (FR10) schedule of reinforcement that simultaneously presented food and foot shock (0.3 mA, 500 ms) on every tenth lever press during a 3 minute period; this component was signaled by illumination of the rear house light and cue lights above each lever. These three components were repeated twice in the same order during the daily 30 minute session.

Testing began when stable rates of responding were observed for 5 days (no significant trends up or down). Animals were tested using a Latin-squares design, on Wednesdays and Fridays. Animals served as their own controls and received all treatments. To maintain baseline performance, animals were also trained the remaining three weekdays.

Testing was performed using 12 adult, male Sprague-Dawley rats, weighing 426-567 g (Charles River Laboratories (Kingston, NY)). Animals were pair-housed in colony rooms maintained at controlled temperature (68-72°F) and a 12-h light/dark cycle (lights on 06:00). Animals were

given free access to water, while food was limited to 15 g of Bacon Lover's Treats (BioServ) after training/testing Monday through Thursday. Friday through Sunday, animals had free access to Lab Diet 5012 Rat Diet (PMI Nutrition International, LLC, Brentwood, MO) until cages were changed and food removed on Sunday.

Testing included multiple tests where each test was performed to evaluate either a reference compound or a compound of the present invention. Reference anxiolytics included chlordiazepoxide, diazepam and buspirone, which were dissolved in saline or water and administered via SC, IP, and/or PO. Test compounds were dissolved in 20% beta-cyclodextrin, and the pH was adjusted to 7 with $NaHCO_3$. For each test, the compound to be evaluated was tested at one or more doses (such as 10, 20, 30 and/or 50 mg/kg) via p.o. administration 60 minutes before the test using an injection volume of 2 mL/kg in comparison with a vehicle control group. Doses were measured in mg drug (salt form) per kg body weight. Data was analyzed using Repeated Measures ANOVA with post-hoc Dunnett's test.

Compounds of the invention have significant anxiolytic activity. For example, Example 1 showed significant activity in both assays (mMB EDmin 3 mg/kg; Geller-Seifter EDmin 10 mg/kg). Example 2 also showed significant activity in both assays (mMB EDmin 30 mg/kg, Geller-Seifter EDmin 20 mg/kg). Example 58 showed significant activity in both assays (mMB EDmin 10 mg/kg, SC; Geller-Seifter EDmin 10 mg/kg, PO); and as shown in the following tables.

Table 5: Statistically Significant Active Dose(s) of Representative Compounds of the Present Invention in Mouse Marble Burying Assay

Example	Active Dose *mg/kg (SC injection)*	Statistical significance*
1	3, 10, 30	F(4,55)=19.6, p<0.01
2	30	F(4,55)=7.2, p<0.01
41	10, 30	F(4,55)=17, p<0.01
58	10, 30	F(4,55)=19, p<0.01
63	30	F(4,55)=5.7, p<0.05
93	30	F(4,54)=6.6, p<0.01
94	3, 10, 30	F(4,55)=46, p<0.01
95	10, 30	F(4,55)=18, p<0.01
96	10, 30	F(4,55)=30, p<0.01
105	30	F(4,55)=11, p<0.01

107	10	t(22)=17, p<0.01
119	10	t(22)=25, p<0.01
145	30	F(4,54)=10, p<0.01
179	10	t(22)=6, p<0.01
183	10	t(22)=4, p<0.01
185	30	F(4,55)=15, p<0.01
191	10, 30	F(4,55)=11, p<0.01

* Statistical significance was determined using one-way ANOVA with post-hoc Dunnett's test or paired students t-test

Table 6: Statistically Significant Active Dose(s) of Representative Compounds of the Present Invention in Geller-Seifter Assay

Example	Active dose(s) *mg/kg (oral injection)*	Statistical significance*
1	50	t(7)=2.99, p<0.05
2	20	t(7)=2.4, p<0.05
41	30	F(3,7)=11.6, p<0.01
58	10, 20	F(3,11)=8, p<0.05
94	20	F(3,8)=2.7, p<0.05
95	10,30	F(3,9)=5.7, p<0.05

* Statistical significance was determined using one-way ANOVA with post-hoc Dunnett's test or paired students t-test

Compounds of the present invention were evaluated *in vivo* for antidepressive effects. An assessment of depression-like actions was measured using a forced swim test similar to that described in [J.F. Cryan, *et al.* Neuroscience and Biobehavioral Reviews **2005**, *29*, 547--569.] Animals used for testing were adult, male NIH Swiss Webster mice (Harlan Laboratories (Frederick, MD)), weighing 22 to 24 g, which were acclimatized and housed as previously described with the mice used in the mMB tests.

For the mouse Forced Swim Test (mFST), mice were individually placed into clear Pyrex® cylinders (11 cm diameter, 16.5 cm height) containing 11 cm deep tap water (23-25 °C) sixty min after the injection of vehicle or test compound, or 30 min after injection of the positive control, imipramine hydrochloride (IMI; Sigma Aldrich, St. Louis, MO). Imipramine was prepared with isotonic saline and test compounds were prepared as described previously with mMB tests. Doses used were as described previously with mMB tests. The percentage of time spent floating, swimming, and struggling ("climbing") was measured during a 6 min session. Swim sessions were video monitored and analyzed in real-time using the Biobserve Automated

FST apparatus and software (Biobserve GmbH, Bonn, Germany). Group size ranged from twelve to thirteen mice. Doses were measured in mg drug (salt form) per kg body weight. Data was analyzed using one-way ANOVA with post-hoc Dunnett's test.

Compounds of the present invention had significant antidepressive effects in the mFST at 3 mg/kg, 10 mg/kg, 30 mg/kg, or a combination thereof. (Statistical significance ($p<0.05$) was determined using one-way ANOVA with post-hoc Dunnett's test.)

An *in vivo* effect of a compound of the present invention may also be evaluated by using the following, non-limiting, examples of *in vivo* behavioral animal models. The following behavioral models are not intended as the only models useful for determining the efficacy of a compound of the present invention to treat the corresponding disorder or disease.

Compounds of the invention also can be evaluated *in vivo* for anxiolytic effects using a light-enhanced startle (LES) reflex method as that described in [Walker and Davis. *Biol. Psychiatry*, **1997**, *42*, 461-471]. The startle response is a coordinated contraction of skeletal muscle groups in response to a high intensity unexpected stimulus. Most sensory modalities can be used, but sound is most frequently employed because it is easily controlled. Thus, when a short burst of sufficient intensity occurs (e.g., 115 dB) an involuntary startle response occurs. High light levels increase the startle response in nocturnal species such as the rat and this effect does not require any pre-conditioning. Anxiolytics – an agent that relieves anxiety - decrease light-enhanced startle.

For the LES test, an apparatus consisting of a commercially available soundproofed startle chamber (e.g., SR-LAB™ Startle Response System, San Diego Instruments, San Diego, CA) can be used. All experimental events and data recording can be controlled by computer program (e.g., SR-LAB™ control unit). Rats are placed within the startle chamber in a small Perspex® cylinder, slightly larger than the rat, which is attached to a base plate containing a strain gauge. Vertical movement of the rat such as occurs during a startle response results in deformation of the base plate, which generates a current in the strain gauge that is proportional to the size of the movement, i.e., the size of the startle response. A loudspeaker is placed directly above the rat to provide background sound and stimuli. A light source (2500 - 3500 Lux) is located in each startle chamber.

The LES test consists of two 20-minute sessions (first with lights off and then with lights on) of which the first 5 minutes are for habituation, during which background noise of 70 dB intensity is provided within the chamber. At the end of each habituation period, 10 stimulations of 110 dB are presented to habituate the animals. Thereafter, thrhee trial types are presented in pseudo random order, 8 times each. Trials are separated by 15-25 seconds. The trial types are 100, 105 or 110 dB startle during which a 40 ms burst of white noise at 100, 105 or 110 dB is presented, resulting in a startle response. A period of 5 minutes without light or noise separates the two sessions. An appropriate rat species that can be use includes male Rj: Wister (Hans) rats (180-280 g weight at start of the testing with a maximum weight range per test of 50 g) (Elevage Janvier, Le Genest-Saint-Isle, France). The rats should be allowed to acclimatize to laboratory conditions at least 5 days before testing with free access to food and water. Acclimatization conditions should be comparable to those described in the scientific literature and/or known to those skilled in the art.

The output from the startle platform is recorded for 40 ms starting from the onset of the startle stimulus. Three variables are recorded for each trial: the average response over the whole recording period, the peak response and the time to peak response. The startle intensity is calculated for each rat by averaging the 8 trials of each type under dark or light conditions and calculating the percentage increase in startle amplitude (average and peak values) caused by light (LES). The time to peak response is a measure of reaction time.

The test is performed un-blinded using, e.g., 12 rats per group. Testing includes multiple tests where each test is performed to evaluate a reference compound (e.g., chlordiazepoxide), comparative compound (e.g., pregabalin) and/or a compound of the present invention. For example, in test 1, a known anxiolytic, such as chlordiazepoxide and pregabalin, is used, followed by test 2 using the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP), and then test 3 is performed using a compound of the present invention. Alternatively, each test can be performed concurrently, or in some combination of sequentially and concurrently. For each test, the compound to be evaluated is tested at one or more doses (such as 1, 3, 10, 30 and/or 100 mg/kg) via p.o. administration 60 minutes before the test in comparison with a vehicle control group. Prior to testing, test compounds can be tested for solubility by cold stirring of the highest intended dose for 10 min in distilled water. If soluble, distilled water can

serve as the vehicle. If insoluble, the test compounds can be suspended in 0.2% hydroxypropylmethylcellulose (HPMC) in distilled water. Doses can be prepared as weight to volume (W/V) stock solutions and then serially diluted (V/V) for compounds in solution or separately weighted (W/V) for compounds in suspension.

For each test, data is analyzed by comparing treated groups with the vehicle control using unpaired Student's t tests. LES in each group will be analyzed by comparing within each treated group the intensity of startle reaction under dark and light conditions using paired Student's t tests.

The "Vogel Conflict Test" as described by Vogel et al *(Psychopharmacologia,* **1971,** *21, 1-7)* can be used to detect anxiolytic activity of a compound because anxiolytics increase punished drinking. In the test, rats are deprived of water for approximately 48 hours and are then placed individually into a transparent Plexiglas® enclosure (15 x 32 x 34 cm) with a floor consisting of stainless steel bars (0.4 cm) spaced 1 cm apart. The back wall of the enclosure is made of opaque Plexiglas® thereby concealing the observer from the experimental animal. In the centre of the opposite wall, 5 cm above the floor, a metal water spout protrudes into the cage and is connected to one pole of a shock generator (Apelex: Type 011346). The other pole of the shock generator is connected to the metal grid floor.

The rat is left to explore until it finds the water spout. Then, every time it drinks, it receives a slight electric shock (1.7 mA, 1 s) 2 seconds after it starts lapping. The number of punished drinks is counted during a 3 minute test.

The test is performed blind with, e.g., 10 rats per group. Testing includes multiple tests using reference compounds and compounds of the present invention that are prepared and administered as previously described LES test. Appropriate animals for testing with acclimatization conditions are, for example, the male Rj: Wistar (Hans) rats as previously described for the LES test. Data is analyzed by comparing treated groups with appropriate controls using unpaired Student's t tests.

Antidepressive effect can be evaluated using the Flinders Sensitive Line (FSL) rat in the FST and social interaction test as described in [D.H. Overstreet and G. Griebel *Pharmacol Biochem Behav.*, **2005**, *82*, 1: 223-227]. More specifically, compounds of the invention are tested at

multiple doses (e.g., 10 mg/kg, 30 mg/kg, etc.) by preparing in 20% HP-beta-cyclodextrin and against vehicle control. In addition to an FSL vehicle control group, Flinders Resistant Line rats' vehicle control group is tested. Test compounds are administered daily by IP injection (2 mg/kg injection volume) for 14 days. Animals are tested in the social interaction and forced swim tests on Day 15, 22-24 hours after the injection on Day 14, as described in Overstreet and Griebel **2005**. Six to eight animals per group are tested.

Anxiolytic and antidepressive effect can also be evaluated using a paradigm for decreased HPA axis feedback (David et al., 2007, SFN meeting in San Diego). This model based on the chronic delivery of corticosterone in the drinking water, causes anxiety- and depression-like behaviors in mice. The model consists of a sustained administration of a high dose (35µg/mL), but not a low dose (7µg/mL), of corticosterone for four or seven weeks. Such a treatment induced anxiety- and depression-like behaviour in C57Bl6/NTac mouse strain as indicated by a decreased time spent and number of entries into center of the arena during the 30 minutes open field test (OF), whereas total ambulation was unaltered. Also, the latency to feed was increased in corticosterone-treated mice submitted to the novelty suppressed feeding (NSF) paradigm. As the corticosterone treatment did not alter food-intake in the home cage (familiar environment), changes in feeding latency were not due to changes in appetite or an underlying metabolic abnormality. Importantly, the adrenocorticotropic hormone (ACTH) and corticosterone (CORT) response to an acute stressor (6 min forced swim test (FST)), measured as plasma-concentrations, was blunted in C57BL/6NTac mice. Theses results were confirmed in CD1 strain mice. Three weeks treatment with the antidepressant imipramine (40 mg/kg/day ip) and fluoxetine (18 mg/kg/day ip) reversed the anxiety- and depression-like effects caused by a seven weeks corticosterone treatment in the OF, NSF and FST.

In such test, 240 adult male mice of C57Bl/6Ntac strain (Taconic Farms (Denmark)), 8-10 weeks old, which are allowed to acclimate to the facility for at least 1 week prior to testing (e.g., 5 per cage under a 12 h (06:00-18:00) light-dark cycle at 22 °C) with food and water freely available.

A compound of the invention (30 or 60 mg/kg, per day in chow), fluoxetine (18 mg/kg per day in drinking water) or vehicle (0.45% β-cyclodextrine, βCD in drinking water) are administered to mice treated via drinking water with either vehicle or corticosterone (35 µg/mL). After 7 weeks of treatment as indicated below, mice are tested in the following behavioral tests: OF, NSF, FST

and sucrose splash grooming test. Treatment is started with either βCD or corticosterone (35 μg/mL) given via the drinking water for 3 weeks (n=200 mice per group). Thereafter, administration with βCD or corticosterone will continue, and mice are divided into 8 groups of 30 mice as indicated below for 4 additional weeks.

Week 1-8	**Week 3-7**
vehicle (βCD)	vehicle
vehicle (βCD)	fluoxetine, 18 mg/kg
vehicle (βCD)	test compound, 30 mg/kg
vehicle (βCD)	test compound, 60 mg/kg
35μg/mL/day corticosterone	vehicle
35μg/mL/day corticosterone	fluoxetine, 18mg/kg
35μg/mL/day corticosterone	test compound, 30 mg/kg
35μg/mL/day corticosterone	test compound, 60 mg/kg

Mice are tested in the behavioral paradigms in this order: OF, NSF, sucrose splash test and then the mouse FST (15 animals/group).

The Open-field test

Motor activity is quantified in Plexiglas® open field boxes 43 x 43 cm^2 (MED associates, Georgia, VT) over a 10 min session. Two sets of 16 pulse-modulated infrared photo beams are placed on opposite walls 2.5 cm apart to record x-y ambulatory movements. A 40-W white bulb placed in the middle of the room provided around 200-lx illumination at floor level. Activity chambers are computer interfaced for data sampling at 100 ms resolution. The computer defined grid lines that divided each open field into center and surrounds regions, with each of four lines being 11 cm from each wall. Dependant measures are total time spent in the center, the numbers of entries into the center and distance traveled in the center divided by total distance traveled. Overall motor activity is quantified as the total distance traveled (cm).

The Novelty-Suppressed Feeding

The novelty suppressed feeding (NSF) is a conflict test that elicits competing motivations: the drive to eat and the fear of venturing into the center of brightly lit arena. Latency to begin eating is used as an index of anxiety-like behavior because classical anxiolytic drugs decrease it. The NSF is carried out during a 5-min period as previously described (Santarelli et al., 2003). Briefly, the testing apparatus consisted of a plastic box 50x50x20 cm. The floor is covered with approximately 2 cm of wooden bedding. Twenty-four hours prior to behavioral testing, all food is removed from the home cage. At the time of testing, a single pellet of food (regular chow) is placed on a white paper platform positioned in the center of the box. An animal is placed in a corner of the maze and a stopwatch is immediately started. The measure of interest (chewing) is scored when the mouse is sitting on its haunches and biting with the use of forepaws. Immediately after this test, mice are transferred to their home cage and the amount of food consumed in 5 min is measured (home cage food consumption). Mice are tested during the light period. Because antidepressants are known to have various effects on appetite, the feeding drive is assessed by returning animals in their home cage (familiar environment) immediately after the test. Then, the amount of food consumed over a 5 min-period is measured.

Splash test

The grooming latency is assessed at the end of the corticosterone regimen (end of seventh week) in the presence or absence of 3-weeks of fluoxetine treatment. This test consists in squirting 200 µl of a 10% sucrose solution on the mouse's snout. The grooming frequency is then recorded

The mouse Forced Swim Test

A modified forced swim test procedure as described in [Dulawa et al., Neuropsychopharmcol., **2004**, *29*, 1321–1330; Holick et al., Neuropsychopharmcol., **2008**, *33*, 2: 406-417] is used. Mice are placed individually into glass cylinders (height: 25 cm, diameter: 10cm) containing 18 cm water that is maintained at 23-25 °C and videotaping will be for 6 min via a tripod-mounted camera positioned directly on the side of the cylinder. An increase of swimming and climbing has been linked to an activation of serotoninergic and noradrenergic system in rats [see, e.g., Cryan and Lucki, Pharmcol. & Exp. Therap., **2000**, 295, 3, 1120-1126] and in mice [see, e.g., Dulawa et al. (**2004**); Holick et al., (**2008**)], respectively. Therefore, the predominant behavior

(swimming, immobility or climbing) is scored here during the last 4 min of the 6 min testing period.

Anxiolytic-like properties also can be evaluated using these additional tests: (1) social interaction described in [S.E. File and P. Seth, *European Journal of Pharmacology*, **2003**, *463*, 35-53], and (2) elevated plus-maze described in [S.M. Korte and S.F. De Boer European Journal of Pharmacology, **2003**, *463*, 163– 175].

Parkinson's disease (PD) can be assessed by measuring the neurotoxicity of MPTP in rats as described in [E. H. Lee *et al. Chin. J. Physiol.*, **1992**, *35*, 4: 317-36]. Also experimentally induced striatal DA depletion in animals is a valid model of Parkinsonism, as described in [W. Schultz *Prog. Neurobiol.*, **1982**, *18*, 2-3: 121-66]. The capacity of certain substances to damage catecholaminergic neurons has been used extensively to produce DA deficiency in animals, as described in [L. E. Annett *et al. Exp. Neurol.*, **1994**, *125*, 2: 228-46]. PD can also be assessed by measuring the neurotoxicity induced by 6-hydroxydopamine (6-OHDA) as described in N. Breysse *et al. J. Neurosci.*, **2002**, *22*, 13: 5669-5678; D. Rylander *et al. J. Pharmacol. Exp. Ther.*, **2009**, 330, 1: 227-235; and L. Chen *et al. Brain Res.*, In Press, Uncorrected Proof, available online 21 June **2009**, doi:10.1016/j.brainres.2009.06.040].

Fragile X Syndrome can be assessed using the *fmr1*^{tm1Cgr} mouse model as described in [Q.J. Yan *et al. Neuropharmacol.*, 2005, 49, 1053-1066] as well as the *Fmr1* knockout mice with a selective reduction in mGluR5 expression as described in [G. Dölen *et al. Neuron*, **2007**, *56*, 955-962].

Preclinically, animals also can be evaluated for blockade/attenuation of symptoms associated with schizophrenia. Positive symptoms in animal models of schizophrenia can be evaluated by measuring changes in the overall level of activity of dopamine (DA) activity with concomitant parallel changes in locomotor activity as described in [R. Depoortere *et al. Neuropsychopharmacology*, **2003**, *28*, 11: 1889-902], D-amphetamine (AMPH) and phencyclidine (PCP) via induction of model psychosis or locomotor hyperactivity as described in [W. J. Freed *et al. Neuropharmacology*, **1984**, *23*, 2A: 175-81; F. Sams-Dodd *Neuropsychopharmacology*, **1998** *19*, 1: 18-25]. For example, Depoortere et al., **2003**, have described tests for evaluating locomotor activity, catalepsy, climbing and stereotypy, which

relate to positive symptomology and side effect profile, by characterizing compounds with typical and atypical antipsychotic efficacy. Attenuation in apomorphine-induced climbing, stereotypy and catalepsy (AIC) can be evaluated as described in [Y. K. Fung et al. *Pharmacol. Biochem. Behav.*, **1986**, *24*, 1: 139-41 and Y. K. Fung *et al. Steroids*, **1987**, *49*, 4-5: 287-94]. Additionally, negative symptoms of schizophrenia can be evaluated by measuring social interaction under the influence of NMDA antagonists such as PCP, as described in F. Sams-Dodd, **1998**, *supra.*

Cognitive symptoms of memory, including those from Alzheimer's disease, can be evaluated by such models as the Fear Conditioning Paradigm described in [T. J. Gould *et al. Behav. Pharmacol.*, **2002**, *13*, 4: 287-94, and A. O. Hamm *et al. Brain*, **2003**, *126*, Pt 2: 267-75] and the Radial Arm Test described in [J. P. Aggleton *et al. Behav. Brain Res.*, **1996**, *19*, 2: 133-46], while spatial reference memory and learning can be evaluated in the Morris watermaze test as described in [Morris. *Learn. Motiv.*, **1981**, *12*, 239-260; B. Bontempi *et al. Eur. J. Neurosci.* **1996**, *8*, 11: 2348-60]. More specifically, in the Morris watermaze test, a circular water tank (150 cm diameter and 45 cm height) is filled with about 30 cm water and maintained at 26–28 °C with an escape platform (15 cm diameter) 18 cm from the perimeter and always in the same position 1.5 cm beneath the surface of the water. The water is made opaque by addition of a non-toxic coloring agent (e.g., milk powder) rendering the platform invisible. Animals are given a single training session over a single day. The training session consists of 4 consecutive trials in the watermaze, each separated by 60 seconds. For each trial, the animal is placed in the watermaze at one of two starting points equidistant from the escape platform and allowed to find the escape platform. The animal is left on the escape platform for 60 seconds before starting a new trial. If the animal does not find the platform within 120 seconds, the animal is removed from the water and placed on the platform for 60 seconds. During the 4 trials, the animals start the watermaze twice from each starting point in a randomly determined order per animal. Appropriate animals for testing with acclimatization conditions are, for example, the male Rj: Wistar (Hans) rats as previously described for the LES test.

The trials are video-recorded and the behavior of animals is analyzed using a video-tracking system (SMART, Panlab, S.L., Cornellà (Barcelona), Spain). The principal measure taken in each trial is the distance traveled to find the platform. Secondary measures taken are the swim

speed and escape latency. The test is performed blind using, for example, 12 rats per test group. Testing includes multiple tests using reference compounds and compounds of the present invention that are prepared and administered as previously described LES test. For each test, data is analyzed by comparing treated groups with vehicle controls using one-way ANOVA followed by Dunnett's t tests. To increase comparability with the aforementioned Vogel conflict test, in all tests, rats are subjected to water-deprivation for approximately 24 h before the test (Day 1); however, testing is performed in non water-deprived rats (Day 2).

Additionally, with respect to cognition, memory and hippocampal hypo-functioning can be assessed by measuring the restoration of synaptic plasticity in ovariectomized (OVX) female rats as described in [M. Day and M. Good *Neurobiol. Learn. Mem.*, **2005**, *83*, 1: 13-21]. Further, changes in attention function because of schizophrenia can be examined by the Five (5) Choice Serial Reaction Time Test (5CSRT) described in [J. L. Muir *et al. Psychopharmacology (Berl)*, **1995**, *118*, 1: 82-92 and Robbins *et al. Ann. N. Y. Acad. Sci.*, **1998**, *846*, 222-37].

Human patients can be evaluated for cognitive diseases or disorders by any of the tests within the skill of those in the art.

Analgesic activity can be evaluated by neuropathic pain model (the "Chung model") as described in [Kim and Chung, *Pain*, **1992**, *50*, 355-363]. Tight ligature of spinal nerves in rats is associated with hyperalgesia, allodynia and spontaneous pain, and therefore constitutes a model for peripheral neuropathic pain in humans. Antihyperalgesics reduce these chronic signs of pain hypersensitivity. Thus, in the Chung model, rats are anesthetized (sodium pentobarbital 50 mg/kg i.p.) and an incision at the L4-S2 level is performed to expose the left L5 nerve after cleaning the flank with chlorhexidine in spray. A cotton thread (standard, non-surgery quality), disinfected with pure alcohol, is placed around the L5 nerve and a simple ligature is tied tightly around the L5 nerve. The wound is then sutured and sprayed with CothiVet® (hydrocotyle tincture spray) (Neogen® Corp., Lexington, KY). The rats receive a s.c. injection of Clamoxyl (0.67 mL/kg) and are allowed to recover. At least 2 weeks after the surgery, when the chronic pain state is fully installed, rats are submitted consecutively to tactile and thermal stimulation of both hindpaws.

For tactile stimulation, the animal is placed under an inverted acrylic plastic box (18 x 11.5 x 13 cm) on a grid floor. The tip of an electronic Von Frey probe (Model 1610, BIOSEB, Vitrolles Cedex, France) is then applied with increasing force first to the non-lesioned and then the lesioned hindpaw and the force required to induce paw-withdrawal is automatically recorded. This procedure is carried out 3 times and the mean force per paw is calculated.

For heat stimulation, the apparatus (No. 7371, Ugo Basile, Comerio VA, Italy) consists of individual acrylic plastic boxes (17 x 11 x 13 cm) placed upon an elevated glass floor. A rat is placed in the box and left free to habituate for 10 minutes. A mobile infrared radiant source (96 ± 10 mW/cm^2) is then focused first under the non-lesioned and then the lesioned hindpaw and the paw-withdrawal latency is automatically recorded. In order to prevent tissue damage, the heat source is automatically turned off after 45 seconds.

Prior to receiving compound treatment all animals are submitted to tactile stimulation of the hindpaws and assigned to treatment groups matched on the basis of the pain response of the lesioned hindpaw. The test is performed blind using, for example, 10 water-deprived rats per group. Appropriate animals for testing are, for example, the male Rj: Wistar (Hans) rats as previously described for the LES test. Testing includes multiple tests using reference compounds and compounds of the present invention. In addition to the pregabalin and MPEP as previously described for the LES test, duloxetine can be used as a reference compound since it is an antihyperalgesic with respect to neuropathic pain associated with diabetes and fibromyalgia. Compounds are prepared and administered as previously described LES test. Testing can be performed using the same batch of operated rats repeatedly, with a minimum wash-out of 1 week between treatments. Also, to increase comparability with the aforementioned Vogel conflict test, in all tests, rats are subjected to water-deprivation for approximately 48 hours before each test. For each Chung model test, data will be analyzed by comparing treated groups with appropriate controls using unpaired Student's t tests.

Additionally, analgesic/anti-inflammatory activity can be evaluated *in vivo* using the Formalin Paw Test in the mouse such as that described by [Wheeler-Aceto et al, *Psychopharmacology*, **1991**, *104*, 35-44). For the test, mice are given an intraplantar injection of 5% formalin (25 µl) into the posterior left paw. This treatment induces paw licking in control animals. The time spent

licking is counted for 5 minutes, beginning immediately after injection of formalin (early phase) and for 15 minutes starting 15 minutes after injection of formalin (late phase).

The test is performed blind using, e.g., 10 mice per group. Appropriate animals for testing are, for example, male Rj: NMRI mice (Elevage Janvier), weighing 20 - 30 g (max. range per experiment = 5 g) at the beginning of testing. Animals are acclimatized as described for the animals used in the LES test. Testing includes multiple tests using reference compounds (e.g., morphine), comparative compounds (e.g., gabapentin and duloxetine), and compounds of the present invention. Compounds of the invention can be evaluated at multiple doses as previously described in the LES test, and administered s.c. 60 minutes before formalin in comparison with a vehicle control group, while morphine (64 mg/kg p.o.), gabapentin (300 mg/kg p.o.) and duloxetine (10 mg/kg p.o.) are administered p.o. 60 minutes before formalin. Data is analyzed by comparing treated groups with vehicle control groups using unpaired Mann-Whitney U tests.

Multiple sclerosis can be evaluated by the experimental autoimmune encephalomyelitis (EAE) model described in [H. Y. Liu *et al. J. Neurosci. Res.*, **2002**, *70*, 2: 238-48].

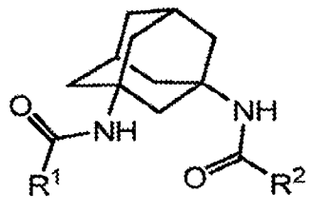
Those skilled in the art will recognize that various changes and/or modifications may be made to aspects or embodiments of this invention and that such changes and/or modifications may be made without departing from the spirit of this invention. Therefore, it is intended that the appended claims cover all such equivalent variations as will fall within the spirit and scope of this invention.

Each reference cited in the present application, including literature references, books, patents and patent applications, is incorporated herein by reference in its entirety.

The present application is a U.S. Nonprovisional Patent Application claiming the benefit of U.S. Provisional Applications Nos. 61/083563 and 61/160804 filed July 25, 2008 and March 17, 2009, respectively, each of which is herein incorporated by reference in its entirety.

What is claimed is:

1) A compound of formula (I):



(I)

wherein:

R^1 and R^2 are each independently alkyl, cycloalkyl, ketocycloalkyl, heterocyclyl, aryl or heteroaryl, wherein each is optionally mono-, di-, or tri-substituted independently with alkyl, alkoxy, halogen, cyano, nitro, trifluoroalkyl, amino, alkylamino, dialkylamino, acyl, aryl, heteroaryl, heterocyclyl, heterocyclyl-R^3, -NHR^3, -N(alkyl)R^3, -$C(O)NHR^3$, -C(O)N(alkyl)R^3, -$NHC(O)R^3$, -N(alkyl)$C(O)R^3$, -OH or -OR^3, wherein:

R^3 is C_1-C_6alkyl or C_1-C_6cycloalkyl, which is optionally substituted with halogen, C_1-C_3alkoxy, OH, -CN, -NH_2, -NH(C_1-C_3alkyl), -N(C_1-C_3alkyl)$_2$, C_1-C_3alkylheterocyclyl, C_1-C_3alkylcarbamate, -C(O)NH(C_1-C_3alkyl), -C(O)N(C_1-C_3alkyl)$_2$, -NHC(O)-C_1-C_3alkyl, -N(C_1-C_3alkyl)-C(O)-C_1-C_3alkyl, OH, or –O-C_1-C_6alkyl;

with the proviso that the compound of formula (I) is not:

N, N'-(1,3-adamantylene)bis(3-methoxy-benzamide);

N, N'-(1,3-adamantylene)bis(4-ethoxy-benzamide);

N, N'-(1,3-adamantylene)bis(4-methoxy-benzamide);

N,N'-(1,3-adamantylene)bis(3,4,5-trimethoxybenzamide);

N, N'-(1,3-adamantylene)bis(2-iodo-benzamide);

N,N'-(1,3-adamantylene)bis-benzamide;

N,N'-(1,3-adamantylene)bis(3-nitrobenzamide); and

N,N'-(1,3-adamantylene)bis-(3-pyridinecarboxamide); or

a pharmaceutically acceptable salt thereof.

2) The compound of claim 1, wherein R^1 and R^2 are both aryl.

3) The compound of claim 1, wherein R^1 and R^2 are both heteroaryl.

4) The compound of claim 1, wherein R^1 is aryl and R^2 is heteroaryl.

5) The compound of claim 1, wherein R^1 is aryl or heteroaryl and R^2 is cycloalkyl, ketocycloalkyl or heterocyclyl.

6) The compound of claim 1, wherein either R^1 or R^2 is heteroaryl

7) The compound of claim 1, wherein either R^1 or R^2 is aryl.

8) The compound of claim 1, wherein either R^1 or R^2 is cycloalkyl.

9) The compound of claim 1, wherein at least one aryl is phenyl.

10) The compound of claim 1, wherein at least one heteroaryl is pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl, pyrazolyl, indazolyl, thiophenyl, furanyl, benzofuranyl, benzo[c]isoxazolyl, benzoxazolyl, benzothiazolyl, dihydrothieno[3,4-b][1,4]dioxinyl, furanyl, imidazo[1,2-a]pyridinyl, indazolyl, indolinyl, indolyl, isoquinolinyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolo[3,2-c]pyridinyl, quinolinyl, quinoxalinyl, thiazolyl, or thiophenyl.

11) The compound of claim 1, wherein cycloalkyl is cyclobutyl, cyclohexyl, cyclopentyl, or cyclopropyl.

12) The compound of claim 1, wherein at least one cycloalkyl, aryl or heteroaryl is substituted as previously defined.

13) The compound of claim 12, wherein the mono-, di-, or tri-substituents are independently selected from the group consisting of methyl, methoxy, dimethylamino-ethoxy, amino, methylamino, dimethylamino, cyano, chloro, cyano, dimethylamino, dimethylamino-ethoxy, methyl, methylamino, methoxy, fluoro, $-C(O)NHCH_3$, furanyl, pyrrolidinyl, thiophenyl and trifluoromethyl.

14) The compound of claim 12, wherein the heteroaryl is pyridinyl, and the pyridinyl is mono-, di-, or tri-substituted as previously defined.

15) The compound of claim 14, wherein the mono-, di-, or tri-substitutions are independently heteroaryl, heterocyclyl, heterocyclyl-R^3, -NHR^3, -N(alkyl)R^3, wherein R^3 is as previously defined.

16) The compound of claim 8, wherein the cycloalkyl is tetra-substituted with fluorine.

17) The compound of claim 1, wherein the compound is:

N,N'-(1,3-adamantylene)bis(6-methyl-pyridine-2-carboxamide);

N,N'-(1,3-adamantylene)bis(2-pyridinecarboxamide);

N,N'-(1,3-adamantylene)bis(3-chloro-benzamide);

N,N'-(1,3-adamantylene)bis(4-pyridinecarboxamide);

N,N'-(1,3-adamantylene)bis(3-cyano-benzamide);

Pyridine-2-carboxylic acid[3-(3-chloro-benzoylamino)-adamantan-1-yl]-amide;

Pyridine-2-carboxylic acid[3-(3-cyano-benzoylamino)-adamantan-1-yl]-amide;

Pyridine-2-carboxylic acid {3-[(1-methyl-5-thiophen-2-yl-1H-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyridine-2-carboxylic acid {3-[(5-furan-2-yl-1-methyl-1H-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide;

2-Methyl-2H-indazole-3-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid (3-benzoylamino-adamantan-1-yl)-amide;

Pyridine-2-carboxylic acid [3-(4-dimethylamino-benzoylamino)-adamantan-1-yl]-amide;

Pyridine-2-carboxylic acid [3-(4-methoxy-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

Pyridine-2-carboxylic acid [3-(3-cyano-benzoylamino)-adamantan-1-yl]-amide;

Pyridine-2-carboxylic acid {3-[(benzofuran-5-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyridine-2-carboxylic acid {3-[4-(2-dimethylamino-ethoxy)-benzoylamino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

N,N'-(1,3-adamantylene)bis(4-methyl-pyridine-2-carboxamide);

N,N'-(1,3-adamantylene)bis(quinoline-2-carboxamide);

N,N'-(1,3-adamantylene)bis(quinoxaline-2-carboxamide);

N,N'-(1,3-adamantylene)bis(thiophene-2-carboxamide);

N,N'-(1,3-adamantylene)bis(3-fluorobenzamide);

N,N'-(1,3-adamantylene)bis(3-methylbenzamide);

N,N'-(1,3-adamantylene)bis(1-methyl-1*H*-pyrazole-3-carboxamide);

5-Methyl-pyrazine-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide;

Thiazole-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(1-methyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Morpholin-4-yl-pyridine-2-carboxylic acid-{3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Trifluoromethyl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyridazine-3-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Cyanomethyl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino] -adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid{3-[(5-cyclopropyl-isoxazole-3-carbonyl)-amino]-adamantan-1-yl}-amide;

[1,8]Naphthyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Methyl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid{3-[(2-methyl-oxazole-4-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(isoxazole-5-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid [3-(3-cyano-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(benzofuran-5-carbonyl)-amino]-adamantan-1-yl}-amide;

Quinoxaline-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrimidine-4-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Benzothiazole-2-carboxylic acid{3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

1-Methyl-1*H*-indazole-3-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(2,3-dihydro-thieno[3,4-b][1,4]dioxine-5-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(5-methyl-isoxazole-3-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(thiazole-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrazine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(1-ethyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid [3-(3-methoxy-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid [3-(3-pyrimidin-2-yl-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid [3-(3-chloromethyl-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid [3-(cyclobutanecarbonyl-amino)-adamantan-1-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(3,3-difluoro-cyclobutanecarbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(2-methyl-cyclopropanecarbonyl)-amino]-adamantan-1-yl}-amide;

2-Methyl-2*H*-indazole-3-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Chloro-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Imidazo[1,2-a]pyridine-7-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Imidazo[1,2-a]pyridine-6-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

5-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

7-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Chloro-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

Pyrimidine-4-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Pyrrolidin-1-yl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Benzo[c]isoxazole-3-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

5-Methyl-pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyridine-2,6-dicarboxylic acid 2-methylamide 6-({3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide);

2-Methyl-benzoxazole-6-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyridine-2-carboxylic acid [3-(cyclobutanecarbonyl-amino)-adamantan-1-yl]-amide;

Pyridine-2-carboxylic acid {3-[(2,2-difluoro-cyclopropanecarbonyl)-amino]-adamantan-1-yl}-amide;

Pyridine-2-carboxylic acid [3-(cyclohexanecarbonyl-amino)-adamantan-1-yl]-amide;

Pyridine-2-carboxylic acid [3-(cyclopentanecarbonyl-amino)-adamantan-1-yl]-amide;

6-Chloro-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Imidazo[1,2-a]pyridine-7-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Imidazo[1,2-a]pyridine-6-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

7-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

5-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrimidine-4-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

5-Methyl-pyrazine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

Pyrazine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

1-Methyl-1*H*-pyrazole-3-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Chloro-imidazo[1,2-a]pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

Imidazo[1,2-a]pyridine-7-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

Imidazo[1,2-a]pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

Imidazo[1,2-a]pyridine-6-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

5-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

7-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Morpholin-4-yl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(4-Methyl-piperazin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(3-Dimethylamino-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Hydroxy-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl-6'-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(3-Hydroxy-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-[(2-Hydroxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(3-Hydroxy-propylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-[(2-Dimethylamino-ethyl)-methyl-amino]-pyridine-2-carboxylic acid{3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(3-Hydroxy-pyrrolidin-1-yl)-pyridine-2-carboxylic acid{3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Hydroxy-3,4,5,6-tetrahydro-2*H*-[1,2]bipyridinyl-6-carboxylic acid{3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-[(2-Methoxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(2-Hydroxy-ethylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-[(2-Hydroxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(3-Hydroxy-propylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Morpholin-4-yl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(2-Hydroxy-ethylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-[(2-Hydroxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-(3-Hydroxy-propylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Morpholin-4-yl-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-(4-Methyl-piperazin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-(3-Dimethylamino-pyrrolidin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

4-Hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-(3-Hydroxy-pyrrolidin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-(3-Methoxy-propylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-[(3-Dimethylamino-propyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(2-Dimethylamino-ethylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(2-Acetylamino-ethylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(2-Methoxy-ethylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-[(2-Methoxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(3-Dimethylamino-propylamino)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-[(2-Dimethylamino-ethyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-((S)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-((R)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-((S)-2-Carbamoyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(3-Methoxy-propylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(2-Dimethylamino-ethylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-[(3-Dimethylamino-propyl)-methyl-amino]-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(2-Acetylamino-ethylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(2-Methoxy-ethylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(3-Dimethylamino-propylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-((S)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-((R)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-((S)-2-Carbamoyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(2-Carbamoyl-ethylamino)-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-(3-Methoxy-propylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-(2-Dimethylamino-ethylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-[(3-Dimethylamino-propyl)-methyl-amino]-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-(2-Acetylamino-ethylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-(2-Methoxy-ethylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-[(2-Methoxy-ethyl)-methyl-amino]-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-(3-Dimethylamino-propylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-[(2-Dimethylamino-ethyl)-methyl-amino]-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-((S)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-((R)-2-Hydroxymethyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-((S)-2-Carbamoyl-pyrrolidin-1-yl)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-(2-Carbamoyl-ethylamino)-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Imidazol-1-yl-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Imidazol-1-yl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Imidazol-1-yl-pyridine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-(4-Fluoro-phenyl)-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Phenyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrimidine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Methyl-pyrimidine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Trifluromethyl-pyrimidine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

2-Methyl-pyrimidine-4-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

2-Trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

5-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrimidine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Methyl-pyrimidine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Trifluoromethyl-pyrimidine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

2-Methyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

2-Trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

5-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

5-Fluoro-pyridine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

5-Fluoro-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrazine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

5-Methyl-pyrazine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

5-Trifluoromethyl-pyrazine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrimidine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Methyl-pyrimidine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Trifluoromethyl-pyrimidine-2-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

2-Trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

2-Methyl-pyrimidine-4-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrimidine-4-carboxylic acid {3-[(5-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrimidine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

4-Methyl-pyrimidine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

4-Trifluoromethyl-pyrimidine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

2-Trifluoromethyl-pyrimidine-4-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Trifluoromethyl-pyrazine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

5-Trifluoromethyl-pyrazine-2-carboxylic acid [3-(3-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[3-(2-hydroxy-ethoxy)-benzoylamino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid (3-{[4-(2-hydroxy-ethoxy)-pyridine-2-carbonyl]-amino}-adamantan-1-yl)-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[3-(2-hydroxy-2-methyl-propoxy)-benzoylamino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid (3-{[4-(2-hydroxy-2-methyl-propoxy)-pyridine-2-carbonyl]-amino}-adamantan-1-yl)-amide;

Pyrazine-2-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

2,6-Dimethyl-pyrimidine-4-carboxylic acid {3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Fluoro-pyridine-2-carboxylic acid{3-[(pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyridine-2-carboxylic acid {3-[(1,5-dimethyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyridine-2-carboxylic acid {3-[(2-methyl-thiazole-4-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid [3-(3-dimethylamino-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(pyridine-3-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(6-aminopyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

2,6-Dimethyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(thiazole-4-carbonyl)-amino]-adamantan-1-yl}-amide;

Benzoxazole-5-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

[1,6]Naphthyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(4-fluoropyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4,6-Dimethyl-pyridine-2-carboxylic acid {3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(1,5-dimethyl-1*H*-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(4-methoxypyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(3-fluoropyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(5-methylpyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(4-hydroxypyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyridine-2,6-dicarboxylic acid 2-amide 6-({3-[(6-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide);

6-Methyl-pyridine-2-carboxylic acid {3-[(6-hydroxymethylpyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(6-fluoropyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(2-methyl-thiazole-4-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(4-bromopyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-{3-[(6-Methyl-pyridine-2-carbonyl)-amino]-adamantan-1-ylcarbamoyl}-pyridine-2-carboxylic acid methyl ester;

6-Methyl-pyridine-2-carboxylic acid {3-[(6-acetylpyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(6-(1-hydroxy-ethyl)-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyridine-2-carboxylic acid {3-[(6-(1-hydroxy-1-methyl-ethyl)-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

N,N'-(1,3-adamantylene)bis(6-methyl-pyrazine-2-carboxamide);

6-Methyl-pyrazine-2-carboxylic acid [3-(3-methoxy-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(3-ethoxy-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(2,5-difluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(3-chloro-4-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(2-fluoro-3-trifluoromethyl-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(6-methoxy-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(3-chloro-2-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(4-methoxy-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(2-methoxy-pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(2-ethoxy-pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(2-methyl-pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(2-methyl-thiazole-4-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(3-fluoro-5-methyl-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(4-fluoro-3-methoxy-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(2-fluoro-pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(5-chloro-2-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(3-difluoromethoxy-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(3-chloro-5-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(6-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(5-methyl-pyridine-3-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(4-fluoro-3-methyl-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(2-fluoro-3-methoxy-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(3-methyl-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(2-fluoro-5 trifluoromethyl-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(5-chloro-pyridine-3-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(4-fluoro-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrimidine-2-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

2-Methyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

[1,6]Naphthyridine-2-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Benzoxazole-5-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(4-bromo-pyridine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

6-Methyl-pyrazine-2-carboxylic acid [3-(4-fluoro-benzoylamino)-adamantan-1-yl]-amide;

6-Methyl-pyrazine-2-carboxylic acid {3-[(2-bromo-pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide;

2-Trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Trifluoromethyl-pyrimidine-2-carboxylic acid {3-[(6-methyl-pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrazine-2-carboxylic acid {3-[(2-bromo-pyridine-4-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrazine-2-carboxylic acid {3-[(2-methyl-thiazole-4-carbonyl)-amino]-adamantan-1-yl}-amide;

Pyrazine-2-carboxylic acid {3-[(5-cyclopropyl-2H-pyrazole-3-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Methyl-pyrimidine-2-carboxylic acid {3-[(pyrazine-2-carbonyl)-amino] -adamantan-1-yl}-amide;

2-Trifluoromethyl-pyrimidine-4-carboxylic acid {3-[(pyrazine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Trifluoromethyl-pyrimidine-2-carboxylic acid {3-[(2-methyl-pyrimidine-4-carbonyl)-amino]-adamantan-1-yl}-amide;

2-Methyl-pyrimidine-4-carboxylic acid {3-[(4-methyl-pyrimidine-2-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Methyl-pyrimidine-2-carboxylic acid {3-[(pyrimidine-4-carbonyl)-amino]-adamantan-1-yl}-amide;

4-Trifluoromethyl-pyrimidine-2-carboxylic acid {3-[(pyrimidine-4-carbonyl)-amino]-adamantan-1-yl}-amide; or

a pharmaceutically acceptable salt thereof.

18) A pharmaceutical composition comprising at least one compound of claim 1 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

19) A method of treating a disease or disorder, the method comprises administering a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt thereof to a mammal in need thereof, wherein the disease or disorder is a central nervous system disease or disorder.

20) The method of claim 19, wherein the mammal is a human.

21) The method of claim 19, wherein the central nervous system disease or disorder is a cognitive, neurodegenerative, psychiatric or neurological disease or disorder.

22) The method of claim 21, wherein the cognitive or neurodegenerative disease or disorder is selected from a group consisting of a mood disorder, an anxiety, a schizophrenia,

Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's chorea, amyotrophic lateral sclerosis, Creutzfeld-Jakob disease, a trauma-induced neurodegeneration, AIDS-induced encephalopathy, a non-AIDS-induced encephalopathy, Fragile X syndrome, an autism spectrum disorder, and a combination thereof.

23) The method claim 22, wherein the mood disorder is a depression.

24) The method of claim 23, wherein the depression is selected from the group consisting of atypical depression, bipolar depression, unipolar depression, major depression, endogenous depression, involutional depression, reactive depression, postpartum depression, primary depression, psychotic depression, secondary depression, a combination thereof.

25) The method of claim 22, wherein the anxiety disease or disorder is selected from a group comprising generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, an adjustment disorder, a hypochondriacal disorder, separation anxiety disorder, agoraphobia, a specific phobia, anxiety disorder due to general medical condition, substance-induced anxiety disorder, alcohol withdrawal-induced anxiety, and a combination thereof.

26) The method of claim 19, wherein the central nervous system disease or disorder is a pain disease or disorder selected from the group consisting of inflammatory pain, neuropathic pain and migraine pain.

27) The method of claim 26, wherein the neuropathic pain or migraine pain disease or disorder is selected from the group consisting of allodynia, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathy, neuropathic pain related to migraine, and a combination thereof.

28) The method of claim 19, wherein the central nervous system disease or disorder is a neuronal hyperexcitation state disease or disorder.

29) The method of claim 28, wherein the neuronal hyperexcitation state disease or disorder is a neuronal hyperexcitation state in medicament withdrawal, a neuronal hyperexcitation state in intoxication, or a combination thereof.

30) The method of claim 21, wherein at least one symptom of the disease or disorder is treated.

31) The method of claim 30, wherein the disease or disorder is a depression.

32) The method of claim 32, wherein the at least one symptom of the depression is depressed feeling, depressed mood, loss of interest or pleasure in some or all activities, changes in appetite, changes in weight, changes in sleep patterns, lack of energy, fatigue, low self esteem, diminished capacity for thinking, concentration, or decisiveness, feelings of hopelessness or worthlessness, psychomotor agitation or retardation, self-reproach, inappropriate guilt, frequent thoughts of death or suicide, plans or attempts to commit suicide, or a combination thereof.

33) The method of claim 30, wherein the disease or disorder is an anxiety.

34) The method of claim 33, wherein the at least one symptom of the anxiety is apprehension, fear, trembling, muscle aches, insomnia, abdominal upsets, dizziness, irritability, persistent, recurring thoughts, compulsions, heart palpitations, chest pain, chest discomfort, sweating, tingling sensations, feeling of choking, fear of losing control, flashbacks, nightmares, intrusive thoughts, intrusive recollections, avoidance behaviors, emotional numbing, an inability to sleep, anxious feelings, overactive startle response, hypervigilance, outbursts of anger, faintness, blushing, profuse sweating, gastroesophageal reflux or a combination thereof.

35) The method of claim 30, wherein the disease or disorder is schizophrenia.

36) The method of claim 35, wherein the at least one symptom of schizophrenia is a positive symptom selected from the group consisting of hallucination, delusion, paranoia, and a combination thereof.

37) The method of claim 35, wherein the at least one symptom of schizophrenia is a negative symptom selected from the group consisting of social withdrawal, flat affect, anhedonia, decreased motivation, and a combination thereof.

38) The method of claim 35, wherein the at least one symptom of schizophrenia is a cognitive symptom selected from the group consisting of severe deficit in attention, severe deficit in object naming, severe deficit in working memory, severe deficit in long-term memory storage, severe deficit in executive functioning, a slowing of information processing, a slowing of neural activity, long term depression, and a combination thereof.

39) The method of claim 30, wherein the disease or disorder is Parkinson's disease.

40) The method of claim 39, wherein the at least one symptom of Parkinson's disease is levodopa-induced dyskinesia, poor balance, Parkinsonian gait, bradykinesia, rigidity, tremor, change in speech, loss of facial expression, micrographia, difficulty swallowing, drooling, pain, dementia, confusion, a sleep disturbance, constipation, a skin problem, depression, fear, anxiety, difficulty with memory, slowed thinking, sexual dysfunction, an urinary problem, fatigue, aching, loss of energy, or a combination thereof.

41) The method of claim 30, wherein the disease or disorder is Alzheimer's disease.

42) The method of claim 41, wherein the at least one symptom of Alzheimer's disease is impairment in memory, impairment in attention, impairment in judgment, impairment in decision-making, impairment in orientation to physical surroundings, language impairment, impairment in speed-dependent activities, impairment in abstract reasoning, impairment in visuospatial abilities, impairment in executive functioning, impairment in behavioral disturbances, disinterest and passivity, apathy, inappropriate dressing, poor self care, agitation, violent outburst, aggression, depression, anxiety, hallucination, delusion, change in personality, change in mood, dementia, or a combination thereof.

43) The method of claim 30, wherein the cognitive or neurodegenerative disease or disorder is multiple sclerosis.

44) The method of claim 43, wherein the at least one symptom of multiple sclerosis is optic neuritis blurred vision, eye pain, loss of color vision, blindness, diplopia double vision, nystagmus jerky eye movements, ocular dysmetria, constant under- or over-shooting eye movements, internuclear ophthalmoplegia, nystagmus, diplopia, movement and sound phosphenes, diplopia, afferent pupillary defect, motor paresis, monoparesis, paraparesis, hemiparesis, quadraparesis plegia, paraplegia, hemiplegia, tetraplegia, quadraplegia, spasticity, dysarthria, muscle atrophy, spasms, cramps, hypotonia, clonus, myoclonus, myokymia, restless leg syndrome, footdrop dysfunctional reflexes (MRSs, Babinski's, Hoffman's, Chaddock's), paraesthesia, anaesthesia, neuralgia, neuropathic pain, neurogenic pain, l'hermilte's, proprioceptive dysfunction, trigeminal neuralgia, ataxia, intention tremor, dysmetria, vestibular ataxia, vertigo, speech ataxia, dystonia,

dysdiadochokinesia, frequent micturation, bladder spasticity, flaccid bladder, detrusor-sphincter dyssynergia, erectile dysfunction, anorgasmy, retrograde ejaculation, frigidity, constipation, fecal urgency, depression, cognitive dysfunction, dementia, mood swings, emotional lability, euphoria, bipolar syndrome, anxiety, aphasia, dysphasia, fatigue, uhthoffs symptom, gastroesophageal reflux, a sleeping disorder, or a combination thereof.

45) A method of treating gastroesophageal reflux, the method comprises administering a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt thereof to a mammal in need thereof.

46) A method of treating alcohol dependence, the method comprises administering a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt thereof to a mammal in need thereof

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DERIVADOS ADAMANTIL DIAMIDA Y USOS DE LOS MISMOS

CAMPO DE LA INVENCION

La presente invención provee derivados adamantil diamida, así como también composiciones farmacéuticas y métodos de tratamiento en los que se usan los mismos

ANTECEDENTES DE LA INVENCION

Esta invención se refiere a derivados adamantil diamida, que actúan como moduladores aloestéricos del receptor 5 glutamato metabotrópico (receptores mGlu5 o mGluR5), así como también composiciones farmacéuticas y métodos de tratamiento que utilizan estos compuestos.

El glutamato es el neurotransmisor exitatorio principal del sistema nervioso central de los mamíferos. Un medio de modulación de la neurotransmisión de glutamato es a través de receptores glutamato metabotrópicos (mGluRs); otros medios son receptores ionotrópicos. Hasta el presente se han clonado ocho mGluRs y se han clasificado en tres grupos basados en homología de secuencia, via de transducción de señales preferida y farmacología. El Grupo I de mGluRs incluye mGluR1 y mGluR5, mientras que el Grupo II comprende mGluR2 y mGluR3 y el Grupo III comprende receptores mGlu 4, 6, 7 y 8.

Los receptores mGlu cumplen una función esencial en las funciones normales del cerebro, así como también en los trastornos neurológicos, psiquiátricos y neuromusculares. Los receptores mGlu5 están situados principalmente post–sinápticamente y están altamente expresados en las regiones límbicas cerebrales. Los receptores mGlu5 están también expresados en el tálamo, la médula espinal, los sistemas nerviosos vagales, así como también periféricamente en la piel o en las terminaciones nerviosas y fibras C.

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Los ligandos para los receptores mGlu5 han demostrado ser prometedores para los trastornos del sistema nervioso periférico y central. Ver por ejemplo, G. Jaeschke *et al.*, "mGlu5 receptor antagonists y their therapeutic potential," *Expert Opin. Ther. Patents*, **2008**, *18*, 2: 123–142. Sin embargo algunos proponen que los análogos de glutamato que alcanzan el sitio de adhesión ortoestérico pueden estar limitados por una baja penetración en el cerebro, e insuficiente selectividad con respecto a los subtipos mGluRs diferentes. Los agonistas sintéticos pueden conducir a una estimulación continua del receptor debido a que a menudo están

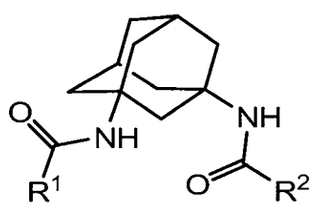
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diseñados para ser metabólicamente estables. Esta estimulación continua no es necesariamente deseable debido a los potenciales problemas de desensibilización del receptor. Asimismo, con respecto a la ocupancia del receptor, los antagonistas sintéticos pueden conducir a bloqueo prolongado de la función receptora, lo cual puede no ser compatible con la cinética de la patología de un transtorno del sistema nervioso central.

Sin embargo, una seletividad una acción "fine–tuning" más selectiva y controlada sobre el receptor mGlu5 es factible a través de modulación alostérica. Ver por ejemplo, P. Bach *et al.*, "Metabotropic glutamate receptor 5 modulators y their potential therapeutic applications," *Expert Opin. Ther. Patents,* **2007**, *17,* 4: 371–381. La modulación alostérica se refiere a la adhesión mediante un ligando modulador a un sitio en un receptor diferente del sustrato primario ortoestérico o del sitio de adhesión al ligando. Este proceso de adhesión al ligando da como resultado cambios conformacionales, que pueden influenciar profundamente la función de la proteína ((por ejemplo, receptores acoplados a proteína G tales como mGluRs, incluyendo mGluR5). Los nuevos ligandos mGluR5 que modulan alostéricamente el receptor mGlu5 pueden mejorar la ventana terapéutica de los agentes tradicionales del sistema nervioso central y/o el tratamiento de los trastornos del sistema nervioso central. La presente invención está dirigida a estos y otros objetivos importantes.

COMPENDIO DE LA INVENCION

La presente invención provee un compuesto de fórmula (I):



(I)

;

donde:

R^1 y R^2 son cada uno independientemente alquilo, cicloalquilo, cetocicloalquilo, heterociclilo, arilo o heteroarilo, que están opcionalmente mono–, di–, o tri–sustituidos con alquilo, alcoxi, halógeno, ciano, nitro, trifluoralquilo, amino, alquilamino, dialquilamino, acilo, arilo, heteroarilo, heterociclilo, heterociclilo–R^3, –NHR^3, –N(alquilo)R^3, –$C(O)NHR^3$, –C(O)N(alquilo)R^3, –$NHC(O)R^3$, –N(alquilo)$C(O)R^3$, –OH o –OR^3, donde:

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R^3 es alquilo C_1–C_6 o cicloalquilo C_1–C_6, que está opcionalmente sustituido con halógeno, alcoxi C_1–C_3, OH, –CN, $–NH_2$, –NH(alquilo C_1–C_3), –N(alquilo C_1–$C_3)_2$, alquilheterociclilo C_1–$_3$, alquilcarbamato C_1–C_3, –C(O)NH(alquilo C_1–C_3), –C(O)N(alquilo C_1–$C_3)_2$, –NHC(O)–alquilo C_1–C_3, –N(alquilo C_1–C_3)–C(O)–alquilo C_1–C_3, OH, o –O–alquilo C_1–C_6;

con la condición que que el compuesto de fórmula (I) no es:

N, N'–(1,3–adamantilen)bis(3–metoxi–benzamida);

N, N'–(1,3–adamantilen)bis(4–etoxi–benzamida);

N, N'–(1,3–adamantilen)bis(4–metoxi–benzamida);

N,N'–(1,3–adamantilen)bis(3,4,5–trimetoxibenzamida);

N, N'–(1,3–adamantilen)bis(2–yodo–benzamida);

N,N'–(1,3–adamantilen)bis–benzamida;

N,N'–(1,3–adamantilen)bis(3–nitrobenzamida); y

N,N'–(1,3–adamantilen)bis–(3–piridincarboxamida); o

o una sal farmacéuticamente aceptable del mismo.

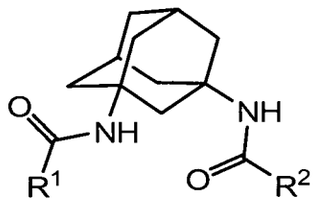
La presente invención provee también una composición farmacéutica que comprende por lo menos un compuesto de la invención o una sal farmacéuticamente aceptable del mismo, y por lo menos un portador farmacéuticamente aceptable.

La presente invención provee también un método de tratamiento de una enfermedad o trastorno, el método comprende la administración de una cantidad terapéuticamente eficaz de por lo menos un compuesto de la presente invención o una sal farmacéuticamente aceptable del mismo a un mamífero que lo necesita, donde la enfermedad o trastorno es una enfermedad o trastorno del sistema nervioso central. En algunas realizaciones del método, se trata un síntoma de la enfermedad o trastorno.

DESCRIPCION DETALLADA DE LA INVENCION

En un aspecto, la presente invención provee derivados adamantil diamida. La presente invención comprende un compuesto de fórmula (I):

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(I)

;

donde:

R^1 y R^2 son cada uno independientemente alquilo, cicloalquilo, cetocicloalquilo, heterociclilo, arilo o heteroarilo, que está opcionalmente mono–, di–, o tri–sustituido independientemente con alquilo, alcoxi, halógeno, ciano, nitro, trifluoralquilo, amino, alquilamino, dialquilamino, acilo, arilo, heteroarilo, heterociclilo, heterociclilo–R^3, –NHR^3, –N(alquilo)R^3, –C(O)NHR^3, –C(O)N(alquilo)R^3, –$NHC(O)R^3$, –N(alquilo)$C(O)R^3$, –OH o –OR^3, donde:

R^3 es alquilo C_1–C_6 o cicloalquilo C_1–C_6, que está opcionalmente sustituido con halógeno, alcoxi C_1–C_3, OH, –CN, –NH_2, –NH(alquilo C_1–C_3), –N(alquilo C_1–$C_3)_2$, alquilheterociclilo C_1–C_3, alquilcarbamato C_1–C_3, –C(O)NH(alquilo C_1–C_3), –C(O)N(alquilo C_1–$C_3)_2$, –NHC(O)–alquilo C_1–C_3, –N(alquilo C_1–C_3)–C(O)–alquilo C_1–C_3, OH, o –O–alquilo C_1–C_6;

con la condición de que el compuesto de fórmula (I) no es:

N, N'–(1,3–adamantilen)bis(3–metoxi–benzamida) (es decir, el compuesto que tiene el número de registro CAS 899289–36–2);

N, N'–(1,3–adamantilen)bis(4–etoxi–benzamida) (es decir, el compuesto que tiene el número de registro CAS 899289–24–8);

N, N'–(1,3–adamantilen)bis(4–metoxi–benzamida) (es decir, el compuesto que tiene el número de registro 899259–96–2);

N,N'–(1,3–adamantilen)bis(3,4,5–trimetoxibenzamida) ((es decir, el compuesto que tiene el número de registro 173068–46–7);

N, N'–(1,3–adamantilen)bis(2–yodo–benzamida) (es decir, el compuesto que tiene el número de registro 899259–92–8);

N,N'–(1,3–adamantilen)bis–benzamida (es decir, el compuesto que tiene el número de registro 103307–81–9);

N,N'–(1,3–adamantilen)bis(3–nitrobenzamida) (es decir, el compuesto que tiene el número de registro 350024–39–4); y

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N,N'–(1,3–adamantilen)bis–(3–piridincarboxamida) (es decir, el compuesto que tiene el número de registro 371933–95–8); o

una sal farmacéuticamente acetpable del mismo.

El término "alquilo", empleado solo o como parte de un grupo, se define aquí, a menos que se indique lo contrario, como un hidrocarburo saturado de cadena recta o ramificada de 1 a 8 átomos de carbono. En algunas realizaciones, la porción alquilo contiene 8, 7, 6, 5, 4, 3, 2 o 1 átomos de carbono. Cuando el término "alquilo" aparece aquí sin un rango de los átomos de carbono, significa un rango de C_1–C_8. Ejemplos de porciones alquilo de hidrocarburo saturado incluyen pero no están limitadas a grupos químicos tales como metilo, etilo, *n*–propilo, *iso*propilo, *n*–butilo, *ter*–butilo, *iso*–butilo, *sec*–butilo, *n*–pentilo, *n*–hexilo, y similares.

El término alcoxi", empleado solo o en combinación con otros términos, se define aquí, a menos que se indique lo contrario, como –O–alquilo, donde "alquilo" es tal como se ha definido aquí previamente. Ejemplos de porciones alcoxi incluyen, pero no están limitadas a grupos químicos tales como metoxi, etoxi, *iso*–propoxi, *sec*–butoxi, *ter*–butoxi, y homólogos, isómeros, y similares. Alcoxi se refiere también a porciones –O–alquilo donde el grupo alquilo está sustituido con hidroxi, ciano, alcoxi, alquilamino, dialquilamino, alquilamida, dialquilamida, y similares, incluyendo sin limitación, –Oalquilo C_1–C_4–OH, –Oalquilo C_1–C_4–OCH_3, –Oalquilo C_1–C_4–$NHCH_3$, –Oalquilo C_1–C_4–$N(CH_3)_2$, –Oalquilo C_1–C_4–$CONHCH_3$, –Oalquilo C_1–C_4–$CON(CH_3)_2$, –Oalquilo C_1–C_4–$NHCOCH_3$, y –Oalquilo C_1–C_4–$N(CH_3)COCH_3$.

Tal como se usa aquí, el término "cicloalquilo", empleado solo o en combinación con otros términos, se define aquí, a menos que se indique lo contrario, como un grupo alquilo ciclizado que tiene de 3 a 8 átomos de carbono en el anillo, donde "alquilo" es tal como se define aquí. Ejemplos de porciones cicloalquilo incluyen, pero no están limitadas a, grupos químicos tales como ciclopropilo, ciclobutilo, ciclopentilo, y ciclohexilo.

Tal como se usa aquí, el término "cetocicloalquilo", empleado solo o en combinación con otros términos, se define aquí, a menos que se indique lo contrario, como un cicloalquilo que tiene un radical ceto unido al mismo, donde "cicloalquilo" es tal como se define aquí. Ejemplos incluyen ciclopentanona o ciclohexanona.

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Los términos "halo" o "halógeno", empleados solo o en combinación con otros términos, se definen aquí, a menos que se indique lo contrario, como fluor, cloro, bromo, o yodo.

El término "arilo", empleado solo o en combinación con otros términos, se define aquí, a menos que se indique lo contrario, como un hidrocarburo aromático de hasta 14 átomos de carbono, que puede ser un anillo único (monocíclico) o anillos múltiples (por ejemplo, biciclico, tricíclico, policíclico) fusionados conjuntamente o ligados covalentemente. Cualquier posición del anillo apropiada de la porción arilo puede estar ligada covalentemente a la estructura química definida. Ejemplos de porciones arilo incluyen, pero no están limitados a, grupos químicos tales como fenilo, bencilo, 1–naftilo, 2–naftilo, y similares. Un grupo arilo puede estar no sustituido o sustituido tal como se describe aquí.

El término "heteroarilo" empleado solo o en combinación con otros términos, se define aquí, a menos que se indique lo contrario, como un anillo hidrocarbonado, aromático, monocíclico o policíclico (fusionado conjuntamente o ligado covalentemente) que comprende uno o más heteroátomos seleccionados independientemente entre nitrógeno, oxígeno, y azúfre. Un grupo heteroarilo comprende hasta 14 átomos de carbono y 1 a 6 heteroátomos. Ejemplos de grupos heteroarilo incluyen, pero no están limitados a piridinilo, piridazinilo, triazinilo, pirrolilo, pirazolilo, imidazolilo, (1,2,3,)– y (1,2,4)–triazolilo, pirazinilo, pirimidinilo, tetrazolilo, furilo, tienilo, isoxazolilo, tiazolilo, oxazolilo, 2–quinolinilo, 2–quinazolinilo, 3–fenil–2–quinolinilo y similares. Un grupo heteroarilo puede estar no sustituido o sustituido tal como se describe aquí

El término "heterociclilo" empleado solo o en combinación con otros términos, se define aquí, a menos que se indique lo contrario, como un grupo univalente formado por remoción de un átomo de hidrógeno de cualquier átomo de anillo de un heterociclo.

El término "acilo" empleado solo o en combinación con otros términos, se define aquí, a menos que se indique lo contrario, como grupos de fórmula –C(O)– alquilo, donde alquilo es tal como se ha descrito previamente aquí, es decir, un alquilcarbonilo, tal como formilo, acetilo y similares.

El término "aminoalquilo" empleado solo o en combinación con otros términos, se define aquí, a menos que se indique lo contrario, como alquil–amino, donde el término "alquilo" es tal como se ha definido previamente aquí y el término "amino"

es $-NH_2$, –NH–, o –N<. Ejemplos no limitativos incluyen $-CH_3NH-$, CH_3CH_2NH-, (alquilo C_1-C_3)NH–, (alquilo $C_1-C_3)_2N-$, y similares.

El término "alquilamino" empleado solo o en combinación con otros términos, se define aquí, a menos que se indique lo contrario, como amin–alquilo, donde el término "alquilo" es tal como se definió previamente aquí y el término "amino" es $-NH_2$, –NH–, o –N<. Ejemplos no limitativos incluyen $-NHCH_3$, $-NHCH_2CH_3$, –NH(alquilo C_1-C_3), –N(alquilo $C_1-C_3)_2$, y similares.

En algunas realizaciones de la invención, R^1 y R^2 son ambos arilo. En algunas realizaciones, R^1 y R^2 son ambos heteroarilo. En algunas realizaciones, R^1 es arilo y R^2 es heteroarilo. En algunas realizaciones de la invención, por lo menos un arilo es fenilo. En algunas realizaciones, por lo menos un heteroarilo es piridinilo, pirimidinilo, piridazinilo, tiazolilo, pirazolilo, indazolilo, tiofenilo, furanilo, o benzofuranilo. En algunas realizaciones, ambos arilos son fenilo. En algunas realizaciones, ambos heteroarilos están seleccionados del grupo que consiste en piridinilo, pirimidinilo, piridazinilo, tiazolilo, pirazolilo, indazolilo, tiofenilo, furanilo, y benzofuranilo.

En algunas realizaciones de la invención, por lo menos un arilo o heteroarilo está sustituido tal como ha sido descrito previamente. En algunas de dichas realizaciones, los 1, 2, o 3 substituyentes están independientemente seleccionados del grupo que consiste en metilo, metoxi, dimetilamin–etoxi, amino, metilamino, dimetilamino, ciano, cloro, fluor, furanilo y tiofenilo.

En algunas realizaciones, R^1 y R^2 están cada uno independientemente seleccionados del grupo que consiste en fenilo, 3 o 4–metil–fenilo, 3 o 4–cloro–fenilo, 3 o 4–fluor–fenilo, 3 o 4–dimetilamin–etoxi–fenilo, 3 o 4–dimetilamin–fenilo, 3 o 4–ciano–fenilo, 3–(5–metil–[1,2,4]oxadiazol–3–il)–fenilo, 1*H*–indol–5–ilo, 1*H*–indol–6–ilo, 1*H*–benzimidazol–5–ilo, piridilo, 2–piridilo, 4–piridilo, 4– o 5–metil–piridin–2–ilo, 6–metil–piridin–2–ilo, 6–cloro–piridin–2–ilo, pirazin–2–ilo, tiazol–2–ilo, 5–(tiofen–2–il)–*1H*–pirazol–3–ilo, 1–metil–5–(tiofen–2–il)–*1H*–pirazol–3–ilo, 5–(furan–2–il)–1–metil–*1H*–pirazol–3–ilo, indazol–3–ilo, 2–metil–*2H*–indazol–3–ilo, benzofuranilo, benzofuran–5–ilo.

En algunas realizaciones, el compuesto de la presente invención es un compuesto descrito en la Sección Experimental siguiente. En algunas realizaciones, el compuesto es uno de la Tabla 1, 2, 3, o 4, siguiente.

En algunas realizaciones de la invención, R^1 y R^2 son ambos arilo. En algunas realizaciones, R^1 y R^2 son ambos heteroarilo. En algunas realizaciones, R^1 es

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arilo y R^2 es heteroarilo. En algunas realizaciones, cualquiera de R^1 o R^2 es heteroarilo. En algunas realizaciones, cualquiera de R^1 o R^2 es arilo.

En algunas realizaciones de la invención , por lo menos un arilo es fenilo. En algunas realizaciones, por lo menos un heteroarilo es benzofuranilo, benzo[c]isoxazolilo, benzooxazolilo, benzotiazolilo, dihidrotieno[3,4–b][1,4]dioxinilo, furanilo, imidazo[1,2–a]piridinilo, indazolilo, indolinilo, indolilo, isoquinolinilo, isoxazolilo, naftiridinilo, oxazolilo, pirazinilo, pirazolilo, piridazinilo, piridinilo, pirimidinilo, pirrolo[3,2–c]piridina, quinolinilo, quinoxalinilo, tiazolilo, o tiofenilo.

En algunas realizaciones, ambos arilos son fenilo. En algunas realizaciones, ambos heteroarilos están seleccionados de un grupo que consiste en por lo menos un heteroarilo que es benzofuranilo, benzo[c]isoxazolilo, benzoxazolilo, benzotiazolilo, dihidrotieno[3,4–b][1,4]dioxinilo, furanilo, imidazo[1,2–a]piridinilo, indazolilo, indolinilo, indolilo, isoquinolinilo, isoxazolilo, naftiridinilo, oxazolilo, pirazinilo, pirazolilo, piridazinilo, piridinilo, pirimidinilo, pirrolo[3,2–c]piridinilo, quinolinilo, quinoxalinilo, tiazolilo, o tiofenilo.

En algunas realizaciones, el heteroarilo es piridinilo, y el piridinilo está mono–, di–, o tri–sustituido tal como se ha definido previamente. En algunas realizaciones, las mono–, di–, o tri–sustituciones son independientemente heteroarilo, heterociclilo, heterociclilo–R^3, –NHR^3, –N(alquilo)R^3, donde R^3 e tal como se ha definido previamente.

En algunas realizaciones de la invención , R^1 es arilo o heteroarilo y R^2 es cicloalquilo, cetocicloalquilo o heterociclilo. En algunas realizaciones, cualquiera de R^1 o R^2 es cicloalquilo. En algunas realizaciones, por lo menos un cicloalquilo es ciclobutilo, ciclohexilo, ciclopentilo, o ciclopropilo. En algunas realizaciones, el cicloalquilo está además sustituido más allá de la tri–sustitución previamente definida, es decir, el cicloalquilo está sustituido más de tres veces tal como se ha descrito previamente, por ejemplo, el cicloalquilo está tetra–sustituido con flúor.

En algunas realizaciones de la invención, por lo menos un cicloalquilo, cetocicloalquilo, heterociclilo, arilo, o heteroarilo está sustituido tal como se ha definido previamente. En algunas realizaciones los 1, 2, o 3 sustituyentes están independientemente seleccionados del grupo que consiste en metilo, metoxi, dimetilamin–etoxi, amino, metilamino, dimetilamino, ciano, cloro, fluor, furanilo y tiofenilo.

En algunas realizaciones, los mono–, di–, o tri–sustituyentes están independientemente seleccionados del grupo que consiste en amino, cloro, ciano, dimetilamino, dimetilamin–etoxi, metilo, metilamino, metoxi, fluor, $–C(O)NHCH_3$, furanilo, pirrolidinilo, tiofenilo y trifluormetilo.

En algunas realizaciones, el compuesto de la presente invención es un compuesto descrito en la Sección Experimental siguiente. En algunas realizaciones, el compuesto es uno de la Tabla 1, Tabla 2, Tabla 3 o Tabla 4, siguiente.

Otro aspecto de la presente invención es una composición que comprende una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con la presente invención, y un portador o excipiente farmacéuticamente aceptable.

Una composición de la presente invención puede adaptarse a cualquier modo de administración, tal como por vía oral (incluyendo sublingual), a través de implantos, parenteralmente (incluyendo inyecciones intravenosas, intraperitoneales, intraarticulares y subcutáneas), rectalmente, intranasalmente, tópicamente, ocularmente (a través de gotas para los ojos), vaginalmente, y transdermicamente.

Un compuesto de la presente invención puede usarse como una base libre o en forma de una sal derivada de ácidos o bases farmacéuticamente aceptables. La sal incluye sin limitación las siguientes: sales con ácidos inorgánicos, por ejemplo, sales con ácidos inorgánicos, por ejemplo, ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, y ácido fosfórico, y ácidos orgánicos, por ejemplo, ácido acético, ácido oxálico, ácido cítrico, ácido tartárico, ácido succínico, ácido maleico, ácido benzoico, ácido bencen–sulfónico, ácido fumárico, ácido málico, ácido metan sulfónico, ácido pamoico, y ácido para–toluen sulfónico. Otras sales incluyen sales com metales álcali o metales alcalino térreos, por ejemplo, sodio, potasio, calcio, y magnesio, o con bases orgánicas, incluyendo sales de amonio cuaternarias. Ejemplos adicionales no limitativos de sales de adición de ácidos orgánicos e inorgánicos farmacéuticamente aceptables incluyen aquellos citados en [S.M. Berge *et al.*, *J. Pharm. Sci.* **1977**, *66,* 1: 2, y G.S. Paulekuhn, *et al.*, *J. Med. Chem.* **2007**, *50*, 26: 6665–6672].

Un compuesto de la presente invención puede usarse también en forma de un éster, carbamato, y otra forma de profármaco convencional, que generalmente consistirá en un derivado funcional del compuesto que es rápidamente convertido a la porción activa *in vivo*. Asimismo, se incluyen los metabolitos de un

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compuesto de la presente invención definidos como especies activas producidas por introducción del compuesto en un sistema biológico.

Cuando se emplea un compuesto de la presente invención tal como se describió anteriormente, puede combinarse con uno o más excipientes o portadores farmacéuticamente aceptables, por ejemplo, solventes, diluyentes y similares. Dichas preparaciones farmacéuticas pueden administrarse oralmente en formas tales como tabletas, cápsulas (incluyendo por ejemplo, formulaciones de liberación regulada y de liberación prolongada) pastillas, caramelos, aerosoles, polvos dispersables, granulados, soluciones, suspensiones (que contienen por ejemplo, un agente suspendedor, a, por ejemplo, desde aproximadamente, 0,05 hasta aproximadamente 5% de agente suspendedor), jarabes, (que contienen por ejemplo, azúcar o sustitutos de azúcar tales como aspartamo, a, por ejemplo, aproximadamente 10 hasta aproximadamente 50% de azúcar o sustituto de azúcar), elixires y similares, o parenteralmente en forma de soluciones inyectables, suspensiones, o emulsiones estériles que contienen por ejemplo, desde aproximadamente 0,05 hasta aproximadamente 5% de agente suspendedor en un medio isotónico. Dichas preparaciones pueden contener, por ejemplo, desde aproximadamente 25 hasta aproximadamente 90% del ingrediente activo en combinación con el portador, más habitualmente desde aproximadamente 5% y aproximadamente 60% en peso. La dosis eficaz de ingrediente activo empleado (por ejemplo, un compuesto o sal de la presente invención y un profármaco o metabolito del mismo) que se emplea puede variar dependiendo del compuesto particular, sal, profármaco o metabolito usado, el modo de administración, edad, peso, sexo y el estado médico del paciente, y la gravedad de la enfermedad, trastorno, afección, y/o sistema que se está tratando. La selección de la administración apropiada y la forma de dosificación para un mamífero individual resultará aparente para aquellos expertos en la materia. Dichas determinaciones son rutinarias para un médico, veterinario o clínico de experiencia normal en la materia (ver, por ejemplo, *Harrison's Principles of Internal Medicine*, Anthony Fauci *et al.* (eds.) 14th ed. New York: McGraw Hill (1998)). Además, el régimen de dosificación puede ajustarse para proporcionar una respuesta terapéutica óptima. Por ejemplo, pueden administrarse diariamente varias dosis divididas o bien la dosis puede ser proporcionalmente reducida según se indiquen las necesidades de la situación terapéutica.

Los portadores sólidos, por ejemplo, almidón, lactosa, fosfato dicálcico, celulosa microcristalina, sucrosa y caolín, portadores líquidos, por ejemplo, agua

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estéril, polietilen glicoles, glicerol, surfactantes no–iónicos y aceites comestibles tales como aceites de maíz, maní, y de sésamo, pueden emplearse según sean apropiados para la naturaleza del ingrediente activo y la forma particular deseada de administración. Pueden incluirse ventajosamente coadyuvantes empleados usualmente en la preparación de composiciones farmacéuticas. Ejemplos no limitativos de coadyuvantes incluyen agentes saborizantes, agentes colorantes, agentes preservadores, y antioxidantes, tales como vitamina E, ácido ascórbico, BHT y BHA.

Un compuesto activo puede administrarse también parenteralmente o intraperitonealmente. Las soluciones o suspensiones del compuesto activo en forma de base libre, compuesto neutro o sal farmacéuticamente aceptable pueden prepararse en agua mezclada convenientemente con un surfactante tal como hidroxipropilcelulosa. La dispersión puede también prepararse en glicerol, polietilen glicoles líquidos y mezclas de los mismos en aceites. Estas preparaciones pueden contener un preservante para prevenir el desarrollo de microorganismos bajo condiciones comúnes de almacenamiento y uso.

Las formas farmacéuticamente apropiadas para uso inyectable o para infusión incluyen soluciones, suspensiones o dispersiones acuosas estériles, y polvos estériles para la preparación extemporánea de soluciones inyectables o de infusión estériles, suspensiones o dispersiones. En todos los casos, la forma debe ser estéril, y debe ser fluida hasta el grado de que exista una fácil inyectabilidad e infusión. Debe ser estable bajo condiciones de manufactura y almacenamiento y debe preservarse contra la acción contaminante de microorganismos. El portador puede ser un medio solvente o de dispersión que contiene por ejemplo, agua, etanol, y poliol (por ejemplo, glicerol, propilen glicol, y polietilen glicol líquido), mezclas apropiadas de los mismos y aceites vegetales.

Además, los compuestos activos de la presente invención pueden administrarse intranasalmente o transdérmicamente usando vehículos apropiados para liberación intranasal o transdermica conocidas por los expertos en la materia. La administración transdérmica incluye todas las administraciones a través de la superficie del cuerpo y de las túnicas internas de pasajes corporales incluyendo tejidos epiteliales y mucosales, usandos sistemas portadores tales como lociones, cremas, espumas, pastas, parches, suspensiones, soluciones y supositorios (rectal y vaginal). Las cremas y ungüentos pueden ser emulsiones viscosas líquidas o semisólidas de cualquiera de los tipos de aceite en agua o agua en aceite. También pueden ser apropiadas pastas constituidas por polvos

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absorbentes dispersados en petróleo o en petróleo hidrofílico que contiene el ingrediente activo. Pueden usarse una variedad de dispositivos oclusivos para liberar el ingrediente activo dentro de la corriente sanguínea tal como una membrana semi–permeable que cubra un reservorio que contiene el ingrediente activo con o sin portador, o una matriz que contiene el ingrediente activo. Otros dispositivos oclusivos son conocidos en la literatura. Cuando se usa un sistema de liberación transdérmica, la administración de la dosis será continua en vez de dosis únicas o divididas diarias

Un compuesto de la presente invención puede administrarse también en forma de un sistema de liberación de liposomas donde la bicapa lípida liposomal se forma de una variedad de fosfolípidos. Un compuesto de la presente invención puede ser liberado mediante el uso de un portador tal como anticuerpos monoclonales a los cuales se acopla el compuesto. Otros portadores a los cuales el compuesto de la presente invención puede acoplarse también son un polímero soluble o un polímero biodegradable útil para lograr la liberación controlada de un ingrediente activo.

Los que llevan a la práctica la técnica pueden comprender que algunos de los compuestos de la presente invención pueden contener uno o más centros asimétricos, y por lo tanto pueden dar lugar a enantiómeros y diastereómeros. La presente invención incluye todos los estereoisómeros incluyendo diaestereómeros individuales y resueltos, estereoisómeros enantioméricamente puros, así como también racematos, y todas las otras variaciones de estereoisómeros, y mezclas y sales farmacéuticamente aceptables de los mismos, que poseen la actividad indicada. Los isómeros ópticos pueden obtenerse en forma pura mediante procedimientos usuales conocidos por los expertos en la materia, e incluyen, pero no están limitados a separaciones cromatográficas quirales, formación de sal diaestereomérica, resolución cinética, y sintesis asimétrica. Se comprenderá también que esta invención abarca todos los posibles regioisomeros, endo–exo isómeros, y mezclas de los mismos que poseen la actividad indicada. Dichos isómeros pueden obtenerse en forma pura mediante procedimientos usuales conocidos por aquellos expertos en la materia, e incluyen pero no están limitados a, cromatografía en columna, cromatografía de capa delgada, y cromatografía líquida de alto rendimiento. Los que llevan a la práctica la materia comprenderán que algunos de los compuestos de la presente invención pueden ser quirales debido a la rotación impedida, y dan lugar a atropisómeros, los cuales pueden resolverse y obtenerse en forma pura mediante

procedimientos usuales conocidos por aquellos expertos en la materia. Los que llevan a la práctica la materia comprenderán también que algunos compuestos de la presente invención incluyen isómeros estructurales, incluyendo tautómeros.

Se incluyen también en esta invención todos los polimorfos e hidratos de los compuestos de la presente invención.

Otro aspecto de la presente invención es un método para el uso de los compuestos de la invención . Se comprenderá que la invención abarca el uso simultáneos, consecutivo o separado de cualquier combinación de los compuestos de la invención con cualquier composición farmacéutica útil en los métodos descritos aquí.

En algunas realizaciones, el método incluye administrar una cantidad eficaz de una combinación de dos o más compuestos descritos aquí, o sales de los mismos. Se pretende específicamente que las frases "combinación de dos o más de los compuestos descritos aquí, o sales de los mismos," o "por lo menos un compuesto tal como se describe aquí, o una sal farmacéuticamente aceptable del mismo," o lenguaje similar que describe compuestos específicos, incluyendo la administración de dichos compuestos en cualquier proporción y combinación de sal, formas de base neutra o libre; es decir, es decir incluye la administración de dichos compuestos, cada uno en forma de base, cada uno en forma neutra o cada uno en forma salina o uno o más en la forma básica y uno o más en la forma neutra, o uno o más en la forma básica y uno o más en la forma salina o uno o más en la forma neutra y uno o más en la forma salina, en cualquier proporción de los compuestos y/o sales neutros y/o básicos.

Tal como se usa aquí, la frase "cantidad eficaz" cuando se aplica a un compuesto de la invención, está destinada a denotar una cantidad suficiente que cause un efecto biológico determinado. La frase "cantidad terapéuticamente eficaz" cuando se aplica a un compuesto de la invención pretende denotar una cantidad del compuesto que es suficiente para mejorar, paliar, estabilizar, revertir en forma lenta o demorada el avance de un un trastorno o enfermedad o de un síntoma del trastorno o enfermedad. En algunas realizaciones, el método de la presente invención provee la administración de combinaciones de los compuestos. En dichos casos, la "cantidad eficaz" es la cantidad de la combinación suficiente para causar el efecto biológico propuesto.

El término "tratamiento" o "tratar" tal como se usa aquí significa curar, mejorar, o invertir el progreso de una enfermedad o trastorno o mejorar o invertir uno o

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más síntomas o efectos secundarios de dicha enfermedad o trastorno. "Tratamiento o tratar" tal como se usa aquí significa inhibir o bloquear, así como también retardar, detener, restringir, impedir u obstruir, el progreso de un sistema, condición o estado de una enfermedad o trastorno. Para los propósitos de esta invención, "tratamiento" o "tratar" significa además una realización para obtener resultados clínicos beneficiosos o deseados, donde "resultados clínicos deseados o beneficiosos" incluyen sin limitación alivio de un síntoma, disminución del grado de un trastorno o enfermedad, estado del trastorno o enfermedad estabilizado, (es decir, que no empeora), demorar o enlentecer una enfermedad o un trastorno, mejorar o paliar una enfermedad o trastorno y la remisión de una enfermedad o trastorno, ya sea parcial o total, detectable o indetectable.

El término "prevenir" o "previniendo" tal como se usa aquí significa impedir que ocurra o exista. El término "administrar" tal como se usa aquí se refiere a la administración directa de un compuesto de la presente invención o bien a la administración de un profármaco, derivado, o análogo del mismo, que formarán una cantidad eficaz de un compuesto dentro de un mamífero.

La presente invención provee también un método para el tratamiento de una enfermedad o trastorno, donde dicho método comprende administrar una cantidad terapéuticamente eficaz de por lo menos un compuesto de la presente invención o una sal farmacéuticamente aceptable del mismo a un mamífero que lo necesita, donde la enfermedad o trastorno es una enfermedad o trastorno del sistema nervioso central.

Un compuesto de la presente invención puede modular aloestéricamente el receptor mGlu5. Un modulador aloestérico que mejora o que potencia la afinidad de un ligando ortoestérico para el receptor mGluR5 y/o que realza o potencia una eficacia de agonista ortoestérico es un mejorador alostérico (o potenciador) o un modulador alostérico positivo (PAM). Ver por ejemplo, May, L.T. *Annu. Rev. Pharmacol. Toxicol.* **2007,** *47,* 1–51. Un modulador alostérico que reduce o disminuye la afinidad de un ligando ortostérico para el receptor mGluR5 y/o que reduce o disminuye una eficacia de un agonista ortostérico es un antagonista alostérico (o inhibidor) o un modulador alostérico negativo (NAM). *Id.*

En algunas realizaciones, el mamífero del método de la invención es un ser humano.

En algunas realizaciones del método de la invención, la enfermedad o trastorno del sistema nervioso central es una enfermedad o trastorno cognitivo,

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neurodegenerativo, psiquiátrico, o neurológico. En algunas de dichas realizaciones, el trastorno o enfermedad cognitivo, neurodegenerativo, psiquiátrico, o neurológico está seleccionado de un grupo que consiste en un trastorno del talante, un transtorno de ansiedad, esquizofrenia (incluyendo trastornos esquizoafectivos), enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis múltiple, corea de Huntington, esclerosis lateral amiotrófica, enfermedad de Creutzfeld–Jakob, neurodegeneración inducida por trauma, encafalopatía inducida por SIDA, otra encefalopatía relacionada con infección (es decir, una encefalopatía no inducida por SIDA), síndrome X Frágil, un trastorno en el espectro de autismo, y una combinación de los mismos.

Tal como se usa aquí, la frase "trastorno del talante" se refiere a cualquiera de varios trastornos psicológicos que se caracterizan por anormalidades de estados emocionales, tales como, sin limitación, trastornos bipolares, trastornos depresivos, trastornos ciclotímicos, trastornos distímicos, trastornos del talante debidos a una afección médica general, trastorno del talante no especificados y trastornos del talante inducidos por sustancias; y caracterizado por el *Diagnostic y Statistical Manual of Mental Disorders*, Fourth Edition (DSM–IV) (American Psychiatric Association: Arlington, VA, 1994).

Tal como se usa aquí, la frase "trastorno de espectro de autismo" (ASD) se refiere al trastorno que causa daños graves y pervasivos en el pensamiento, en sentimiento, el lenguaje y la capacidad de relacionarse con los demás, el cual es a menudo diagnosticado primero en la temprana infancia y van desde una forma grave, denominada "trastorno autistico" (autismo "clásico"), a través de un trastorno de desarrollo pervasivo no especificado de otra manera (PDD–NOS), hasta una forma mucho más leve, síndrome de Asperger. La frase tal como se usa aquí, incluye también síndrome de Rett y trastorno desintegrante de la infancia, y tal como se usa aquí, es sinónimo de la frase "trastornos de desarrollo pervasivo" (PDDs).

En algunas realizaciones, el trastorno del talante es una depresión (es decir, un trastorno depresivo). En muchas de dichas realizaciones, la depresión está seleccionada del grupo que consiste en depresión atípica, depresión bipolar, depresión unipolar, depresión principal, depresión endógena (es decir, depresión aguda sin causa obvia), depresión involucional (es decir, depresión que ocurre a mediados de la vida, o en la gente mayor) depresión reactiva (es decir, depresión causada por un episodio traumático obvio de la vida), depresión de post–parto, depresión primaria (es decir, depresión que no tiene causa física o psicológica tal

como una enfermedad o trastorno médico), depresión psicótica y depresión secundaria (es decir, depresión que parece ser causada por algunas otras alteraciones subyacentes, tal como otra enfermedad o trastorno médico).

En algunas de dichas realizaciones, la enfermedad o trastorno de ansiedad está seleccionada del grupo que comprende trastorno de ansiedad generalizada, ansiedad por pánico, trastorno obsesivo compulsivo, fobia social, ansiedad por estado general, trastorno por estrés post–traumático, reacción de estrés aguda, trastorno de ajuste, trastorno hipocondríaco, un trastorno de ansiedad por separación, agorafobia, una fobia específica, un trastorno de ansiedad debido a una afección médica general, trastorno de ansiedad inducida por sustancia, ansiedad inducida por abstinencia de alcohol y una combinación de los mismos.

En algunas realizaciones, la enfermedad o trastorno del sistema nervioso central del método de la invención es una enfermedad o trastorno apopléjico. En algunas realizaciones, la enfermedad o trastorno apopléjico está seleccionado del grupo que consiste en convulsión, epilepsia, estado epiléptico, y una combinación de los mismos.

En algunas realizaciones, la enfermedad o trastorno del sistema nervioso central del método de la invención es un trastorno o enfermedad dolorosa seleccionada del grupo que consiste en dolor inflamatorio, dolor neuropático y dolor de migraña. En algunas realizaciones, el dolor neuropático o trastorno o enfermedad de dolor de migraña está seleccionado del grupo que consiste en alodinia, dolor hiperalgésico, dolor fantasma, dolor neuropático relacionado con neuropatía diabética, dolor neuropático relacionado con migraña, y una combinación de los mismos.

En algunas realizaciones, la enfermedad o trastorno del sistema nervioso central del método de la invención es una enfermedad o trastorno de un estado de hiperexitación neuronal. En algunas realizaciones, el estado o trastorno de hiperexitación neuronal es un estado de hiperexitación neuronal por retiro de medicamento, un estado de hiperexitación neuronal en intoxicaciones, o una combinación de los mismos.

En algunas realizaciones del método de la invención, se trata por lo menos un síntoma de la enfermedad o trastorno cognitivo neurodegenerativo psiquiático o neurológico.

En algunas realizaciones, la enfermedad o trastorno cognitivo, neurodegenerativo, psiquiátrico o neurológico es una depresión. En algunas de

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dichas realizaciones, el por lo menos un síntoma de la depresión es sensación de depresión, talante deprimido, pérdida de interés o placer en alguna o todas las actividades, cambios en el apetito, cambios en el peso, cambios en los patrones del sueño, falta de energía, fatiga, baja autoestima, capacidad disminuida para pensar, concentrarse o decidir, sentimientos de desilución o inutilidad, agitación o retardo psicomotores, auto–reproche, culpamiento inapropiado, frecuentes pensamientos de muerte o suicidio, planes o intentos para cometer suicidio o una combinación de los mismos.

En algunas realizaciones, la enfermedad o trastorno cognitivo, neurodegenerativo, psiquiátrico o neurológico es un trastorno de ansiedad. En algunas de dichas realizaciones, el por lo menos un síntoma de ansiedad es aprehensión, miedo, temblor, dolores musculares, insomio, malestares abdominales, mareos, irritabilidad, pensamientos persistentes, recurrentes, compulsiones, palpitaciones cardíacas, dolor torácico, molestia torácica, transpiración, sensaciones de hormigueo, sensación de ahogo, miedo a la pérdida de control, retrocesos, pesadillas, pensamientos intrusivos, recuerdos intrusivos, comportamientos de evitación, aturdimiento emocional e incapacidad de dormir, sentimientos de ansiedad, respuesta hiperactiva de sobresaltos, hipervigilia, explosión de cólera, lipotimia, sonrojo, transpiración profusa o una combinación de los mismos.

En algunas realizaciones, la enfermedad o trastorno cognitivo, neurodegenerativo, psiquiátrico o neurológico es esquizofrenia. En algunas de dichas realizaciones, el por lo menos un síntoma de esquizofrenia es un síntoma positivo seleccionado del grupo que consiste en alucinación, delirio, paranoia, y una combinación de los mismos. En algunas de dichas realizaciones, el síntoma de esquizofrenia es un síntoma negativo seleccionado del grupo que consiste en retraimiento social, sentimiento de abatimiento, anhedonia, motivación disminuida y una combinación de los mismos. En algunas de dichas realizaciones, el síntoma de esquizofrenia es un síntoma cognitivo seleccionado del grupo que consiste en déficit grave de atención, déficit grave en la denominación de objetos, grave déficit en el funcionamiento de la memoria, grave déficit en el almacenamiento a largo término en la memoria, grave déficit en el funcionamiento ejecutivo, un enlentecimiento del proceso de información, un enlentecimiento de la actividad neural, depresión a largo término y una combinación de los mismos.

En algunas realizaciones del método de la invención, la enfermedad o trastorno cognitivo, neurodegenerativo, psiquiátrico o neurológico es la

enfermedad de Parkinson. En algunas de dichas realizaciones, el por lo menos un síntoma de la enfermedad de Parkinson es disquinecia inducida por levodopa, falta de equilibrio, paso lento parkinsoniano, bradiquinesia, rigidez, temblor, cambio en el habla, pérdida de la expresión facial, micrografía, dificultad para tragar, babeo, dolor, demencia, confusión, disturbio del sueño, constipación, problemas de piel, depresión, temor, ansiedad, dificultad de la memoria, raciocinio lento, disfunción sexual, problema urinario, fatiga, dolor, pérdida de energía o una combinación de los mismos.

En algunas realizaciones, la enfermedad o trastorno cognitivo, neurodegenerativo, psiquiátrico o neurológico es la enfermedad deAlzheimer. En algunas de dichas realizaciones, el por lo menos un síntoma de enfermedad de Alzheimer es la alteración de la memoria, la alteración de la atención, la alteración del juicio, la alteración en la toma de decisiones, la alteración en la orientación de contornos físicos, alteración del lenguaje, la alteración de las actividades que dependen del habla, alteración del razonamiento abstracto, alteración en las capacidades visoespaciales, alteración en el funcionamiento ejecutivo, alteración en los trastornos de comportamiento, desinterés y pasividad, apatía, acicalamiento inapropiado, autocuidado defectuoso, agitación, explosión violenta, agresión, depresión, ansiedad, alucinación, delirio, cambios en la personalidad, cambios en el talante, demencia o combinación de los mismos.

En algunas realizaciones, de a enfermedad o trastorno cognitivo, neurodegenerativo, psiquiátrico o neurológico es esclerosis múltiple. En algunas de dichas realizaciones, el por lo menos un síntoma de esclerosis múltiple es visión borrosa por neuritis óptica, dolor en los ojos, pérdida del color de la visión, ceguera, visión doble por dipoplia, movimientos de nistagmus rítmico oculares, dismetría ocular, movimientos oculares sub– o hiperfulgurantes, oftalmoplejía internuclear, nistagmus, diplopia, fosfenos con movimiento y sonido, diplopia, defecto pupilar aferente, paresia motora, monoparesia, paraparesia, hemiparesia, cuadraparesia plejía, paraplejía, hemiplejía, tetraplejía, cuadraplejía, espasiticidad, disartria, atrofia muscular, espasmos, calambres, hipotonia, clono, mioclono, mioquimia, síndrome de pierna inquieta, reflejos disfuncionales de pie extendido (MRSs, Babinski's, Hoffman's, Chaddock's), parestesia, anestesia, neuralgia, dolor neuropático, dolor neurogénico, l'hermitte's, disfunción propioceptiva, neuralgia trigeminal, ataxia, temblor intencional, dismetria, ataxia vestibular, vértigo, ataxia del habla, distonia, disdiadocoquinesia, micción frecuente, espasticidad de la vejiga, vejiga fláccida, disinergia de esfínter

detrusor, disfunción eréctil, anorgasmo, eyaculación retrograda, frigidez, constipación, urgencia fecal, depresión, disfunción cognitiva, demencia, cambios de talante, labilidad emocional, euforia, síndrome bipolar, ansiedad, afasia, disfagia, fatiga, síntoma de uhthoffs, reflujo gastroesofágico, trastorno del sueño, o una combinación de los mismos.

La presente invención provee un método para tratar el reflujo gastroesofagico, donde dicho método comprende administrar una cantidad terapéuticamente eficaz de por lo menos un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo a un mamífero que lo necesita.

La presente invención provee además un método para tratar la dependencia al alcohol, el método comprende administrar una cantidad terapéuticamente eficaz de por lo menos un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo a un mamífero que lo necesita.

En algunas realizaciones, el compuesto de la presente invención se usa en la preparación de un medicamento para el tratamiento de una enfermedad o trastorno del sistema nervioso central. En algunas realizaciones, la enfermedad o trastorno del sistema nervioso central es tal como se ha definido previamente.

Otro aspecto de la presente invención es un procedimiento para producir los compuestos de la presente invención.

PREPARACION DE LOS COMPUESTOS DE LA PRESENTE INVENCION

Los compuestos de la presente invención pueden prepararse, sin limitación, de acuerdo con uno de los métodos generales descritos a continuación. Por ejemplo, los Esquemas 1–11 que siguen son una ilustración de algunas realizaciones de la invención y los mismos no implican una limitación de la presente invención.

Lo que sigue a continuación define acrónimos tal como se usan aquí a menos que se especifique de otra forma lo contrario en un caso particular.

BOP = hexafluorfosfato de benzotriazol–1–il–oxi–tris–(dimetilamino)–fosfonio, CAS No. 56602–33–6

DCM = cloruro de diclorometano o metileno

DIEA = *N,N*–diisopropiletilamina, CAS No. 7087–68–5

DMA = *N,N*–dimetilacetamida, CAS No. 127–19–5

DMC = cloruro de dimetilimidazolinio

DMF = *N,N*–dimetilformamida, CAS No. 68–12–2

DPPA = azida de difenilfosforilo, CAS No. 26386–88–9

EDCI = Clorhidrato de *N*–etil–*N'*–(3–dimetilaminopropil)carbodiimida, CAS No. 93128–40–6

HBTU = hexafluorfosfato de 2–(1*H*–benzotriazol–1–il)–1,1,3,3–tetrametiluronio, CAS No. 94790–37–1

NMP = *N*–metil–pirrolidona, CAS No. 872–50–4

PyBOP = hexafluorfosfato de benzotriazol–1–il–oxitripirrolidinofosfonio, CAS No. 128625–52–5

RT o rt = temperatura ambiente

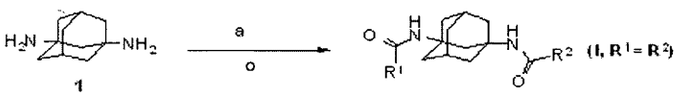
TBTU = tetrafluorborato de O–(benzotriazol–1–il)–N,N,N',N'–tetrametiluronio, CAS No. 125700–67–6

TEA = trietanolamina, CAS No. 102–71–6

THF = tetrahidrofurano, CAS No. 109–99–9

Pueden prepararse amidas simétricas de fórmula (I) ($R^1 = R^2$) *a través* del procedimiento descrito en el **Esquema 1** usando procedimientos de amidación convencionales a partir del compuesto **1** comercialmente obtenible, adamantan–1,3–diamina, donde R^1 es igual a R^2, y R^1 y R^2 son tal como se describieron aquí previamente.

Esquema 1

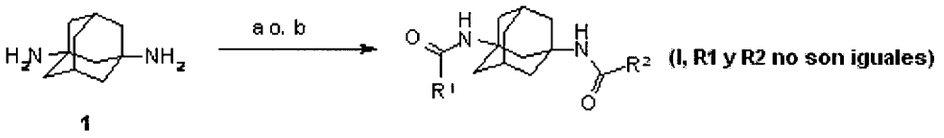


a) R^1CO_2H, PyBOP (o BOP o. EDCI), N,N diisopropiletilamina (DIEA) o Et_3N, CH_2Cl_2 (o THF o. DMF)
b) R^1COCl, DIEA o Et_3N, CH_2Cl_2

Pueden prepararse también amidas asimétricas de fórmula (I) ($R^1 \neq R^2$) *a través* de los procedimientos descritos en los **Esquemas 2 y 3**, donde R^1 y R^2 son tal como se han definido aquí previamente.

Esquema 2

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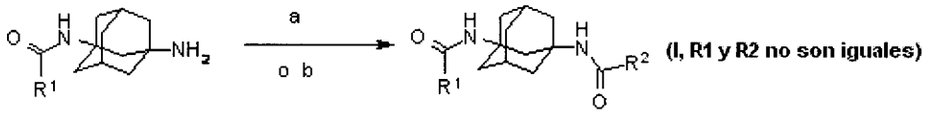


1

a) 1.1 eq. R^1CO_2H, 1.1 eq. R^2CO_2H, DIEA, PyBOP (o BOP, DMC, EDCI), CH_2Cl_2
b) 1.1 eq. R^1COCl, 1.1 eq. R^2COCl, DIEA, CH_2Cl_2

La amidación del compuesto **1** con una mezcla de R^1COCl y R^2COCl, o una mezcla de R^1CO_2H y R^2CO_2H usando procedimientos convencionales de amidación proporciona amidas asimétricas de fórmula (I).

Esquema 3



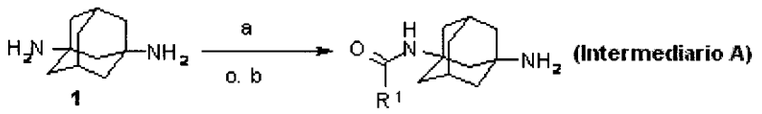
Intermediario A

a) R^2CO_2H, PyBOP (o. BOP or DMC o EDCI o. HBTU etc.), DIEA o TEA, CH_2Cl_2 (o THF o DMF o CH_3CN etc);
b) R^2COCl, DIEA o TEA, CH_2Cl_2; o' R^2COCl, aq. NaOH, THF/CH_2Cl_2

La amidación del Intermdiario A con R^2CO_2H o R^2COCl usando procedimientos de amidación convencionales proporciona amidas asimétricas de fórmula (I).

El Intermediario A puede prepararse *a través* de procedimientos descritos en los Esquemas 4–6.

Esquema 4

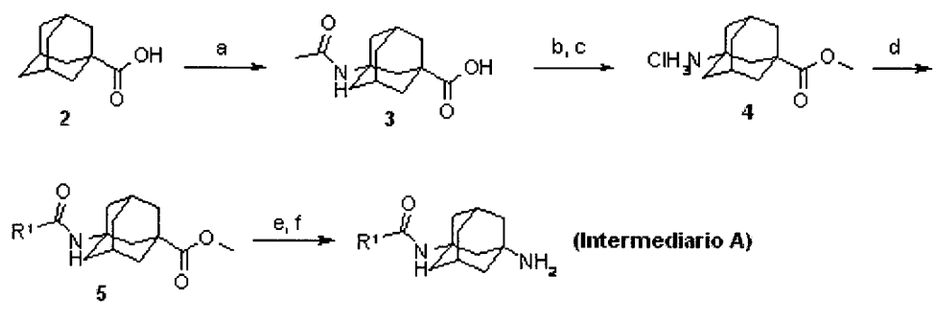


1

a) R^1CO_2H, PyBOP (o. BOP, DMC, EDCI), DIEA o TEA, CH_2Cl_2 (o THF, DMF, CH_3CN)
b) R^1COCl, DIEA, CH_2Cl_2 o. R^1COCl, aq. NaOH, THF/CH_2Cl_2

La amidación del compuesto **1** con R^1CO_2H o R^1COCl usando procedimientos de amidación convencionales proporciona el Intermediario A. El rendimiento de esta vía es inferior debido a la formación de bis–amidas.

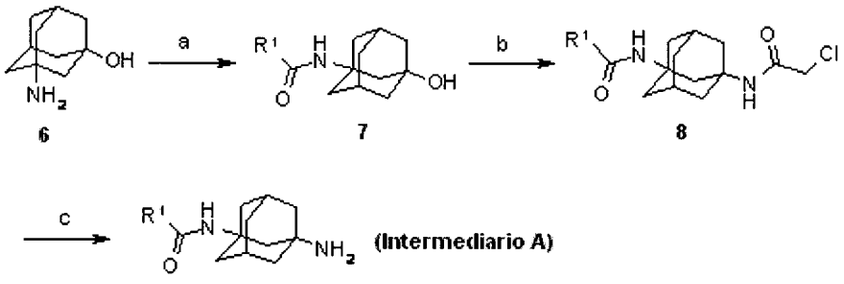
Esquema 5



a) H_2SO_4, HNO_3, MeCN; b) HCl, H_2O; c) $SOCl_2$, MeOH; d) R^1COCl, NEt_3, DCM; o, R^1CO_2H, PyBOP, NEt_3, DCM; e) LiOH, H_2O, THF; f) DPPA, NEt_3, Tolueno, luego HCl, H2O

El ácido 1–adamantancarboxílico comercialmente obtenible (compuesto **2**) puede convertirse a acetamida **3** *a través* de la reacción de Ritter. La hidrólisis del compuesto **3** bajo condiciones ácidas proporciona la sal de amina correspondiente, que se convierte luego a éster metílico **4.** La amidación convencional del compuesto **4** proporciona el compuesto **5**. La hidrólisis del éster **5** seguido de una reordenamiento de Curtius standard proporciona el Intermediario A.

Esquema 6

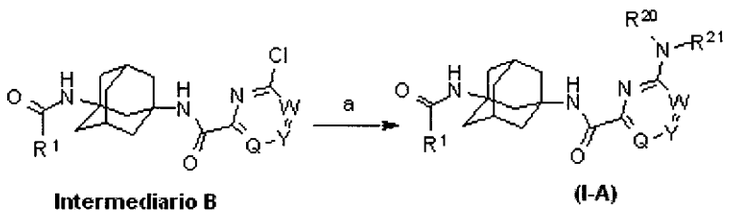


a) R^1CO_2H, HBTU, Et_3N, DMF; b) $ClCH_2CN$, H_2SO_4; c) Tiourea, , EtOH, HOAc, 80ºC

La amidación convencional de 3–amin–adamantan–1–ol comercialmente obtenible (compuesto **6**) proporciona monoamida **7**, que se convierte luego al compuesto **8** *a través* de la reacción de Ritter. La hidrólisis del compuesto **8** proporciona el Intermediario A.

Pueden prepararse amidas con grupos de solubilización (fórmula I–A, I–B y I–C) *a través* de los procedimientos descritos en los Esquemas 7–9.

Esquema 7

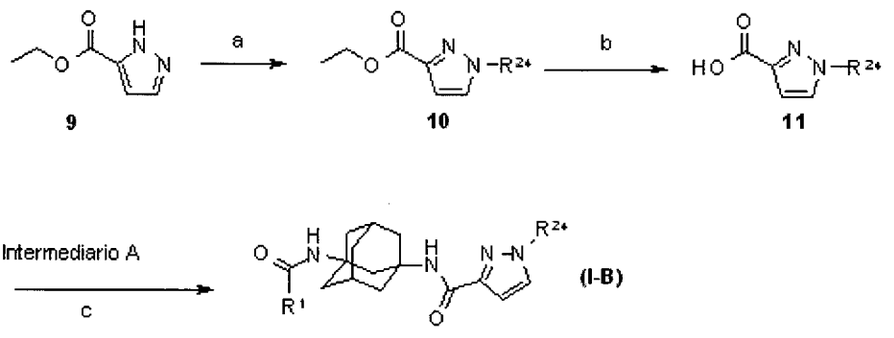


Intermediario B (I-A)

a) $(R^{20})NH(R^{21})$, K_2CO_3 or Cs_2CO_3, DMA o NMP, , horno microondas, 180°C

El desplazamiento de cloruro del Intermediario B con aminas $(R^{20})NH(R^{21})$ bajo condiciones básicas con irradiación de microondas proporciona compuestos de fórmula (I–A), donde R^{20} y R^{21} son alquilo o ligados conjuntamente para formar un heterociclo que está opcionalmente sustituido con hidroxilo, alcoxi, amina, alquilamina, dialquilamina, –C(O)NH–alquilo, –C(O)N(dialquilo), –NHC(O)–alquilo, –N(alquilo)–C(O)–alquilo; o uno de R^{20} y R^{21} es H y el otro es alquilo, cicloalquilo o heterociclo que está opcionalmente sustituido con hidroxilo, ciano, alcoxi, amina, alquilamina, dialquilamina, $–C(O)–NH_2$, –C(O)NH–alquilo, –C(O)N(dialquilo), –NHC(O)–alquilo, –N(alquilo)–C(O)–alquilo; Q, Y y W son CR^{23}, donde R^{23} es H, alquilo o cicloalquilo; o uno de Q, Y y W es nitrógeno.

Esquema 8



9 10 11

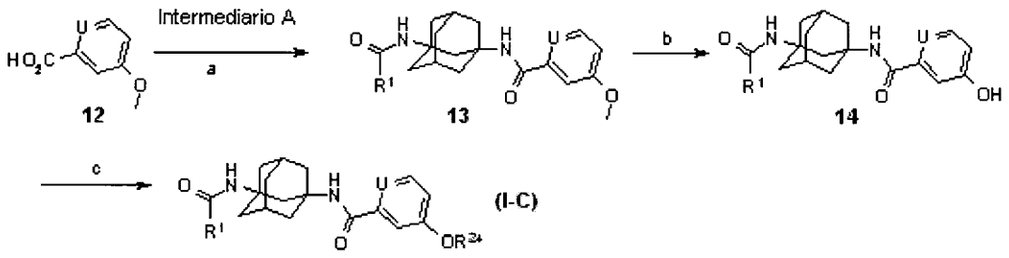
Intermediario A (I-B)

a) $R^{24}Br$ o $R^{24}OMs$ o $R^{24}OTs$, base, DMF; b) aq. NaOH, EtOH; c) Et_3N, PyBOP, DCM

La alquilación del compuesto **9** comercialmente obtenible con $R^{24}Br$, $R^{24}OMs$ o $R^{24}OTs$ bajo condiciones básicas tales como K_2CO_3 o Cs_2CO_3 en DMF proporciona el compuesto **10**. $R^{24}OMs$ o $R^{24}OTs$ puede prepararse fácilmente a partir del correspondiente $R^{24}OH$ y $MeSO_2Cl$ o cloruro de 4–metilbencensulfonilo. La saponificación del éster **10** proporciona el ácido carboxílico **11**. La amidación del compuesto **11** con el intermediario A usando procedimientos convencionales puede proporcionar compuestos de fórmula (I–B), donde R^{24} es alquilo, cicloalquilo o heterociclo que está opcionalmente sustituido con hidroxilo, alcoxi, amina, alquilamina, dialquilamina, –C(O)NH–alquilo, –C(O)N(dialquilo), –NHC(O)–alquilo, –N(alquilo)–C(O)–alquilo.

175

Esquema 9

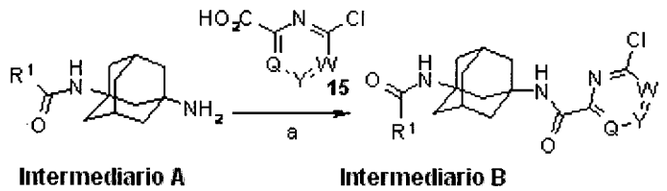


a) PyBOP, Et_3N, DCM; b) BBr_3, DCM;
c) $R^{24}OH$, Reacción Mitsonobu ; o $R^{24}Br$ ($R^{24}OMs$ or $R^{24}OTs$), base, DMF (o THF), 60-100ºC

La amidación convencional del ácido carboxílico **12** comercialmente obtenible con el Intermediario A proporciona el compuesto **13**, que mediante demetilación proporciona el compuesto **14**. La reacción Mitsunobu del compuesto **14** con $R^{24}OH$, o alquilación del compuesto **14** con $R^{24}Br$, $R^{24}OMs$ o $R^{24}OTs$ bajo condiciones básicas, tales como K_2CO_3 o Cs_2CO_3 en DMF, THF o CH_3CN, proporciona los compuestos de fórmula de (I–C), donde U es CH o N, y R^{24} es tal como se ha definido anteriormente.

El Intermediario B puede prepararse a través del procedimiento descrito a continuación en el Esquema 10.

Esquema 10

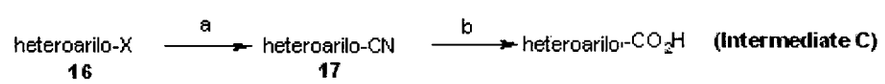


a) R^1CO_2H, PyBOP (o BOP o HBTU o EDCI o DMC), DIEA o Et_3N, DCM (o DMF o CH_3CN)

La amidación convencional del Intermediario A con el ácido carboxílico **15** proporciona el Intermediario B.

Los ácidos carboxílicos no obtenibles comercialmente pueden prepararse a través del procedimiento descrito a continuación en el Esquema 11.

Esquema 11



a) $Zn(CN)_2$, Ph_2-pentedienona Pd y $(Ph_2P)_2$-ferroceno, DMF, 100ºC
b) HCl, agua, reflujo, o 1) NaOH, agua, 90ºC; 2) HCl y agua

1720

El desplazamiento del halógeno X (X= F, Cl, Br o I) del compuesto **16** con ciano usando procedimientos convencionales, tales como $Zn(CN)_2$, y catalizador Ph_2–pentedienona Pd con ligando $(Ph_2P)_2$–ferroceno en DMF a 100 °C para proporcionar el compuesto **17**, que mediante hidrólisis bajo condiciones ácidas o básicas proporciona el Intermediario C.

SECCION EXPERIMENTAL

1. Métodos Generales

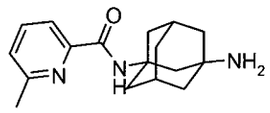
A menos que se especifique de otra forma, los procedimientos experimentales se llevan a cabo bajo las siguientes condiciones. Todas las operaciones se llevan a cabo a temperatura ambiente (aproximadamente 18 °C hasta aproximadamente 25 °C) bajo atmósfera de nitrógeno. La evaporación del solvente se lleva a cabo usando un evaporador giratorio bajo presión reducida o en un sistema de evaporación de solvente de alto rendimiento HT–4X (Genevac Inc., Gardiner, NY, USA). El curso de la reacción fue seguido cromatografía de capa delgada (TLC) o espectrometría de masa de cromatografía líquida (LC–MS), y los tiempos de reacción se dan solo con fines ilustrativos. La cromatografía de gel de sílice se llevo a cabo en un sistema Combi*Flash*® (Teledyne Isco, Inc., Lincoln, NE, USA) con un cartucho de gel de sílice pre–cargado o se lleva a cabo en gel de sílice Merck 60 (malla 230–400). La estructura y pureza de todos los productos finales se aseguró mediante por lo menos uno de los siguientes métodos analíticos: resonancia magnética nuclear (RMN) y LC–EM. La espectrometría RMN se registró en un espectrómetro Bruker Avance™ 300 (Bruker BioSpin Corp., Billerica, MA, USA) o un Varian UNITY *INOVA*® 400 (Varian, Inc., Palo Alto, CA, USA) usando el solvente indicado. El cambio químico (δ) se da en partes por millón (ppm) con relación al tetrametilsilano (TMS) como patrón interno. Las constantes de acoplamiento (J) que se expresan en hertz (Hz), y las abreviaturas convencionales usadas para señalar la forma son: s = singlete; d = doblete; t = triplete; m = multiplete; br = ancho; etc. A menos que se indique lo contrario, la espectrografía de masa se obtuvo usando ionización por electrorocío (ESMS) a través de un sistema Micromass® Platform II o bien del sistema Quattro micro™ (ambos de Waters Corp., Milford, MA, USA) y $(M+H)^+$.

2. Preparación de los Intermediarios de la Invención

A menos que se especifique lo contrario, los reactivos usados en la preparación de los compuestos, incluyendo intermediarios, de la presente

invención son comercializados por Sigma–Aldrich Corporation (St. Louis, MO, USA).

Intermediario 1: (3–amin–adamantan–1–il)–amida de ácido 6–metil–piridin–2–carboxílico



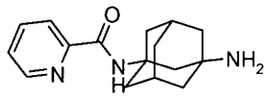
Se preparó el intermediario 1 a través del procedimiento del **Esquema 4**, *supra*, de la manera siguiente:

A un frasco que contenía (3–amin–adamantan–1–il)–amida de ácido 6–metil–piridin–2–carboxílico (1.0 g, 7 mmol) en DCM (75 mL), se agregó por goteo DIEA (2 mL, 10 mmol), y hexafluorfosfato de benzotriazol–1–iloxitris(dimetilamino)–fosfonio (3.2 g, 7.3 mmol), seguido de una solución de adamantan–1,3–diamina (1.3 g, 8 mmol, Zerenex Molecular Ltd., Greater Manchester, UK) en DCM (25 mL). Después de agitar a temperatura ambiente durante 16 h, la mezcla de reacción se lavó con bicarbonato de sodio saturado. La capa orgánica se secó sobre sulfato de sodio y se concentró bajo presión reducida. El residuo se purificó sobre un sistema de purificación de cromatografía líquida de fase inversa/espectrometría de masa (RP–HPLC/MS) (Gradiente: acetonitrilo en agua, 18–95%, en 3,9 min con un ciclo de tiempo de 5 min. Se usó un gradiente superficial entre 19–30% de acetonitrilo entre 0,7–2,5 min para separar las impurezas de la elución.. Régimen de flujo: 100 mL/min. Aditivo de fase móvil: 25 mM de formiato de amonio. Columna: Inertsil® C18, 30 x 50 mm, tamaño de partícula 5 um (GL Sciences, Tokyo, Japan)) para proporcionar 0,5 g (20%) del compuesto del título, (3–amin–adamantan–1–il)–amida de ácido 6–metil–piridin–2–carboxílico, en forma de un sólido blanco. ^{1}H RMN (400 MHz, CD_3OD) δ 7.89–7.81 (m, 2H), 7.46–7.42 (m, 1H), 2.59 (s, 3H), 2.44–2.06 (m, 6H), 2.09–1.67 (m, 8H). ESI–EM m/z: 286.1 $(M+H)^+$.

El intermediario 1 puede prepararse también a través de los mismos procedimientos sintéticos para el Intermediario 2 (ver a continuación). A partir de clorhidrato de éster metílico de ácido 3–amin–adamantan–1–carboxílico (14.9 g, 60.8 mmol), el acoplamiento con ácido 6–metil–piridin–2–carboxílico proporcionó éster metílico de ácido 3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–carboxílico (14.9 g, 75%). El éster metílico se hidrolizó luego para proporcionar ácido 3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–carboxílico (12.2 g, 86%). Finalmente, el reordenamiento de Curtius del ácido 3–[(6–metil–piridin–2–

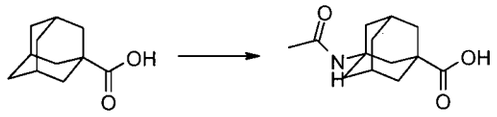
carbonil)–amino]–adamantan–1–carboxílico (10.0 g, 31.8 mmol) proporcionó el Intermediario 1 (8.48 g, 93%).

Intermediario 2: (3–amin–adamantan–1–il)–amida de ácido piridin–2–carboxílico



El intermediario 2 se sintetizó a través del procedimiento del Esquema **5**, *supra*, tal como sigue a continuación:

Etapa 1: Acido 3–acetilamin–adamantan–1–carboxílico



A un reactor de 10–L se agregó ácido 1–adamantancarboxílico (503 g, 2.79 mol; TCI America, Wellesley Hills, MA, USA) y 70% de ácido nítrico (400 mL, 6.72 mol), y la suspensión resultante se enfrió a 0 °C con un enfriador recirculante. A la mezcla se agregó lentamente 98% de ácido sulfúrico (3.00 L, 55.5 mol) a un régimen tal que la temperatura se mantuvo por debajo de los 10 °C. Una vez que se completó la adición, se agregó acetonitrilo (2.00 L, 38.5 mol) a un régimen tal que la temperatura se mantuvo por debajo de los 10 °C. Después de agregar todo el acetonitrilo, la reacción se agitó a 0 °C durante 1 hora. La reacción cruda se agregó luego a un reactor de 20–L llenado con aproximadamente 10–L de hielo mezclado con una pequeña cantidad de agua y la mezcla resultante se agitó y se dejó calentar a temperatura ambiente. Los sólidos luego se filtraron y se lavaron con agua. Precipitaron más sólidos a partir de la capa acuosa ácida y estos se filtraron y lavaron con agua. El material sólido combinado se secó luego bajo alto vacío a 50 °C durante 2 días para proporcionar 432 g (73%) del compuesto del título, ácido 3–acetilamin–adamantan–1–carboxílico, en forma de un sólido blanco.

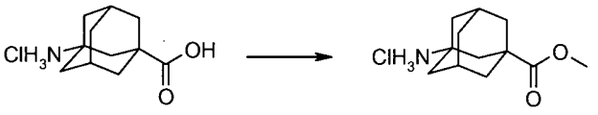
Etapa 2: clorhidrato de 3–amin–adamantan–1–carboxílico



A un frasco de 3 cuellos de 5–L equipado con un condensador de reflujo, un agitador mecánico y una sonda de temperatura se agregó ácido 3–acetilamin–adamantan–1–carboxílico (432 g, 1.82 mol), agua (1.00 L) y ácido clorhídrico concentrado (2.44 L), y la mezcla resultante se calentó a 95 °C durante 6 días.

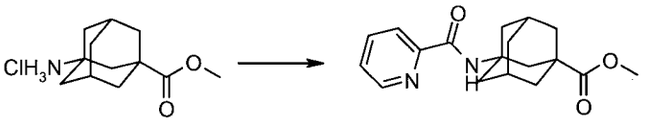
Durante este tiempo, el material sólido precipitó a partir de la solución. Después de enfriamiento a 0 °C, los sólidos se filtraron y se lavaron con acetona. El sólido se secó luego bajo alto vacío a 50 °C durante aproximadamente 2 horas para proporcionar 328 g (78%) del compuesto del título, clorhidrato de ácido 3–amin–adamantan–1–carboxílico, en forma de un sólido blanco. ^{1}H RMN (300 MHz, DMSO–d_6) δ 12.35 (br s, 1H), 8.27 (br s, 3H), 2.22–2.12 (m, 2H), 1.92–1.85 (m, 2H), 1.83–1.71 (m, 6H), 1.69–1.48 (m, 4H).

Etapa 3: Clorhidrato de éster metílico de ácido 3–amin–adamantan–1–carboxílico



A un frasco de 3 cuellos de 2–L equipado con un condensador a reflujo y una sonda de temperatura se agregó clorhidrato de ácido 3–amin–adamantan–1–carboxílico (100 g, 432 mmol) y metanol (1.0 L). A esta solución se agregó lentamente cloruro de tionilo (15.7 mL, 216 mmol) y la reacción se calentó a 60 °C durante 4 horas. Una vez enfriada a temperatura ambiente, la mezcla de reacción cruda se concentró bajo presión reducida para remover la mayor cantidad de metanol. Se agregó luego heptano (aproximadamente 1–L) y la mezcla se concentró una vez más bajo presión reducida, punto en el cual el sólido comenzó a precipitar. Este procedimiento se repitió tres veces más, luego se filtraron los sólidos, se lavaron con heptano y se dejaron secar al aire para proporcionar 97.2 g (92%) del compuesto del título, clorhidrato de éster metílico de ácido 3–amin–adamantan–1–carboxílico, en forma de un sólido blanco. ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.46 (br s, 3H), 3.65 (s, 3H), 2.33–2.24 (m, 2H), 2.23–2.16 (m, 2H), 2.11–1.95 (m, 4H), 1.94–1.78 (m, 4H), 1.75–1.62 (m, 2H).

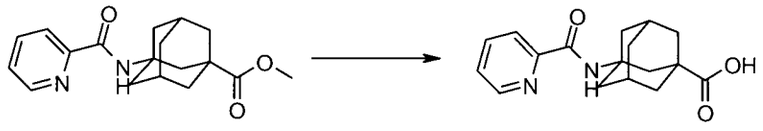
Etapa 4: Ester metílico de ácido 3–[(piridin–2–carbonil)–amino]–adamantan–1–carboxílico



A un frasco de fondo redondo se agregó clorhidrato de éster metílico de ácido 3–amin–adamantan–1–carboxílico (20.0 g, 81.4 mmol) y cloruro de metileno (500 mL) y la solución se enfrió a 0 °C. A ester solución se agregó luego trietilamina

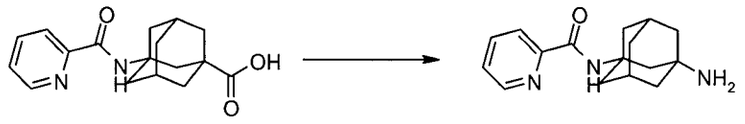
(57 mL, 0.41 mol) seguido de clorhidrato de cloruro de picolinoilo (15.2 g, 85.4 mmol; TCI America, Wellesley Hills, MA, USA) y la reacción se agitó a 0 °C durante 30 minutos, luego a temperatura ambiente durante 6 horas. A la reacción se agregó bicarbonato de sodio acuoso saturado (500 mL) y la mezcla bifásica se agitó vigorosamente por unos pocos minutos, luego se transfirió a un embudo separador de 2–L. Se extrajo la mezcla, se separaron las capas y la capa acuosa se extrajo nuevamente con cloruro de metileno (2 x 200 mL). Las capas orgánicas combinadas se lavaron con salmuera (300 mL), se secaron sobre sulfato de sodio, se filtraron y se concentraron bajo presión reducida para proporcionar 24.8 g (97%) del compuesto del título, éster metílico de ácido 3–[(piridin–2–carbonil)–amino]–adamantan–1–carboxílico, en forma de un sólido marrón pálido. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8.54–8.49 (m, 1H), 8.16 (dt, J = 7.8, 1.0 Hz, 1H), 7.96 (br s, 1H), 7.83 (td, J = 7.8, 1.8 Hz, 1H), 7.40 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 3.66 (s, 3H), 2.34–2.30 (m, 2H), 2.29–2.23 (m, 2H), 2.17–2.13 (m, 4H), 1.97–1.80 (m, 4H), 1.78–1.62 (m, 2H). ESI–EM m/z: 315.0 $(M+H)^+$.

Etapa 5: Acido 3–[(Piridin–2–carbonil)–amino]–adamantan–1–carboxílico



A un frasco de fondo redondo se agregó éster metílico de ácido 3–[(piridin–2–carbonil)–amino]–adamantan–1–carboxílico (24.8 g, 78.9 mmol), tetrahidrofurano (250 mL), agua (250 mL) y monohidrato de hidróxido de litio (14.9 g, 355 mmol) y la mezcla se agitó vigorosamente a temperatura ambiente durante 25 horas. La mezcla cruda se concentró bajo presión reducida para remover la mayor cantidad de tetrahidrofurano, luego la solución acuosa se diluyó con agua (200 mL) y el pH se ajustó hasta aproximadamente 3–4 mediante adición de monohidrato de ácido nitrico sólido. Apareció un voluminoso precipitado blanco que se filtró, se lavó con agua y se secó bajo alto vacío a 50 °C para proporcionar 22.1 g (93%) del compuesto del título, ácido 3–[(piridin–2–carbonil)–amino]–adamantan–1–carboxílico, en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8.55–8.50 (m, 1H), 8.18 (d, J = 7.7 Hz, 1H), 7.97 (br s, 1H), 7.85 (td, J = 7.8, 1.8 Hz, 1H), 7.42 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 2.35–2.31 (m, 2H), 2.31–2.25 (m, 2H), 2.25–2.09 (m, 4H), 2.00–1.86 (m, 4H), 1.80–1.64 (m, 2H). ESI–EM m/z: 301.0 $(M+H)^+$.

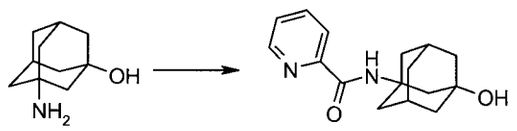
Etapa 6: (3–amin–adamantan–1–il)–amida de ácido piridin–2–carboxílico



A un frasco de fondo redondo se agregó ácido 3–[(piridin–2–carbonil)–amino]–adamantan–1–carboxílico (10.0 g, 33.3 mmol) y tolueno (100 mL). A la suspensión se agregó trietilamina (5.6 mL, 40 mmol) y la mezcla se agitó durante unos pocos minutos hasta que se disolvieron la mayor parte de los sólidos. A la mezcla se agregó luego azida difenilfosfónica (7.9 mL, 37 mmol) y la reacción se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se transfirió a un embudo de adición y se agregó por goteo a un frasco de fondo redondo de 3 cuellos equipado con un condensador a reflujo que contenía tolueno (70 mL) y se calentó a 90 °C. Después de adición, la reacción se agitó a 90 °C durante dos horas más, luego se dejó enfriar a temperatura ambiente. La mezcla de reacción se agregó luego lentamente a un frasco que contenía ácido clorhídrico acuoso 6,0 N (55 mL, 330 mmol) y se agitó vigorosamente durante 1 hora. La mezcla bifásica se transfirió a un embudo separador y la capa de tolueno se descartó. La capa acuosa ácida se trató luego lentamente con carbonato de sodio sólido hasta que se obtuvo un pH de 10. La capa acuosa se transfirió a un embudo separador de 500–mL y se extrajo con cloruro de metileno (3 x 100 mL). Las capas orgánicas combinadas se lavaron luego con salmuera, se secaron sobre sulfato de sodio, se filtraron y concentraron bajo presión reducida para proporcionar 8,38 g (93%) del compuesto del título, (3–amin–adamantan–1–il)–amida de ácido piridin–2–carboxílico, en forma de una espuma gomosa. ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.55–8.50 (m, 1H), 8.16 (d, J = 7.9 Hz, 1H), 7.94 (br s, 1H), 7.84 (td, J = 7.7, 1.7 Hz, 1H), 7.40 (ddd, J = 7.6, 4.7, 1.3 Hz, 1H), 2.31–2.21 (m, 2H), 2.13–1.97 (m, 6H), 1.71–1.51 (m, 6H). ESI–EM m/z: 272 $(M+H)^+$.

El Intermediario 2 puede prepararse también a través del procedimiento del **Esquema 6**, *supra*, tal como sigue a continuación:

Etapa 1: (3–hidroxi–adamantan–1–ilo)–amida de ácido piridin–2–carboxílico

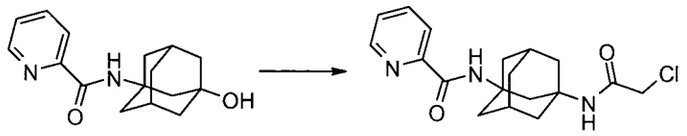


A un frasco de 40 ml se agregó ácido picolínico (0.68 g, 5.5 mmol), DMF (15 ml), trietilamina (0.90 mL, 6.4 mmol), y hexafluorfosfato de *O*–(Benzotriazol–1–il)–*N,N,N',N'*–tetrametiluronio (HBTU, 2.3 g, 6.0 mmol). La mezcla se agitó a temperatura ambiente durante 5 minutos para obtener una solución clara. Se

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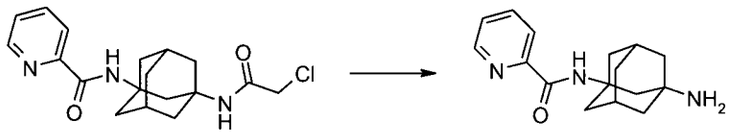
agregó 3–amin–adamantanol (0.84 g, 5.0 mmol; AK Scientific, 897–4G Independence Ave., Mountain View, CA 94043) a la solución anterior y se agitó a temperatura ambiente durante 2 horas. Se removió el DMF en Genevac y el residuo se disolvió en DCM (20 mL), se lavó con NaOH acuoso 1N, agua y salmuera, se secó sobre Na_2SO_4, y se concentró bajo presión reducida para proporcionar 1.32 g (97%) del compuesto del título crudo, (3–hidroxi–adamantan–1–il)–amida de ácido piridin–2–carboxílico, en forma de un aceite, que se tornó un sólido incoloro manteniéndolo a temperatura ambiente. LC/MS (Gradiente: acetonitrilo en agua, 20–85%, en 1,7 minutos con un ciclo de tiempo de 2 minutos. Régimen de flujo de 2 min. Régimen de flujo: 5,0 mL/min. Fase aditiva móvil: 30 mM de formiato de amonio. Columna Inertsil® ODS–3, 50 x 4.6 mm, tamaño de partícula 3 um (GL Sciences, Tokyo, Japan)): Tiempo de retención: 0,79 min; pureza (UV_{254}): 100%; ESI–EM m/z: 273 $(M+H)^+$. Esto se usó en la siguiente etapa sin purificación adicional.

Etapa 2: [3–(2–cloro–acetilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico



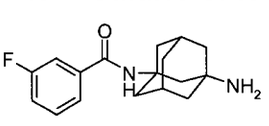
Se enfrió cloroacetonitrilo (2.0 mL, 32 mmol) a 0 °C. Se agregó lentamente ácido sulfúrico (1.0 mL, 19 mmol) a 0 °C. Después de completar la adición, la mezcla se agitó a 0 °C durante 5 minutos. Se agregó en una porción (3–hidroxi–adamantan–1–il)–amida de ácido piridin–2–carboxílico (0.42 g, 1.56 mmol, a partir de la Etapa 1) y la mezcla se agitó a temperatura ambiente durante la noche. La solución espesa se vertió en agua helada (10 mL). Se agregó DCM (10 mL). Mientras que la mezcla se enfrió con un baño de hielo, el pH de la fase acuosa (top) se ajustó a 10–13 con NaOH ac. 10 N. La capa acuosa se extrajo con DCM. La capa orgánica combinada se lavó con agua y salmuera, se secó sobre Na_2SO_4, y se concentró bajo presión reducida para proporcionar 0,53 g (96.9%) del compuesto del título crudo, [3–(2–cloro–acetilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico, en forma de un aceite, que se tornó un sólido incoloro maneniéndolo a temperatura ambiente. LC–EM (Gradiente: acetonitrilo en agua, 20–85%, en 1,7 minutos con un ciclo de tiempo de 2 min. Régimen de Flujo: 5,0 mL/min. Aditivo de fase móvil: 30 mM de formiato de amonio. Columna: Inertsil® ODS, 50 x 4.6 mm, tamaño de partícula 3 um (GL Sciences, Tokyo, Japan)): Tiempo de Retención: 1,08 min; pureza (UV_{254}): 100%; ESI–EM m/z: 348 $(M+H)^+$. Esto se usó en la etapa siguiente sin purificación adicional.

Etapa 3: (3–amin–adamantan–1–il)–amida de ácido piridin–2–carboxílico



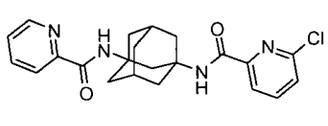
A un frasco de 40 ml que contenía [3–(2–cloro–acetilamino) adamantan–1–il]–amida de ácido piridin–2–carboxílico (1,69 g, 4.85 mmol, de la Etapa 2) y tiourea (0.56g, 7.4 mmol), se agregó etanol (20.0 mL), y ácido acético (4,0 mL). La mezcla se agitó a 78 °C durante la noche. La solución de reacción se enfrió a temperatura ambiente, se vertió en agua (100 mL), y el pH de la solución se ajustó a 10–13 usando NaOH ac. 10 N. La mezcla se transfirió a un embudo de separación, y se extrajo con DCM (3 x 150 mL). La capa orgánica combinada se lavó con agua y salmuera, se secó sobre Na_2SO_4, y se concentró bajo presión reducida para proporcionar 1,35 g (95.4%) del compuesto del título crudo, (3–amin–adamantan–1–il)–amida de ácido piridin–2–carboxílico, en forma de un aceite, que se tornó un sólido incoloro manteniéndolo a temperatura ambiente. LC–EM (Gradiente: acetonitrilo en agua, 10–85%, en 1,7 minutos con un ciclo de tiempo de 2 min. Régimen de flujo: 5,0 mL/min. Aditivo de fase móvil: 30 mM de formiato de amonio. Columna: Inertsil® C8, 50 x 4.6 mm, tamaño de partícula 3 um (GL Sciences, Tokyo, Japan)): Tiempo de retención: 0,63 min; pureza (UV_{254}): 93%; ESI–EM m/z: 272 $(M+H)^+$. Esto se usó en la siguiente etapa de amidación, sin purificación adicional.

Intermediario 3: N–(3–Amin–adamantan–1–il)–3–fluor–benzamida



Usando el mismo procedimiento que en la síntesis del Intermediario 2, se preparó el Intermediario 3 a una escala de reacción de 4,33 mmol, y se obtuvo 1.26 g (95,6%) del producto crudo. LC–EM (Gradiente: acetonitrilo en agua, 10–85%, en 1,7 minutos con un ciclo de tiempo de 2 min. Régimen de Flujo: 5,0 mL/min. Aditivo de fase móvil: 30 mM de formiato de amonio. Columna: Inertsil® C8, 50 x 4.6 mm, tamaño de partícula 3 um (GL Sciences, Tokyo, Japan)): Tiempo de retención: 0.70 min; pureza (UV_{254}): 95%. ESI–EM m/z: 289 $(M+H)^+$. Esto se usó en la etapa siguiente sin purificación adicional.

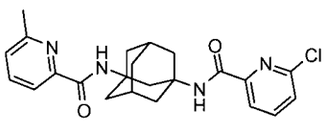
Intermediario 4: {3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Cloro–piridin–2–carboxílico



Se preparó el Intermediario 4 a partir del Intermediario 2 a través del procedimiento del **Esquema 10**, *supra*,de la manera siguiente:

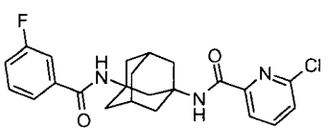
A un frasco de 40 ml se agregó ácido 6–cloropiridin–2–carboxílico (0.79 g, 5.0 mmol), DMF (15 ml), trietilamina (0.90 mL, 6.4 mmol), y hexafluorfosfato de O–(benzotriazol–1–il)–*N,N,N',N'*–tetrametiluronio (2.3 g, 6.0 mmol). La mezcla se agitó a temperatura ambiente durante 5 minutos hasta obtener una solución clara. Se agregó a la solución (3–amin–adamantan–1–il)–amida de ácido piridin–2–carboxílico (Intermediario 2, 1.38 g, 4.73 mmol)y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. Se removió el DMF en Genevac. El residuo se disolvió en DCM (20 mL), se lavó con NaOH ac. 1N (15 mL), agua (15 mL) y salmuera (15 mL), y se secó sobre Na_2SO_4. El solvente se removió bajo presión reducida para proporcionar 1,85 g (95.2%) del compuesto del título crudo, {3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–cloro–piridin–2–carboxílico. LC–EM (Gradiente: acetonitrilo en agua, 30–90%, en 1,7 minutos con un ciclo de tiempo de 2 min. Régimen de Flujo: 5,0 mL/min. Aditivo de fase móvil: 30 mM de formiato de amonio. Columna: Inertsil® C8, 50 x 4.6 mm, tamaño de partícula 3 um (GL Sciences, Tokyo, Japan)): Tiempo de retención: 1.17 min; pureza (UV_{254}): 100%. ESI–EM m/z: 411 $(M+H)^+$. Esto se usó en la etapa siguiente sin purificación adicional.

Intermediario 5: {3–[(6–metilpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–cloro–piridin–2–carboxílico



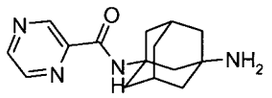
De manera similar al Intermediario 4, el Intermediario 5 se preparó a partir del Intermediario 1 (2.00 g, 7.01 mmol). Después de purificación mediante cromatografía de gel de sílice, se obtuvo el Intermediario 5 (1.94 g, 65%) en forma de un sólido blanco. ^1H RMN (300 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 8.09 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.84–7.69 (m, 3H), 7.44 (d, J = 7.7 Hz, 1H), 7.26 (d, 1H), 2.60–2.55 (m, 5H), 2.40–2.32 (m, 2H), 2.31–2.12 (m, 8H), 1.76–1.70 (m, 2H). ESI–EM m/z: 425.0 $(M+H)^+$.

Intermediario 6: [3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–cloro–piridin–2–carboxílico



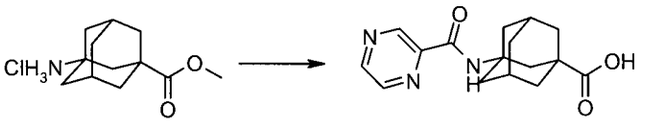
De manera similar al Intermediario 4, se preparó el Intermediario 6 a partir del Intermediario 3 a una escala de reacción de 4,6 mmol. Se obtuvo el producto crudo (1.99 g, 97%). LC–EM (Gradiente: acetonitrilo en agua, 30–90%, en 1,7 minutos con un ciclo de tiempo de 2 min.Régimen de flujo: 5,0 mL/min. Aditivo de fase móvil: 30 mM de formiato de amonio. Columna: Inertsil® C8, 50 x 4.6 mm, tamaño de partícula 3 um (GL Sciences, Tokyo, Japan)): Tiempo de retención: 1.21 min; pureza (UV_{254}):100%. ESI–EM m/z: 428 $(M+H)^+$. Esto se usó en la etapa siguiente sin purificación adicional.

Intermediario 7: (3–amin–adamantan–1–il)–amida de ácido pirazin–2–carboxílico



Se sintetizó el Intermediario 7 a través del procedimiento del **Esquema 5** a partir del compuesto 4, *supra*,de la manera siguiente:

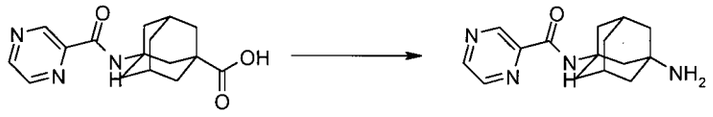
Etapa 1: Acido 3–[(pirazin–2–carbonil)–amino]–adamantan–1–carboxílico



A un frasco de fondo redondo se agregó clorhidrato de éster metílico de ácido 3–amin–adamantan–1–carboxílico (7.00 g, 28.5 mmol), ácido 2–pirazincarboxílico (3.71 g, 29.9 mmol) y cloruro de metileno (200 mL). La mezcla se agitó vigorosamente y se trató con PyBOP® (15.6 g, 29.9 mmol) seguido de trietilamina (9.9 mL, 71 mmol), y luego se agitó a temperatura ambiente durante 16 horas. A la reacción se agregó bicarbonato de sodio acuoso saturado (200 mL) y la mezcla bifásica se agitó vigorosamente durante unos pocos minutos, luego se transfirió a un embudo separador de 1–L. Se extrajo la mezcla, se separaron las capas, y la capa acuosa se extrajo nuevamente con cloruro de metileno (200 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron bajo presión reducida. El residuo se disolvió luego en tetrahidrofurano (200 mL) y se agregó agua (200 mL). A la mezcla bifásica se agregó monohidrato de hidróxido de litio (5.38 g, 128 mmol), y la mezcla resultante se agitó vigorosamente a temperatura ambiente durante 22 horas. Se removió la mayor parte de los volátiles bajo presión reducida y la solución acuosa resultante se transfirió a un embudo separador de 500–mL y se lavó con cloruro de metileno (3 x 150 mL). La capa acuosa se diluyó con agua (200 mL) y el pH se ajusó a aproximadamente 3–4 mediante adición de

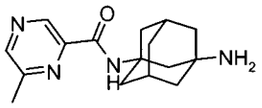
monohidrato de ácido cítrico sólido. Apareció un voluminoso precipitado blanco que se filtró, se lavó con agua y se secó bajo alto vacío a 50 °C para proporcionar 8,11 g (95%) del compuesto del título, ácido 3–[(pirazin–2–carbonil)–amino]–adamantan–1–carboxílico, en forma de un sólido blanco. ^{1}H RMN (300 MHz, $CDCl_3$) δ 11.14–10.07 (br s, 1H), 9.38 (d, J = 1.5 Hz, 1H), 8.74 (d, J = 2.5 Hz, 1H), 8.50 (dd, J = 2.4, 1.5 Hz, 1H), 7.68 (br s, 1H), 2.35–2.25 (m, 4H), 2.23–2.08 (m, 4H), 2.00–1.86 (m, 4H), 1.81–1.64 (m, 2H). ESI–EM m/z: 301.9 $(M+H)^+$.

Etapa 2: (3–amin–adamantan–1–il)–amida de ácido pirazin–2–carboxílico



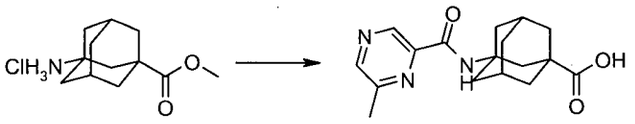
Usando el mismo procedimiento que se usó para preparar el Intermediario 2 en la Etapa 6, a partir de ácido 3–[(pirazin–2–carbonil)–amino]–adamantan–1–carboxílico (4.00 g, 13.3 mmol), el reordenamiento de Curtius proporcionó 3,56 g (99%) del compuesto del título, (3–amin–adamantan–1–il)–amida de ácido pirazin–2–carboxílico, en forma de un solido blancuzco. ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.37 (d, J = 1.4 Hz, 1H), 8.73 (d, J = 2.5 Hz, 1H), 8.49 (dd, J = 2.4, 1.5 Hz, 1H), 7.64 (br s, 1H), 2.31–2.21 (m, 2H), 2.14–1.95 (m, 6H), 1.71–1.51 (m, 6H) (Nota: el $-NH_2$ está oculto entre 2.52–1.78 ppm). ESI–EM m/z: 273.0 $(M+H)^+$.

Intermediario 8: (3–amin–adamantan–1–il)–amida de ácido 6–metil–pirazin–2–carboxílico



El Intermediario 8 se sintetizó a través del procedimiento del **Esquema 5** a partir del compuesto 4, *supra*, de la manera siguiente:

Etapa 1: Acido 3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–carboxílico



Usando el mismo procedimiento que se usó para preparar el Intermediario 7 en la Etapa 1, a partir de clorhidrato de éster metílico de ácido 3–amin–adamantan–1–carboxílico (7.00 g, 28.5 mmol) y ácido 6–metilpirazin–2–carboxílico (4.13 g, 29.9 mmol, RihaChem, Kostalov Czech Republic), la reacción de acoplamiento con PyBOP®, seguido de hidrólisis basica del grupo éster metílico, proporcionó 8.01 g (89%) del compuesto del título, ácido 3–[(6–metil–

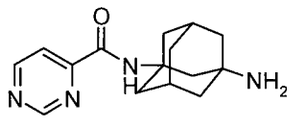
pirazin–2–carbonil)–amino]–adamantan–1–carboxílico, en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 12.03–10.32 (br s, 1H), 9.17 (s, 1H), 8.60 (s, 1H), 7.72 (br s, 1H), 2.60 (s, 3H), 2.35–2.26 (m, 4H), 2.26–2.18 (m, 2H), 2.16–2.07 (m, 2H), 2.00–1.86 (m, 4H), 1.80–1.65 (m, 2H). ESI–EM m/z: 316.0 $(M+H)^+$.

Etapa 2: (3–amin–adamantan–1–il) amida de ácido 6–metil–pirazin–2–carboxílico



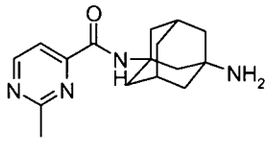
Usando el mismo procedimiento que se usó para preparar el Intermediario 2 en la Etapa 6, a partir de ácido 3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–carboxílico (3.00 g, 9.51 mmol), el reordenamiento de Curtius proporcionó 2,65 g (97%) del compuesto del título (3–amin–adamantan–1–il) amida de ácido 6–metil–pirazin–2–carboxílico, en forma de un sólido blancuzco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.59 (s, 1H), 7.69 (br s, 1H), 2.60 (s, 3H), 2.32–2.21 (m, 2H), 2.13–1.97 (m, 6H), 1.70–1.52 (m, 6H) (Nota: el $–NH_2$ está oculto entre 2.41–1.29 ppm). ESI–EM m/z: 287.0 $(M+H)^+$.

Intermediario 9: (3–amin–adamantan–1–il)–amida de ácido pirimidin–4–carboxílico



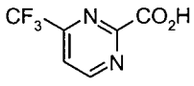
Usando los mismos procedimientos que en la síntesis del Intermediario 7, se preparó el Intermediario 9 a una escala de reacción de 16,8 mmol a partir de clorhidrato de éster metílico de ácido 3–amin–adamantan–1–carboxílico y ácido pirimidin–4–carboxílico (Ark Pharm Inc., Libertyville, ILO, USA), y se obtuvo 4.00 g (88%) del producto crudo. LC–EM (Gradiente: acetonitrilo en agua, 20–85%, en 1,7 minuto con un ciclo de tiempo de 2 min. Régimen de flujo: 5.0 mL/min. Aditivo de fase móvil: 30 mM de formiato de amonio. Columna: Inertsil® ODS, 50 x 4.6 mm, 3 um de tamaño de partícula (GL Sciences)): Tiempo de retención: 0.24 min; pureza (UV_{254}): 95%. ESI–EM m/z: 273 $(M+H)^+$. Esto se usó en la etapa siguiente sin purificación adicional.

Intermediario 10: (3–amin–adamantan–1–il)–amida de ácido 2–metil–pirimidin–4–carboxílico



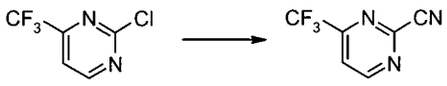
Usando los mismos procedimientos que en la síntesis del Intermediario 7, se preparó el Intermediario 10 a una escala de reacción de 15,8 mmol a partir de clorhidrato de éster metílico de ácido 3–amin–adamantan–1–carboxílico y ácido 2–metil–pirimidin–4–carboxílico (Ark Pharm Inc.), y se obtuvo 4.6 g (100%) del producto crudo. LC–EM (Gradiente: acetonitrilo en agua, 20–85%, en 1,7 minutos con un ciclo de tiempo de 2 min. Régimen de Flujo: 5.0 mL/min. Aditivo de fase móvil: 30 mM de formiato de amonio. Columna: Inertsil® ODS, 50 x 4.6 mm, tamaño de partícula 3 um (GL Sciences)): Tiempo de retención: 0.30 min; pureza (UV_{254}): 82%. ESI–EM m/z: 287 $(M+H)^+$. Esto se usó en la etapa siguiente sin purificación adicional.

Intermediario 11: Acido 4–trifluormetil–pirimidin–2–carboxílico



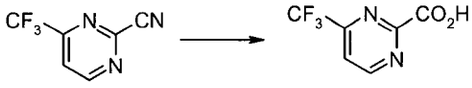
Se preparó el Intermediario 11 a través del procedimiento del **Esquema 11**, supra, de la manera siguiente:

Etapa 1: 4–trifluormetil–pirimidin–2–carbonitrilo



A una solución de 2–cloro–4–(trifluormetil)pirimidina (5.00 g, 27.4 mmol) en sulfóxido de dimetilo (25 mL) se agregó cianuro de sodio (1.68 g, 34.2 mmol). La reacción se agitó a temperatura ambiente durante 30 minutos y se vertió en una solución fría de $NaHCO_3$ acuosa saturada. La mezcla se transfirió a un embudo separador de 100 mL y se extrajo con éter etílico (3 x 50 mL). Las capas orgánicas combinadas se lavaron con salmuera (50 mL), se secaron sobre sulfato de sodio, se filtraron, y se concentraron bajo presión reducida para proporcionar el compuesto del título, 4–trifluormetil–pirimidin–2–carbonitrilo, en forma de un aceite marrón que se usó en la etapa siguiente sin purificación adicional. ^1H RMN (400 MHz, $CDCl_3$) δ 9.16 (d, J=5.1 Hz, 1H), 7.88 (d, J=5.1 Hz, 1H).

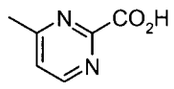
Etapa 2: Acido 4–trifluormetil–pirimidin–2–carboxílico



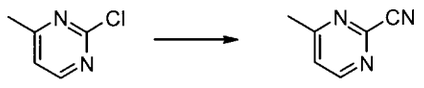
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El 4–trifluormetil–pirimidin–2–carbonitrilo crudo de la Etapa 1 se disolvió en una solución de cloruro de hidrógeno en agua (6 M, 20.0 mL) y se calentó a temperatura de reflujo durante la noche. La mezcla de reacción se enfrió a temperatura ambiente, y se concentró bajo presión reducida. Luego se agregó tolueno (20 mL) y la mezcla se concentró bajo presión reducida. Este procedimiento se repitió con 1,4–dioxano y éter etílico, luego los sólidos se filtraron. El filtrado se concentró bajo presión reducida para proporcionar 4,80 g (82.1%) del compuesto del título, ácido 4–trifluormetil–piridin–2–carboxílico, en forma de un sólido marrón, que se usó en la etapa siguiente sin purificación adicional. ^{1}H RMN (400 MHz, DMSO–d6) δ 9.35 (d, J=5.0 Hz, 1H), 8.25 (d, J=5.1 Hz, 1H).

Intermediario 12: Acido 4–metil–pirimidin–2–carboxílico

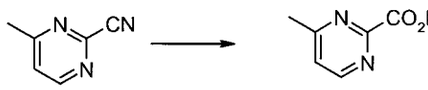


Etapa 1: 4–metil–pirimidin–2–carbonitrilo



A una solución de 2–cloro–4–metilpirimidina (3.00 g, 23.3 mmol; 3B Pharmachem International, China) en éter etílico (24 mL) se agregó una solución de cianuro de sodio (2.86 g, 58.3 mmol) en una solución de trietilamina (1:3, trimetilamina:agua, 24.0 mL). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La capa acuosa se extrajo con éter etílico (3 x 20 mL). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida para proporcionar el compuesto del título, 4–metil–pirimidin–2–carbonitrilo (1.80 g; 64.8%), que se usó en la etapa siguiente sin purificación adicional. ^{1}H RMN (400 MHz, D_2O) δ 8.64 (d, *J*=5.4 Hz, 1H), 7.59 (d, *J*=5.5 Hz, 1H).

Etapa 2: Acido 4–metil–pirimidin–2–carboxílico



La solución de 4–metil–pirimidin–2–carbonitrilo (500 mg, 4.20 mmol) e hidróxido de sodio (504 mg, 12.6 mmol) en agua (12.5 mL) se agitó a 60 °C durante 1 hora. La mezcla de reacción se enfrió a temperatura ambiente, se

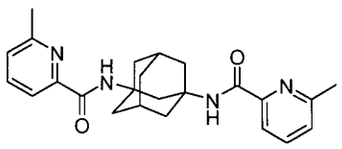
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acidificó a pH ~2 con ácido cítrico y se extrajo con $CHCl_3$:*i*–PrOH (3:1, 2 x 20 mL). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida para proporcionar 0,294 g del compuesto del título, ácido 4–metil–2–pirimidincarboxílico (51%), que se usó en la etapa siguiente sin purificación adicional. ^{1}H RMN (300 MHz, D_2O) δ 8.50 (d, *J*=5.2 Hz, 1H), 7.31 (d, *J*=5.3 Hz, 1H).

3. Preparación de los Compuestos de la Invención

A menos que se especifique lo contrario, los reactivos usados en la preparación de los compuestos, incluyendo intermediarios, de la presente invención se comercializan en Sigma–Aldrich Corporation (St. Louis, MO, USA).

Ejemplo 1: *N,N'*–(1,3–adamantilen)bis(6–metil–piridin–2–carboxamida)

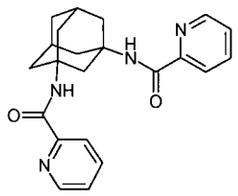


Se preparó el Ejemplo 1 a través del procedimiento del **Esquema 1**, *supra*, de la manera siguiente:

A un frasco que contenía ácido 6–metil picolínico (40 mg, 0,3 mmol), cloruro de metileno (10 mL) y *N,N*–diisopropiletilamina (60 mg, 0.5 mmol), se agregó clorhidrato de *N*–(3–dimetilaminopropil)–*N'*–etilcarbodiimida (60 mg, 0.3 mmol). La mezcla se agitó durante 5 minutos. Se agregó sal de clorhidrato de adamantan–1,3–diamina (20 mg, 0.1 mmol; Zerenex™ Molecular Ltd., Greater Manchester, UK) y la reacción se dejó procesar durante 16 h. La mezcla de reacción se lavó con bicarbonato de sodio saturado, se secó sobre sulfato de sodio y se concentró bajo presión reducida. El residuo se purificó en un sistema de purificación de cromatografía de fase líquida inversa/espectrometría de masa (RP–HPLC/MS) (Gradiente: acetonitrilo en agua, 25–95%, en 3,9 min con un ciclo de tiempo de 5 min. Se usó un gradiente superficial entre 28–58% de acetonitrilo entre 0,75–3,5 min para separar las impurezas de elución. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 25 mM de acetato de amonio. Columna: Inertsil® C8, 30 x 50 mm, 5 um de tamaño de partícula) para proporcionar el compuesto del título (33 mg, 80%) en forma de un aceite blancuzco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8.09 (s,br, 2H), 7.96 (d, *J* = 7.76 Hz, 2H), 7.70 (t, *J* =7.70 Hz, 2 H), 7.27–7.22 (m, 2H), 2.58–2.55 (m, 2H), 2.38–2.13 (m, 10H). 1.75–1.71 (m, 2H) . ESI–EM m/z: 405.0 $(M+H)^+$.

Ejemplo 2: *N,N'*–(1,3–adamantilen)bis(2–piridincarboxamida)

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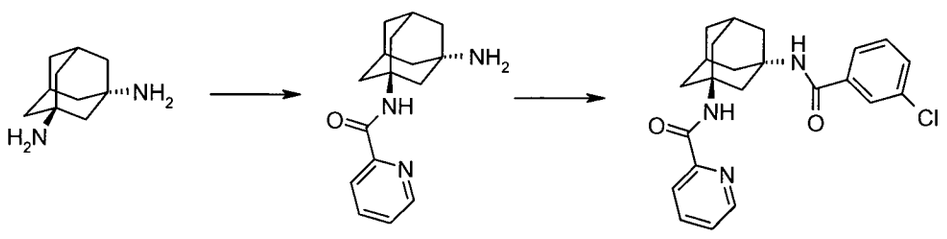


Se preparó el Ejemplo 2 a través del procedimiento del **Esquema 1**, *supra*, de la manera siguiente:

En un frasco que contenía adamantan–1,3–diamina (50 mg, 0.3 mmol; Zerenex™ Molecular Ltd., Greater Manchester, UK) y cloruro de metileno (10 mL) a 0 °C se agregó *N,N*–diisopropiletilamina (200 mg, 2 mmol; Alfa Aesar®, Ward Hill, MA, USA). Se agregó a la reacción cloruro de piridin–2–carbonilo (60 mg, 0.4 mmol; TCI America, Wellesley Hills, MA, USA). Después de agitar a temperatura ambiente durante 16 h, la mezcla de reacción se lavó con bicarbonato de sodio saturado, se secó sobre sulfato de sodio y se concentró bajo presión reducida. El residuo se purificó en un sistema de purificación de cromatografía de fase líquida inversa/espectrometría de masa (RP–HPLC/MS) (Gradiente: acetonitrilo en agua, 30–95%, en 3,9 min con un ciclo de tiempo de 5 min. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 25 mM de formiato de amonio. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um) para obtener el compuesto del título en forma de un aceite amarronado. (58 mg, 50%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.51 (d, J=4.86 Hz, 2H), 8.15 (d, J=7.85 Hz, 2H), 8.03 (s, br 2H), 7.83 (d, J=7.70 Hz, 2H), 7.43–7.37 (m, 2H), 2.58 (s, br, 2H), 2.38–2.31 (m, 2H). 2.20–2.13 (m, 8H), 1.76–1.71 (m, 2H). ESI–EM m/z: 377.0 $(M+H)^+$.

De manera análoga al Ejemplo 2, se prepararon los Ejemplos 3–5 de la Tabla 1 (siguiente) a partir de cloruro de aril o heteroaril carbonilo comercialmente obtenible a escalas de reacción de 0,1 a 0,3 mmoles.

Ejemplo 6: [3–(3–cloro–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico



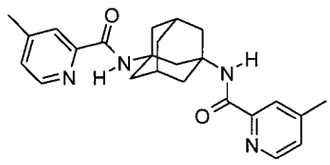
El Ejemplo 6 se preparó a través del procedimiento de los **Esquemas 4** y **3**, *supra*, de la manera siguiente:

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A un frasco que contenía adamantan–1,3–diamina (50 mg, 0.3 mmol) y tetrahidrofurano (5 mL) se agregó por goteo, NaOH acuoso 5M (0.6 mL, 3 mmol). Con vigorosa agitación, se agregó en porciones clorhidrato de cloruro picolinoilo (50 mg, 0.3 mmol). Después de agitación a temperatura ambiente durante 16 h, la mezcla de reacción se dividió en diclorometano y bicarbonato de sodio saturado. La capa orgánica se secó sobre sulfato de sodio y se concentró bajo presión reducida. El residuo se re–extrajo en 5 mL de DCM (diclorometano). A la suspensión se agregó DIEA (*N,N*–diisopropil–etilamina) (160 mg, 1.2 mmol) y cloruro de 3–cloro–benzoilo (79 mg, 0.45 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h, se lavó con bicarbonato de sodio saturado, se secó sobre sulfato de sodio y se concentró bajo presión reducida. El residuo se purificó en un sistema de purificación de cromatografía líquida de fase inversa / espectrometría de masa (RP–HPLC/MS) (Gradiente: acetonitrilo en agua, 25–95%, en 3.9 min con un ciclo de tiempo de 5 min. Se usó un gradiente superficial entre 35–65% de acetonitrilo entre 0.75–3.5 min para separarar las impurezas de elución. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 25 mM de acetato de amonio. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um) para proporcionar el compuesto del título (28 mg, 22%) en forma de un aceite blancuzco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8.51 (d, J=4.75 Hz, 1H), 8.15 (d, J=7.84 Hz, 1H), 8.03 (s, br 1H), 7.83 (t, J=7.72 Hz, 1H), 7.69 (t, J=1.82 Hz, 1H), 7.57 (d, J=7.60 Hz, 1H), 7.46–7.31 (m, 3H), 5.87 (s,br 1H), 2.56 (s, br, 2H), 2.38–2.31 (m, 2H). 2.24–2.12 (m, 8H), 1.76–1.69 (m, 2H). ESI–EM m/z: 410.0 $(M+H)^+$.

De manera análoga al Ejemplo 6, se prepararon los Ejemplos 7–10 en la Tabla 1 (siguiente) a partir de cloruro de aril o heteroaril carbonilo comercialmente obtenible en una escala de reacción de 0,3 mmol.

Ejemplo 11: *N,N'*–(1,3–Adamantilen)bis(4–metil–piridin–2–carboxamida)



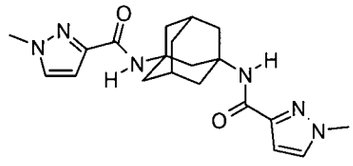
Se sintetizó el Ejemplo 11 a través del procedimiento del Esquema **1**, *supra*,de la manera siguiente:

A un frasco que contenía ácido 4–metil–piridin–2–carboxílico (30 mg, 0.22 mmol) en DMF (1 mL), se agregó hexafluorfosfato de benzotriazol–1–il–oxi–tris–(dimetilamino)–fosfonio (97 mg, 0.22 mmol), DIEA (40 mg, 0.3 mmol; Alfa Aesar, Ward Hill, MA, USA), seguido de adamantan–1,3–diamina (20 mg, 0.1 mmol en 1

mL de THF; Zerenex Molecular Ltd., Greater Manchester, UK). Después de agitación durante 16 h a temperatura ambiente, la mezcla de reacción se dividió entre diclorometano y bicarbonato de sodio saturado. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. El residuo se purificó en un sistema de purificación de cromatografía líquida de fase inversa / espectrometría de masa (RP–HPLC/MS) (Gradiente: acetonitrilo en agua, 30–95%, en 3,7 minutos con un ciclo de tiempo de 5 min. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 25 mM de formiato de amonio. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um (GL Sciences, Tokyo, Japan)) para proporcionar 18 mg (40%) del compuesto del título, *N,N'*–(1,3–adamantilen)bis(4–metil–piridin–2–carboxamida, en forma de un aceite blancuzco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8.35 (d, J = 4.9 Hz, 2H), 8.02 (s, br, 2H), 7.98–7.96 (m, 2H), 7.21–7.19 (m, 2H), 2.57–2.55 (m, 2H), 2.41 (s, 6H), 2.36–2.31 (m, 2H), 2.25–2.13 (m, 8H), 1.74–1.70 (m, 2H). ESI–EM m/z: 405.0 $(M+H)^+$.

De manera análoga al Ejemplo 11, se prepararon los Ejemplos 12–16 en la Tabla 1 (siguiente) a partir de ácidos aril o heteroaril carboxílicos comercialmente obtenibles en escalas de reacción de 0,1 a 0,3 mmoles.

Ejemplo 17: *N,N'*–(1,3–adamantilen)bis(1–metil–1*H*–pirazol–3–carboxamida)

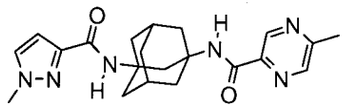


Se sintetizó el Ejemplo 17 a partir de cloruro de heteroaril carbonilo a través del procedimiento del **Esquema 1**, *supra*, de la manera siguiente:

A una solución de adamantan–1,3–diamina (20 mg, 0.1 mmol; Zerenex Molecular Ltd., Greater Manchester, UK) en THF (4 mL), se agregó cloruro de 1–metil–1*H*–pirazol–3–carbonilo (40 mg, 0.3 mmol) y DIEA (40 mg, 0.3 mmol). Después de agitar durante 16 h a temperatura ambiente, la mezcla de reacción se dividió en diclorometano y bicarbonato de sodio saturado. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. El residuo se purificó en un sistema de purificación RP–HPLC/MS (Gradiente: acetonitrilo en agua, 18–95%, en 3,9 minutos con un ciclo de tiempo de 5 min. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 25 mM de acetato de amonio. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um (GL Sciences, Tokyo, Japan)) para proporcionar 19 mg (50%) del compuesto del título, *N,N'*–(1,3–adamantilen)bis(1–metil–1*H*–pirazol–3–carboxamida, en forma

de un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7.32 (d, J = 2.3 Hz, 2H), 6.74–6.71 (m, 4H), 3.89 (s, 6H), 2.49 (s, br, 2H), 2.33–2.26 (m, 2H), 2.23–2.06 (m, 8H), 1.72–1.64 (m, 2H). ESI–EM m/z: 383.1 $(M+H)^+$.

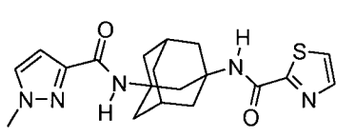
Ejemplo 18: {3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–metil–pirazin–2–carboxílico



El Ejemplo 18 se sintetizó a partir del procedimiento del **Esquema 2** usando ácidos carboxílicos comercialmente obtenibles, *supra*,de la manera siguiente::

A una solución de adamantan–1,3–diamina (20 mg, 0,1 mmol; Zerenex Molecular Ltd., Greater Manchester, UK) in DCM (2 mL) se agregó DIEA (26 mg, 0,15 mmol), ácido 1–metil–1*H*–pirazol–3–carboxílico (14 mg, 0.11 mmol), ácido 5–metil–pirazin–2–carboxílico (15 mg, 0.11 mmol) y hexafluorfosfato de benzotriazol–1–il–oxitripirrolidinfosfonio (110 mg, 0.20 mmol). Después de agitación durante 3 horas a temperatura ambiente, la mezcla de reacción se dividió entre diclorometano y bicarbonato de sodio saturado. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. El residuo se purificó en un sistema de purificación RP–HPLC/MS (Gradiente: acetonitrilo en agua, 25–95%, en 3,4 minutos con un ciclo de tiempo de 5 min. Se usó un gradiente superficial entre 25–50% de acetonitrilo entre 0,75–3,3 min para separar las impurezas de elución. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 25 mM de formiato de amonio. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um (GL Sciences, Tokyo, Japan)) para proporcionar 15 mg (37%) del compuesto del título {3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–metil–pirazin–2–carboxílico, en forma de un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.34–8.33 (m, 1H), 7.67 (s, br, 1H), 7.33 (d, J = 2.3 Hz, 1H), 6.76–6.72 (m, 2H), 3.89 (s, 3H), 2.64 (s, 3H), 2.54 (s, br, 2H), 2.37–2.09 (m, 10H), 1.73–1.68 (m, 2H). ESI–EM m/z: 395.0 $(M+H)^+$.

Ejemplo 19: {3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido tiazol–2–carboxílico

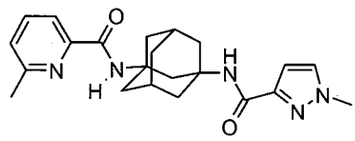


El Ejemplo 19 se sintetizó a través del procedimiento del **Esquema 2** usando cloruros de ácido carboxílico, *supra*, de la siguiente manera:

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A una solución de adamantan–1,3–diamina (17 mg, 0.1 mmol, Zerenex Molecular Ltd., Greater Manchester, UK) en DCM (2 mL) se agregó DIEA (20 mg, 0.15 mmol), cloruro de 1–metil–1*H*–pirazol–3–carbonilo (16 mg, 0.11 mmol; Maybridge Chemical Co., Cornwall, UK) y cloruro de tiazol–2–carbonilo (16 mg, 0.11 mmol; Maybridge Chemical Co., Cornwall, UK). Después de agitar a temperatura ambiente durante 3 h, la mezcla de reacción se dividió entre diclorometano y bicarbonato de sodio saturado. La capa orgánica se secó sobre sulfato de sodio y se concentró bajo presión reducida. El residuo se purificó en un sistema de purificación RP–HPLC/MS (Gradiente: acetonitrilo en agua, 25–95%, en 3,9 minutos con un ciclo de tiempo de 5 min. Se usó un gradiente superficial entre 27–53% de acetonitrilo entre 0.75–3.3 min para separar las impurezas de elución. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 25 mM de formatio a amonio. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um (GL Sciences, Tokyo, Japan)) para proporcionar 15 mg (38%) del compuesto del título {3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido tiazol–2–carboxílico, en forma de un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7.81 (d, J = 3.2 Hz, 1H), 7.53 (d, J = 3.2 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.74–6.71 (m, 2H), 3.89 (s, 3H), 2.55–2.51 (m, 2H), 2.35–2.29 (m, 2H), 2.19–2.11 (m, 8H), 1.71–1.67 (m, 2H), ESI–EM m/z: 386.0 $(M+H)^+$.

Ejemplo 20: {3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico



Se sintetizó el Ejemplo 20 a partir del Intermediario 1 a través del procedimiento del **Esquema 3**, *supra*,de la manera siguiente:

A una solución de (3–amin–adamantan–1–il)–amida de ácido 6–metil–piridin–2–carboxílico (Intermediario 1, 20 mg, 0.07 mmol) en DCM (5 mL) se agregó DIEA (30 mg, 0.2 mmol) y cloruro de 1–metil–1*H*–pirazol–3–carbonilo (20 mg, 0.1 mmol, Maybridge Chemical Co., Cornwall, UK). Después de agitar a temperatura ambiente durante 16 h, la mezcla de reacción se dividió entre diclorometano y bicarbonato de sodio saturado. La capa orgánica se secó sobre sulfato de sodio y se concentró bajo presión reducida. El residuo se purificó en un sistema de purificación RP–HPLC/MS (Gradiente: acetonitrilo en agua, 25–95%, en 3.9 minutos con un ciclo de tiempo de 5 min. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 25 mM de formiato de amonio. Columna: Inertsil® C8, 30 x 50 mm,

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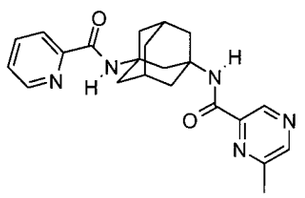
tamaño de partícula 5 um (GL Sciences, Tokyo, Japan)) para proporcionar 10 mg (30%) del compuesto del título, {3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico, en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8.07 (s, br, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.26–7.21 (m, 1H), 6.76–6.72 (m, 2H), 3.89 (s, 3H), 2.55 (s, 3H), 2.54–2.52 (m, 2H), 2.35–2.08 (m, 10H), 1.72–1.69 (m, 2H). ESI–EM m/z: 394.1 $(M+H)^+$.

De manera análoga al Ejemplo 20, se prepararon los Ejemplos 21–57 de la Tabla 1 (siguiente) a partir de aril, heteroaril o ácidos alifáticos carboxílicos o aril, heteroaril o cloruros de carbonilo alifático comercialmente obtenibles en escalas de reacción de 0,05–7,0 mmoles.

De manera análoga al Ejemplo 20, se prepararon los Ejemplos 114–130, 132–139 y 142 de la Tabla 1 (siguiente) a partir de aril, heteroaril o ácidos carboxílicos carboxílicos alifáticos, o cloruros de carbonilo alifático comercialmente obtenibles

De manera análoga al Ejemplo 20, se prepararon los Ejemplos 131 y 141 en la Tabla 1 (siguiente) a partir del ácido 4–trifluormetil–pirimidin–2–carboxilico (Intermediario 11) y ácido 4–metil–pirimidin–2–carboxilico (Intermediario 12).

Ejemplo 58: {3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxílico



El Ejemplo 58 se sintetizó a partir del Intermediario 2 a través del procedimiento del **Esquema 3**, *supra*, de la manera siguiente:

A un frasco de fondo redondo se agregó (3–amin–adamantan–1–il)–amida de ácido piridin–2–carboxílico (3.10 g, 11.0 mmol, Intermediario 2), ácido 6–metilpirazin–2–carboxílico (1.83 g, 13.3 mmol; RihaChem, Kostalov, Czech Republic) y cloruro de metileno (120 mL). A la solución se agregó luego PyBOP® (6.90 g, 13.3 mmol) seguido de trietilamina (3.85 mL, 27.6 mmol) y la reacción se agitó durante dos horas a temperatura ambiente. La reacción se transfirió a un embudo separador de 500–mL con cloruro de metileno (50 mL) y bicarbonato de sodio acuoso saturado (150 mL), y se extrajo con cloruro de metileno. Se separó la capa orgánica y la capa acuosa se extrajo nuevamente con cloruro de metileno (2 x 75 mL). Las capas orgánicas combinadas se lavaron con salmuera (150 mL),

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se secaron sobre sulfato de sodio, se filtraron y se concentraron bajo presión reducida. El residuo se purificó en un sistema de purificación RP–HPLC/MS (Gradiente: acetonitrilo en agua, 27–95%, en 3,5 min con un gradiente superficial a partir de 30–60% entre 0,75–3,4 min y un ciclo de tiempo de 5 min. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 38 mM de acetato de amonio. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um (GL Sciences, Tokyo, Japan). Fase móvil y temperatura de columna: 50 °C). Las fracciones se concentraron luego bajo presión reducida para remover la mayor parte del acetonitrilo, la capa acuosa resultante se preparó básica con bicarbonato de sodio sólido (pH > 10) y la capa acuosa se extrajo con acetato de etilo (3 x 200 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, se filtraron y concentraron bajo presión reducida para proporcionar 3.21 g (74%) del compuesto del título, {3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxilico, en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.58 (s, 1H), 8.54–8.50 (m, 1H), 8.17 (dt, J = 7.8, 1.0 Hz, 1H), 8.06 (br s, 1H), 7.85 (td, J = 7.7, 1.7 Hz, 1H), 7.77 (br s, 1H), 7.42 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 2.61–2.57 (m, 5H), 2.40–2.28 (m, 4H), 2.27–2.19 (m, 2H), 2.18–2.08 (m, 4H), 1.78–1.68 (m, 2H). ESI–EM m/z: 392.0 $(M+H)^+$.

De manera análoga al Ejemplo 58, se prepararon los Ejemplos 59–92 de la Tabla 1 (siguiente) a partir de arilo, heteroarilo o ácidos carboxílicos alifáticos, o arilo, heteroarilo o cloruros de carbonilo alifático comercialmente obtenibles en escalas de reacción de 0,05–0,5 mmoles.

De manera análoga al Ejemplo 58, se prepararon los Ejemplos 105–111 en Tabla 1 (siguiente) a partir de arilo, heteroarilo o ácidos carboxílicos alifáticos, o arilo, heteroarilo o cloruros de carbonilo alifático comercialmente obtenibles.

De manera análoga al Ejemplo 58, se preparó el Ejemplo 113 en la Tabla 1 (siguiente) a partir de ácido 4–trifluormetil–pirimidin–2–carboxílico (Intermediario 11).

De manera similar al Ejemplo 58, se prepararon los Ejemplo 93–104 en la Tabla 1 (siguiente) a partir del Intermediario 3, N–(3–amin–adamantan–1–il)–3–fluor–benzamida, y ácidos carboxílicos heteroarilo comercialmente obtenibles en escalas de reacción de 0,05–0,5 mmoles.

De manera similar al Ejemplo 58, se prepararon los Ejemplo 182 y 184 a partir del Intermediario 3, N–(3–amin–adamantan–1–il)–3–fluor–benzamida, y ácido 4–

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metil–pirimidin–2–carboxílico (Intermediario 12) y ácido 4–trifluormetil–pirimidin–2–carboxílico (Intermediario 11), respectivamente.

De manera similar al Ejemplo 58, se preparó el Ejemplo 183 en la Tabla 1 (siguiente) a partir del Intermediario 3, N–(3–amin–adamantan–1–il)–3–fluor–benzamida, y un ácido heteroaril carboxílico comercialmente obtenible.

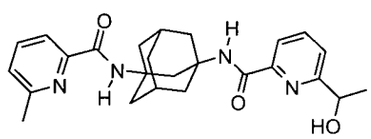
De manera similar al Ejemplo 58, se prepararon los Ejemplos 145–179 en la Tabla 1 (siguiente) a partir del Intermediario 8, (3–amin–adamantan–1–il)–amida de ácido 6–metil–pirazin–2–carboxílico, y ácidos aril o heteroaril carboxílicos comercialmente obtenibles, mientras que el Ejemplo 181 en la Tabla 1 (siguiente) se preparó a partir del Intermediario 8 y ácido 4–trifluormetil–pirimidin–2–carboxilico (Intermediario 11).

De manera similar al Ejemplo 58, se prepararon los Ejemplos 185–188 en la Tabla 1 (siguiente) a partir del Intermediario 7, (3–amin–adamantan–1–il)–amida de ácido pirazin–2–carboxílico, y ácidos heteroaril carboxílicos comercialmente obtenibles; y el Ejemplo 189 se preparó a partir del Intermediario 7 y ácido 4–metil–pirimidin–2–carboxílico (Intermediario 12).

De manera similar al Ejemplo 58, se prepararon los Ejemplos 191–193 en la Tabla 1 (siguiente) a partir del Intermediario 10, (3–amin–adamantan–1–il)–amida de ácido 2–metil–pirimidin–4–carboxílico, y ácido 5–fluor–piridin–2–carboxílico comercialmente obtenible (Beta Pharm, Inc., New Haven, CT, USA), ácido 4–trifluormetil–pirimidin–2–carboxilico (Intermediario 11) o ácido 4–metil–pirimidin–2–carboxílico (Intermediario 12).

De manera similar al Ejemplo 58, se prepararon los Ejemplos 194–196 en la Tabla 1 (siguiente) a partir del Intermediario 9, (3–amin–adamantan–1–il)–amida de ácido pirimidin–4–carboxilico, y ácido 4–metil–pirimidin–2–carboxílico (Intermediario 12), ácido 5–fluor–piridin–2–carboxílico comercialmente obtenible o ácido 4–trifluormetil–pirimidin–2–carboxílico (Intermediario 11).

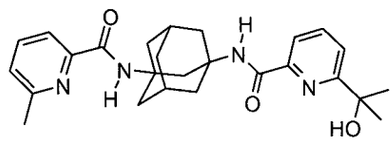
Ejemplo 143: {3–[(6–(1–hidroxi–etil)–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico



Se preparó el Ejemplo 143 en la Tabla 1 (siguiente) a partir del Ejemplo 142 a través de la reducción de $NaBH_4$, *supra*, de la manera siguiente:

En un frasco que contenía {3–[(6–acetil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico (50 mg, 0.1 mmol, Ejemplo 142) en MeOH (2 mL) se agregó borohidruro de sodio (6 mg, 0.17 mmol) a 0 °C. Después de agitar durante 2 h, la mezcla de reacción se concentró y se dividió entre diclorometano y bicarbonato de sodio saturado. La capa orgánica se secó sobre sulfato de sodio y se concentró bajo presión reducida. El residuo se purificó en un sistema de purificación RP–HPLC/MS (Gradiente: acetonitrilo en agua, 25–95%, en 3.6 min con un gradiente superficial desde 33–63% de acetonitrilo entre 0,75–3,3 min y un ciclo de tiempo de 5 min. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 48 mM de formiato de amonio. Columna: Inertsil® C18, 30 x 50 mm, tamaño de partícula 5 um) para proporcionar 45 mg (90%) del compuesto del título, {3–[(6–(1–hidroxi–etil)–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8.07–8.00 (m, 2H), 7.90–(d, J = 7.9 Hz, 1H), 7.78 (t, J = 7.9 Hz, 1H), 7.74 (s, b, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8, Hz 1H), 7.20–7.06 (m, 1H), 4.91–4.85 (m, 1H), 2.50 (s, b, 5H), 2.31–2.26 (m, 2H), 2.21–2.06 (m, 8H), 1.69–1.64 (m, 2H), 1.48 (s, 3H). ESI–EM m/z: 435.0 $(M+H)^+$.

Ejemplo 144: (3–{[6–(1–hidroxi–1–metil–etil)–piridin–2–carbonil]–amino}–adamantan–1–il)–amida de ácido 6–metil–piridin–2–carboxílico

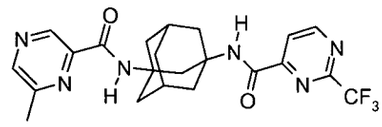


El Ejemplo 144 en la Tabla 1 (siguiente) se preparó a partir del Ejemplo 142 a través de la reacción de Grignard, *supra*, de la manera siguiente:

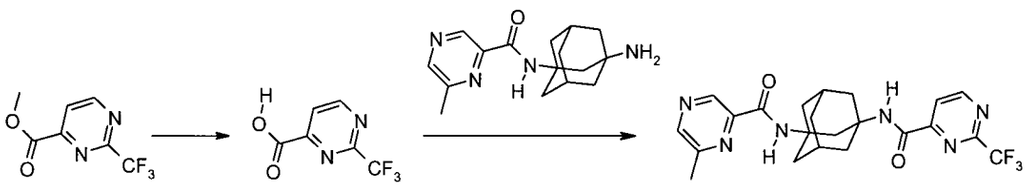
En un frasco que contenía {3–[(6–acetil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico (35 mg, 0.08 mmol, Ejemplo 142) en THF (2 mL) se agregó metil litio 1M (0,4 mL) a –40°C. Después de agitar durante 2 h, la mezcla de reacción se apagó con agua fría, se concentró y dividió entre diclorometano y bicarbonato de sodio saturado. La capa orgánica se secó sobre sulfato de sodio y se concentró bajo presión reducida. El residuo se purificó en un sistema de purificación RP–HPLC/MS (Gradiente: acetonitrilo en agua, 28–95%, en 3.6 min con un gradiente superficial de desde 33–60% de acetonitrilo entre 0.75–3.4 min y un ciclo de tiempo de 5 min. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 48 mM de formiato de amonio. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um) para proporcionar 25 mg (69%) del compuesto del título, (3–{[6–(1–hidroxi–1–metil–

etil)–piridin–2–carbonil]–amino}–adamantan–1–il)–amida de ácido 6–metil–piridin–2–carboxílico. ^{1}H RMN (400 MHz, CDCl3) δ 8.10–8.06 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H), 7.86 (t, J = 7.8 Hz, 1H), 7.75 (s, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.26–7.22 (m, 1H), 2.58–2.55 (m, 5H), 2.39–2.13 (m, 10H), 1.76–1.71 (m, 2H), 1.59 (s, 6H). ESI–EM m/z: 449.0 (M+H)+.

Ejemplo 180: {3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–trifluormetil–pirimidin–4–carboxílico



Se preparó el Ejemplo 180 en la Tabla 1 (siguiente) a través del procedimiento del **Esquema 3** a partir del Intermediario 8 y ácido 2–trifluormetil–pirimidin–4–carboxílico, que se preparó a partir del éster correspondiente, *supra*,de la manera siguiente:



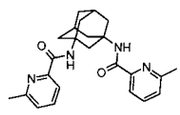
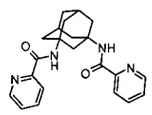
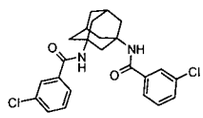
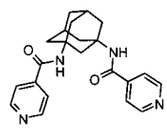
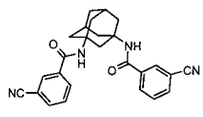
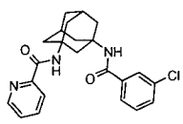
A un frasco de microondas se agregó éster metílico de ácido 2–trifluormetil–pirimidin–4–carboxílico (110 mg, 0.52 mmol, CNH Tech, MA), THF (2 mL), e hidróxido de litio (18 mg, 0.75 mmol) en 200 µL de agua. La mezcla se calentó en un horno de microondas durante 5 minutos a 100 °C, y luego se concentró hasta sequedad bajo presión reducida. Al residuo se le agregó el Intermediario 8, (3–amin–adamantan–1–il)–amida de ácido 6–metil–pirazin–2–carboxílico (100 mg, 0,4 mmol), THF (5 mL), DIEA (90 mg, 0.7 mmol) y TBTU (140 mg, 0.42 mmol, AKSCI, CA). Después de agitar a temperatura ambiente durante 16 horas, la mezcla de reacción se concentró y se dividió entre DCM y bicarbonato de sodio saturado. La capa orgánica se separó, se secó sobre sulfato de sodio, se filtró y se concentró hasta sequedad bajo presión reducida. El producto crudo se purificó en un sistema RP–HPLC/MS (Gradiente: acetonitrilo en agua, 30–95%, en 3,6 min con un ciclo de tiempo de 5 min. con un gradiente superficial de desde 40–68% de acetonitrilo entre 0,75–3,4 min. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 48 mM de formiato de amonio.. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um) para proporcionar 60 mg (40%) del compuesto del título, {3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido

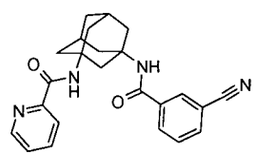
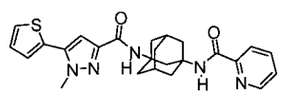
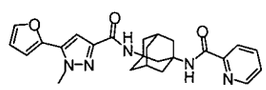
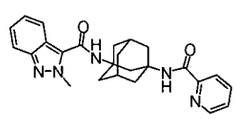
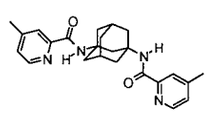
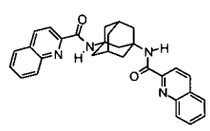
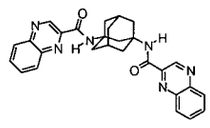
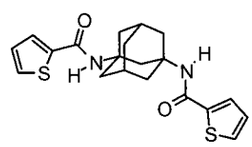
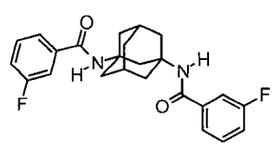
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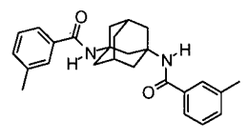
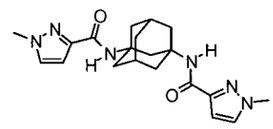
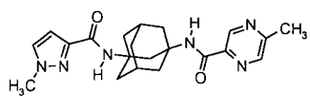
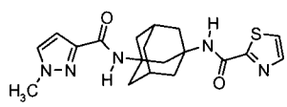
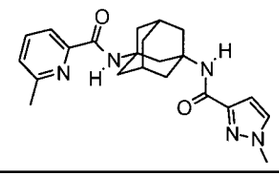
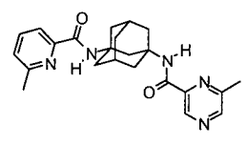
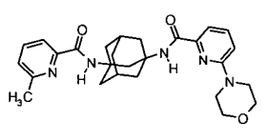
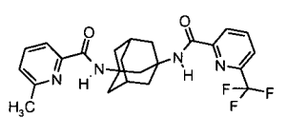
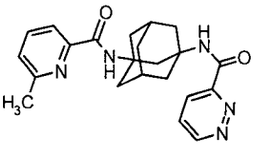
2–trifluormetil–pirimidin–4–carboxílico. ^{1}H RMN (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 9.12 (d, J =5.0, 1H), 8.6 (s, 1H), 8.28 (d, J =5.0, 1H), 7.80–7.75 (m, 2H), 2.6 (s, b, 5H), 2.42–2.36 (m, 2H), 2.23–2.17 (m, 8H), 1.77–1.73(m, 2H). ESI–EM m/z: 460.9 $(M+H)^+$.

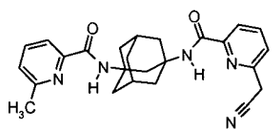
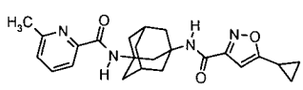
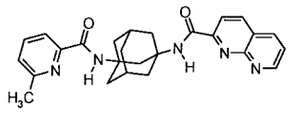
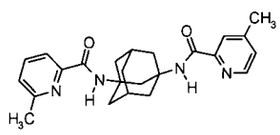
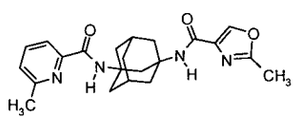
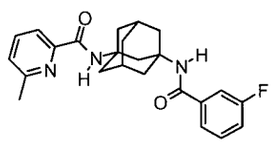
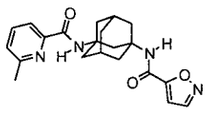
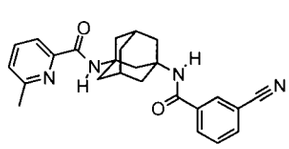
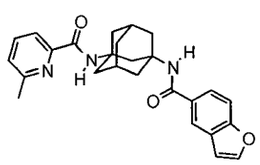
De manera similar al Ejemplo 180, se prepararon los Ejemplos 112, 140 y 190 en la Tabla 1 (siguiente) a partir del Intermediario 2, (3–amin–adamantan–1–il)–amida de ácido piridin–2–carboxílico, Intermediario 1, (3–amin–adamantan–1–il)–amida de ácido 6–metil–piridin–2–carboxilico, e Intermediario 7, (3–amin–adamantan–1–il)–amida de ácido pirazin–2–carboxílico, respectivamente.

Tabla 1

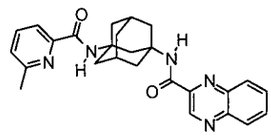
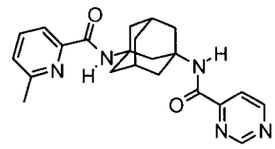
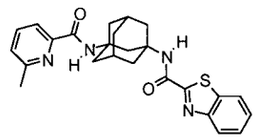
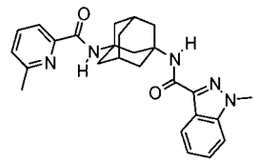
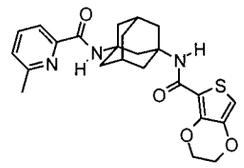
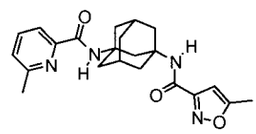
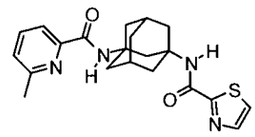
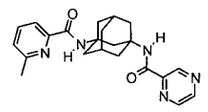
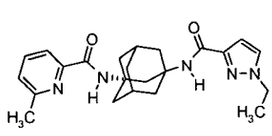
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
1		*N,N'*–(1,3–adamantilen)bis(6–metil–piridin–2–carboxamida)
2		*N,N'*–(1,3–adamantilen)bis(2–piridincarboxamida)
3		*N,N'*–(1,3–adamantilen)bis(3–cloro–benzamida)
4		*N,N'*–(1,3–adamantilen)bis(4–piridincarboxamida)
5		*N,N'*–(1,3–adamantilen)bis(3–ciano–benzamida)
6		[3–(3–cloro–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico

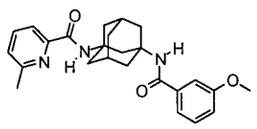
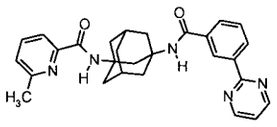
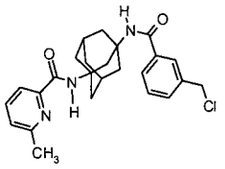
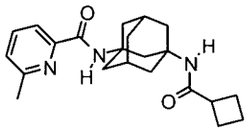
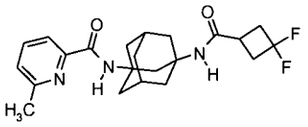
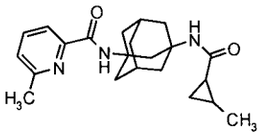
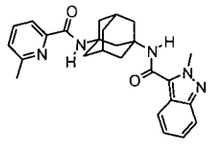
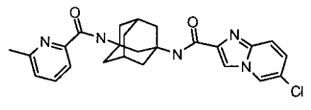
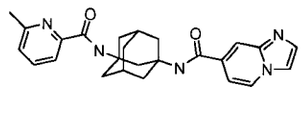
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
7		[3–(3–ciano–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico
8		{3–[(1–metil–5–tiofen–2–il–1H–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico
9		{3–[(5–furan–2–il–1–metil–1H–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico
10		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–metil–2H–indazol–3–carboxílico
11		*N,N'*–(1,3–adamantilen)bis(4–metil–piridin–2–carboxamida)
12		*N,N'*–(1,3–adamantilen)bis(quinolin–2–carboxamida)
13		*N,N'*–(1,3–adamantilen)bis(quinoxalin–2–carboxamida)
14		*N,N'*–(1,3–adamantilen)bis(tiofen–2–carboxamida)
15		*N,N'*–(1,3–adamantilen)bis(3–fluorbenzamida)

EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
16		*N,N'*–(1,3–adamantilen)bis(3–metilbenzamida)
17		*N,N'*–(1,3–adamantilen)bis(1–metil–1*H*–pirazol–3–carboxamida)
18		{3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–metil–pirazin–2–carboxílico
19		{3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido tiazol–2–carboxílico
20		{3–[(1–metil–1H–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
21		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxílico
22		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–morfolin–4–il–piridin–2–carboxílico
23		{3–[(6–metil–piridin–2–carbonil)–amino] –adamantan–1–il}–amida de ácido 6–trifluormetil–piridin–2–carboxílico
24		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido piridazin–3–carboxílico

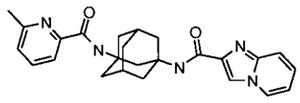
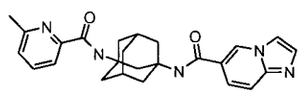
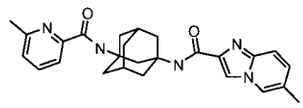
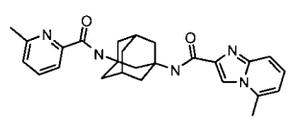
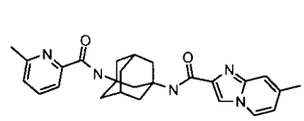
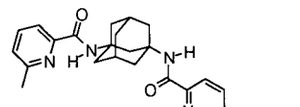
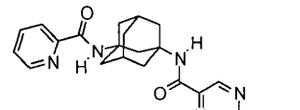
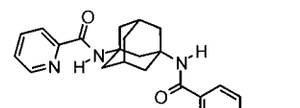
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
25		{3–[(6–metil–piridin–2–carbonil)–amino] –adamantan–1–il}–amida de ácido 6–cianometil–piridin–2–carboxílico
26		{3–[(5–ciclopropil–isoxazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
27		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido [1,8]naftiridin–2–carboxílico
28		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–metil–piridin–2–carboxílico
29		{3–[(2–metil–oxazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
30		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico
31		{3–[(isoxazol–5–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico
32		[3–(3–ciano–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico
33		{3–[(benzofuran–5–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico

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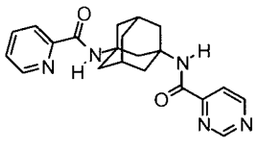
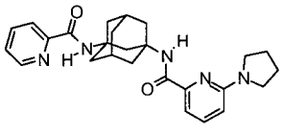
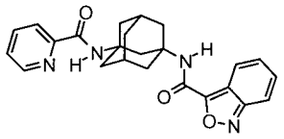
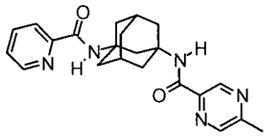
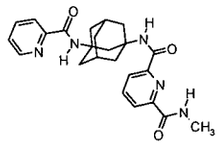
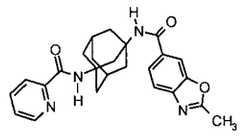
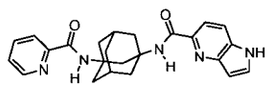
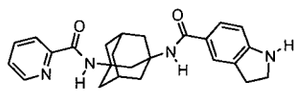
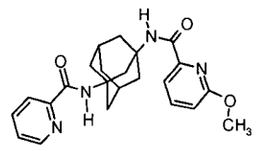
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
34		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido quinoxalin–2–carboxílico
35		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido pirimidin–4–carboxílico
36		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido benzotiazol–2–carboxílico
37		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 1–Metil–1*H*–indazol–3–carboxílico
38		{3–[(2,3–dihidro–tieno[3,4–b][1,4]dioxin–5–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
39		{3–[(5–metil–isoxazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
40		{3–[(tiazol–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
41		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido pirazin–2–carboxílico
42		{3–[(1–etil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico

EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
43		[3–(3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico
44		[3–(3–pirimidin–2–il–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico
45		[3–(3–clorometil–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico
46		[3–(ciclobutancarbonil–amino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico
47		{3–[(3,3–difluor–ciclobutancarbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
48		{3–[(2–metil–ciclopropancarbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
49		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–metil–2*H*–indazol–3–carboxílico
50		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–cloro–imidazo[1,2–a]piridin–2–carboxílico
51		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–7–carboxílico

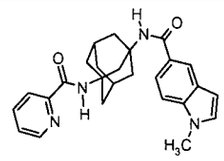
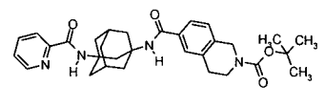
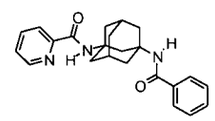
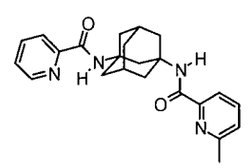
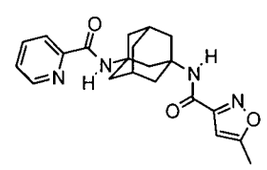
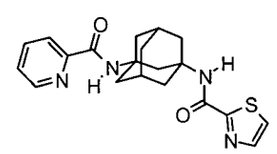
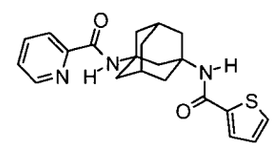
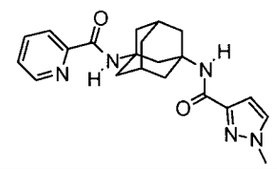
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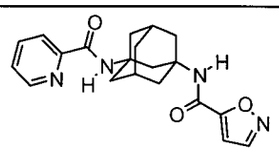
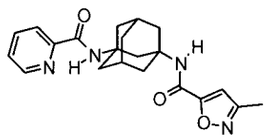
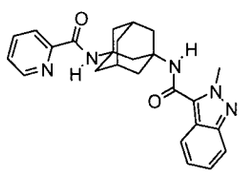
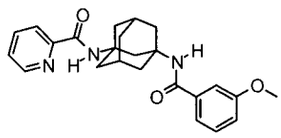
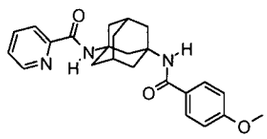
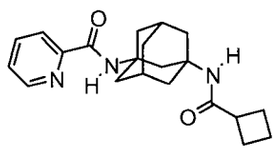
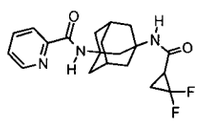
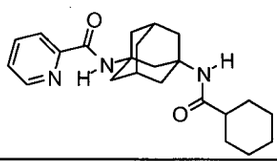
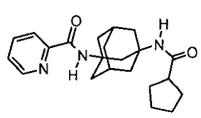
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
52		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–2–carboxílico
53		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–6–carboxílico
54		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–imidazo[1,2–a]piridin–2–carboxílico
55		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–metil–imidazo[1,2–a]piridin–2–carboxílico
56		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 7–metil–imidazo[1,2–a]piridin–2–carboxílico
57		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–cloro–piridin–2–carboxílico
58		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
59		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico

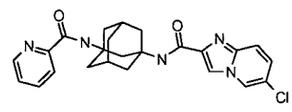
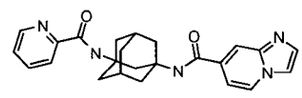
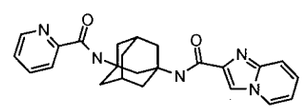
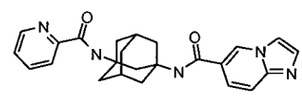
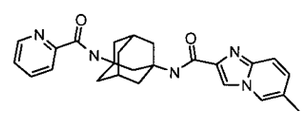
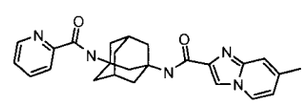
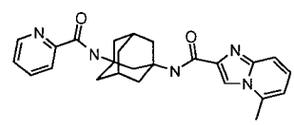
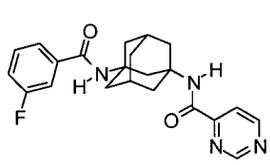
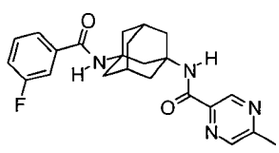
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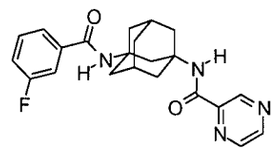
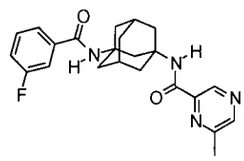
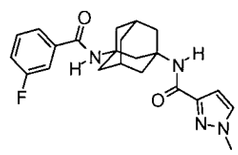
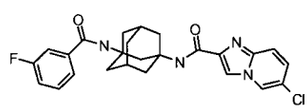
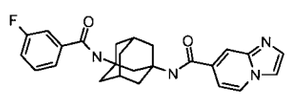
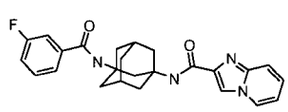
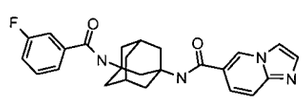
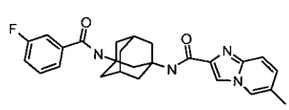
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
60		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido pirimidin–4–carboxílico
61		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–pirrolidin–1–il–piridin–2–carboxílico
62		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Benzo[c]isoxazol–3–carboxílico
63		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–Metil–pirazin–2–carboxílico
64		6–({3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2,6–dicarboxílico 2–metilamida)
65		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–Metil–benzoxazol–6–carboxílico
66		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 1*H*–Pirrol[3,2–b]piridin–5–carboxílico
67		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2,3–dihidro–1*H*–indol–5–carboxílico
68		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metoxi–piridin–2–carboxílico

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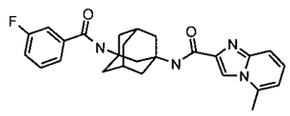
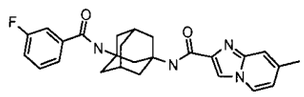
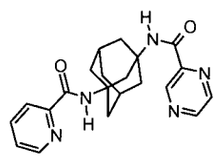
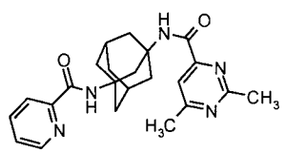
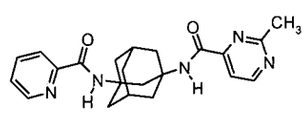
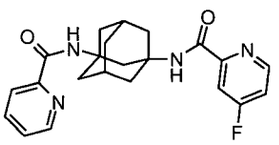
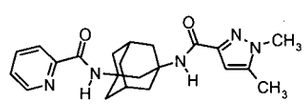
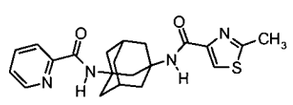
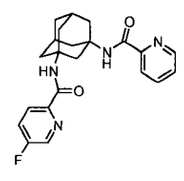
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
69		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 1–Metil–1*H*–indol–5–carboxílico
70		Ester ter–butílico de ácido 6–{3–[(Piridin–2–carbonil)–amino]–adamantan–1–il–carbamoil}–3,4–dihidro–1H–isoquinolin–2–carboxílico
71		(3–benzoilamin–adamantan–1–il)–amida de ácido Piridin–2–carboxílico
72		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico
73		{3–[(5–metil–isoxazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico
74		{3–[(tiazol–2–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico
75		{3–[(tiofen–2–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico
76		{3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico

EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
77		{3–[(isoxazol–5–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2–carboxílico
78		{3–[(3–metil–isoxazol–5–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2–carboxílico
79		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–metil–2*H*–indazol–3–carboxílico
80		[3–(3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido Piridin–2–carboxílico
81		[3–(4–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido Piridin–2–carboxílico
82		[3–(ciclobutancarbonil–amino)–adamantan–1–il]–amida de ácido Piridin–2–carboxílico
83		{3–[(2,2–difluor–ciclopropancarbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2–carboxílico
84		[3–(ciclohexancarbonil–amino)–adamantan–1–il]–amida de ácido Piridin–2–carboxílico
85		[3–(ciclopentancarbonil–amino)–adamantan–1–il]–amida de ácido Piridin–2–carboxílico

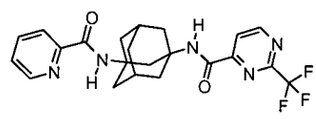
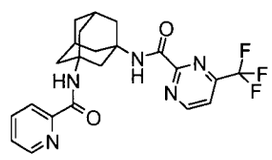
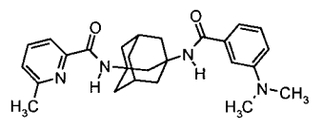
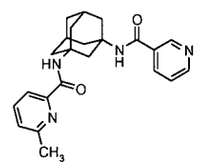
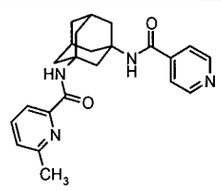
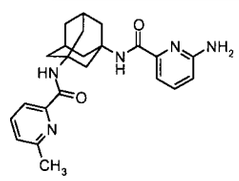
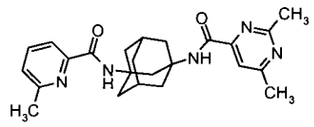
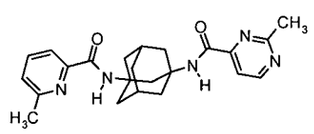
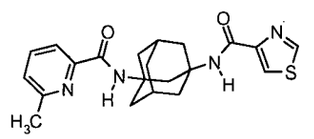
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
86		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Cloro–imidazo[1,2–a]piridin–2–carboxílico
87		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–7–carboxílico
88		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–2–carboxílico
89		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–6–carboxílico
90		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–imidazo[1,2–a]piridin–2–carboxílico
91		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 7–Metil–imidazo[1,2–a]piridin–2–carboxílico
92		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–Metil–imidazo[1,2–a]piridin–2–carboxílico
93		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido Pirimidin–4–carboxílico
94		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 5–Metil–pirazin–2–carboxílico

EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
95		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido Pirazin–2–carboxílico
96		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
97		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 1–Metil–1*H*–pirazol–3–carboxílico
98		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Cloro–imidazo[1,2–a]piridin–2–carboxílico
99		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido Imidazo[1,2–a]piridin–7–carboxílico
100		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido Imidazo[1,2–a]piridin–2–carboxílico
101		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido Imidazo[1,2–a]piridin–6–carboxílico
102		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–imidazo[1,2–a]piridin–2–carboxílico

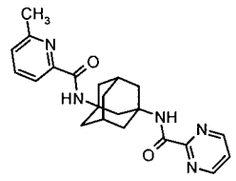
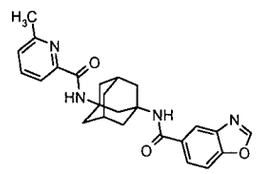
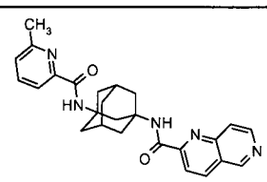
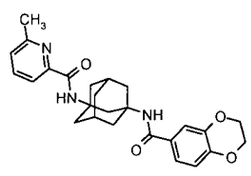
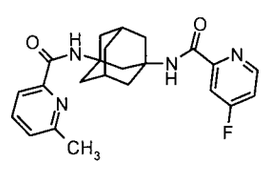
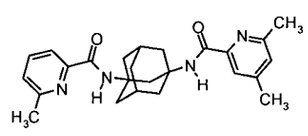
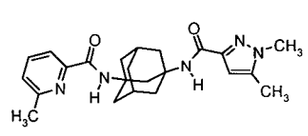
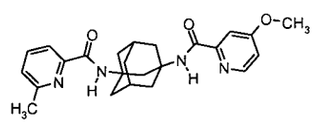
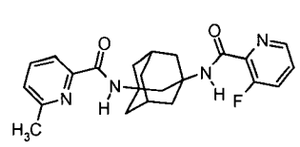
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EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
103		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 5–Metil–imidazo[1,2–a]piridin–2–carboxílico
104		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 7–metil–imidazo[1,2–a]piridin–2–carboxílico
105		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirazin–2–carboxílico
106		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2,6–dimetil–pirimidin–4–carboxílico
107		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–metil–pirimidin–4–carboxílico
108		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–fluor–piridin–2–carboxílico
109		{3–[(1,5–dimetil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico
110		{3–[(2–metil–tiazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico
111		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–fluor–piridin–2–carboxílico

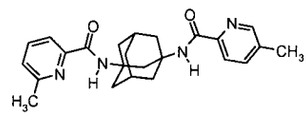
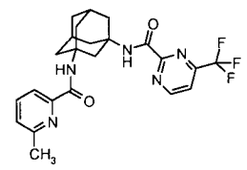
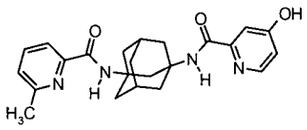
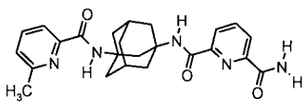
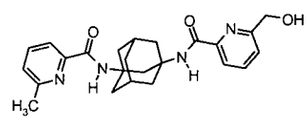
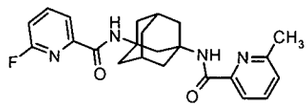
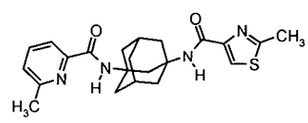
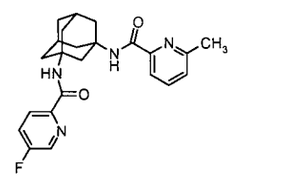
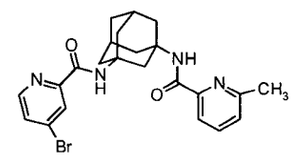
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EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
112		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–trifluormetil–pirimidin–4–carboxílico
113		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–trifluormetil–pirimidin–2–carboxílico
114		[3–(3–dimetilamin–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–piridin–2–carboxílico
115		{3–[(piridin–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico
116		{3–[(piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
117		{3–[(6–aminopiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
118		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2,6–dimetil–pirimidin–4–carboxílico
119		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–Metil–pirimidin–4–carboxílico
120		{3–[(tiazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico

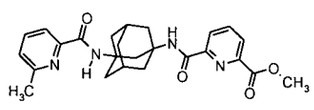
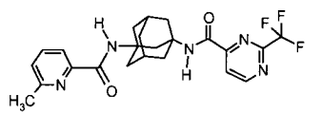
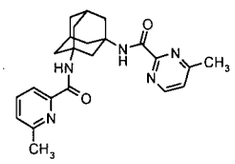
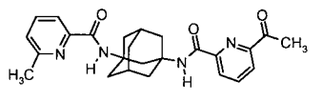
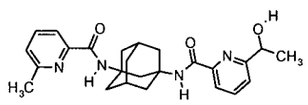
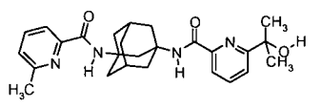
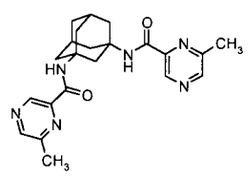
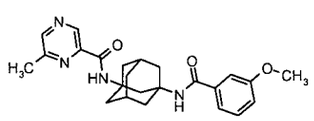
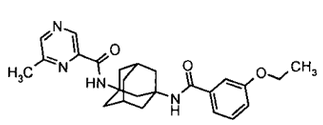
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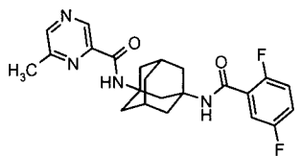
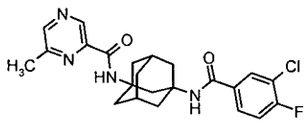
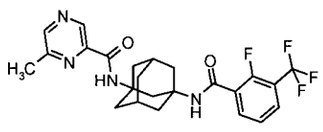
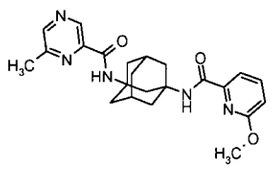
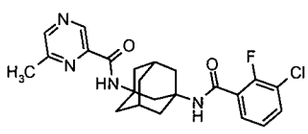
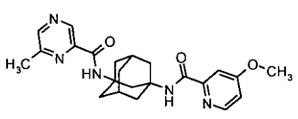
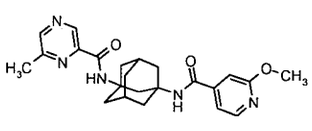
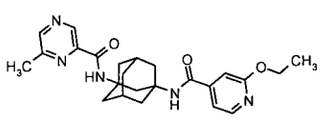
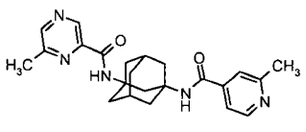
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
121		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido pirimidin–2–carboxílico
122		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido benzoxazol–5–carboxílico
123		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido [1,6]naftiridin–2–carboxílico
124		{3–[(2,3–dihidro–benzo[1,4]dioxin–6–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico
125		{3–[(4–fluorpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico
126		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4,6–dimetil–piridin–2–carboxílico
127		{3–[(1,5–dimetil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
128		{3–[(4–metoxipiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
129		{3–[(3–fluorpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico

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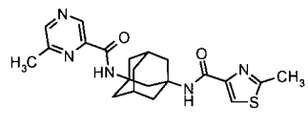
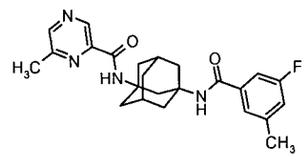
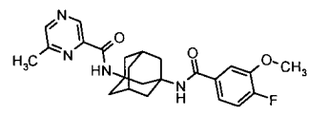
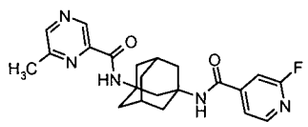
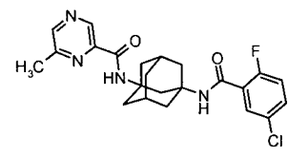
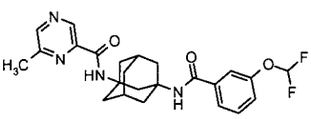
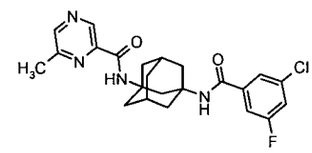
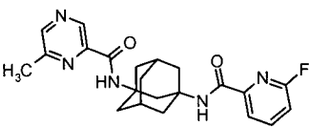
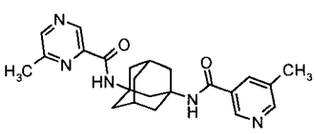
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
130		{3–[(5–metilpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
131		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–trifluormetil–pirimidin–2–carboxílico
132		{3–[(4–hidroxipiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
133		6–({3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2,6–dicarboxílico
134		{3–[(6–hidroximetilpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico
135		{3–[(6–fluorpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico
136		{3–[(2–metil–tiazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico
137		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–fluor–piridin–2–carboxílico
138		{3–[(4–bromopiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico

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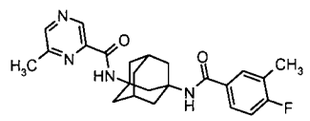
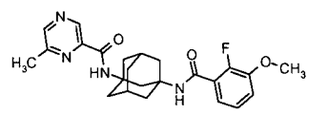
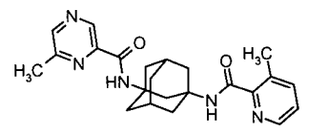
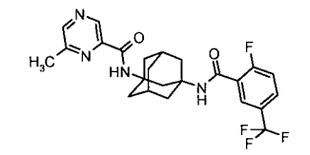
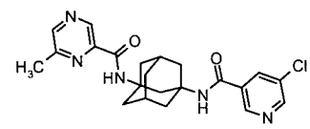
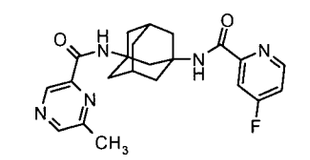
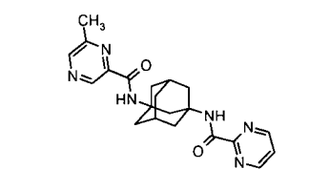
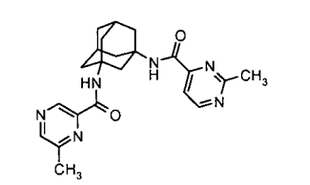
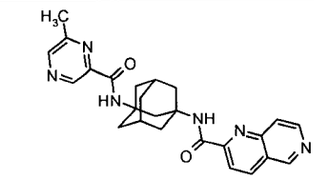
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
139		Ester metílico de ácido 6–{3–[(6–Metil–piridin–2–carbonil)–amino]–adamantan–1–ilcarbamoil}–piridin–2–carboxílico
140		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–trifluormetil–pirimidin–4–carboxílico
141		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–metil–pirimidin–2–carboxílico
142		{3–[(6–acetilpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
143		{3–[(6–(1–hidroxi–etil)–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
144		{3–[(6–(1–hidroxi–1–metil–etil)–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico
145		*N,N'*–(1,3–adamantilen)bis(6–metil–pirazin–2–carboxamida)
146		[3–(3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
147		[3–(3–etoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–pirazin–2–carboxílico

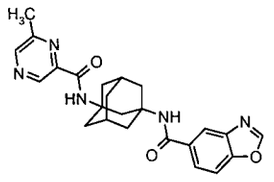
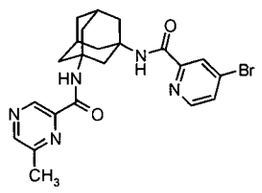
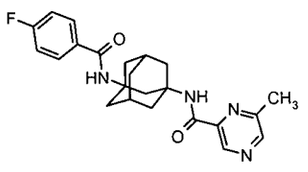
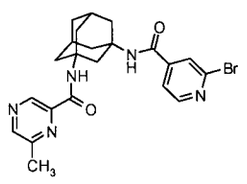
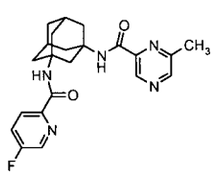
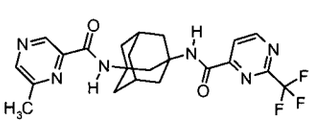
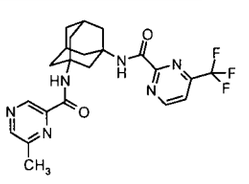
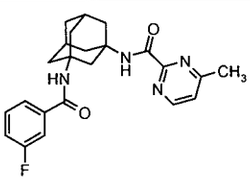
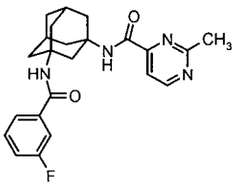
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
148		[3–(2,5–difluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–pirazin–2–carboxílico
149		[3–(3–cloro–4–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
150		[3–(2–fluor–3–trifluormetil–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–pirazin–2–carboxílico
151		{3–[(6–metoxi–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
152		[3–(3–cloro–2–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
153		{3–[(4–metoxi–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
154		{3–[(2–metoxi–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
155		{3–[(2–etoxi–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
156		{3–[(2–metil–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico

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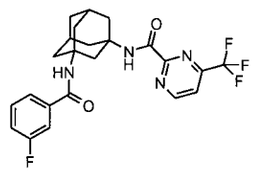
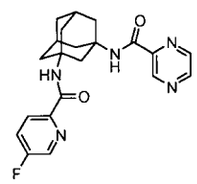
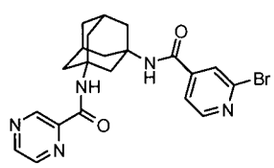
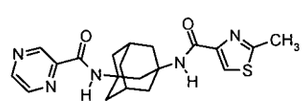
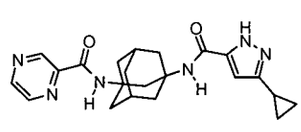
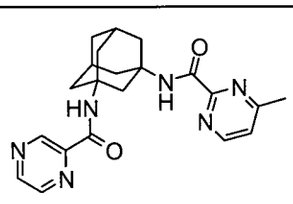
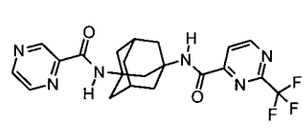
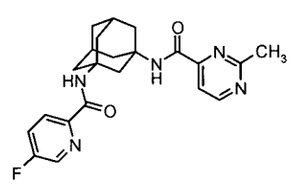
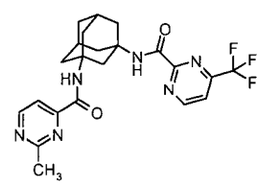
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
157		{3–[(2–metil–tiazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
158		[3–(3–fluor–5–metil–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
159		[3–(4–fluor–3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
160		{3–[(2–fluor–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
161		[3–(5–cloro–2–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
162		[3–(3–difluormetoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
163		[3–(3–cloro–5–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
164		{3–[(6–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
165		{3–[(5–metil–piridin–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico

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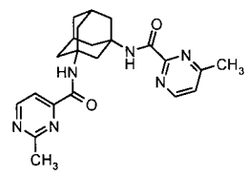
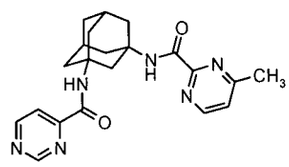
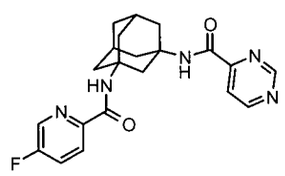
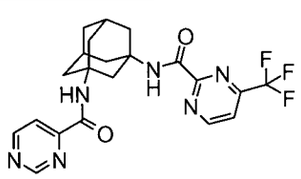
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
166		[3–(4–fluor–3–metil–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
167		[3–(2–fluor–3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
168		{3–[(3–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
169		[3–(2–fluor–5 trifluormetil–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
170		{3–[(5–cloro–piridin–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
171		{3–[(4–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
172		{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirimidin–2–carboxílico
173		{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–Metil–pirimidin–4–carboxílico
174		{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido [1,6]Naftiridin–2–carboxílico

EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
175		{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido benzoxazol–5–carboxílico
176		{3–[(4–bromo–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
177		[3–(4–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico
178		{3–[(2–bromo–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
179		{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
180		{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–trifluormetil–pirimidin–4–carboxílico
181		{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–trifluormetil–pirimidin–2–carboxílico
182		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 4–Metil–pirimidin–2–carboxílico
183		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 2–Metil–pirimidin–4–carboxílico

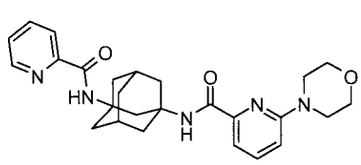
222

EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
184		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 4–trifluormetil–pirimidin–2–carboxílico
185		{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirazin–2–carboxílico
186		{3–[(2–bromo–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido pirazin–2–carboxílico
187		{3–[(2–metil–tiazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirazin–2–carboxílico
188		{3–[(5–ciclopropil–2H–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirazin–2–carboxílico
189		{3–[(pirazin–2–carbonil)–amino] –adamantan–1–il}–amida de ácido 4–Metil–pirimidin–2–carboxílico
190		{3–[(pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–trifluormetil–pirimidin–4–carboxílico
191		{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–metil–pirimidin–4–carboxílico
192		{3–[(2–metil–pirimidin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–trifluormetil–pirimidin–2–carboxílico

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EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
193		{3–[(4–metil–pirimidin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–Metil–pirimidin–4–carboxílico
194		{3–[(pirimidin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Metil–pirimidin–2–carboxílico
195		{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirimidin–4–carboxílico
196		{3–[(pirimidin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–trifluormetil–pirimidin–2–carboxílico

Ejemplo 197: {3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–morfolin–4–il–piridin–2–carboxílico



Se sintetizó el Ejemplo 197 en la Tabla 2 (siguiente) a partir del Intermediario 4 a través del procedimiento del **Esquema 7**, *supra*,de la manera siguiente:

A un frasco de microondas se agregó una barra agitadora, {3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–cloro–piridin–2–carboxílico (Intermediario 4, 20 mg, 0.05 mmol), DMA (1.0 mL), morfolina (0.05 mL) y carbonato de cesio (60 mg, 0.15 mmol). La mezcla se calentó a 180 °C bajo irradiación microondas durante 15 minutos.

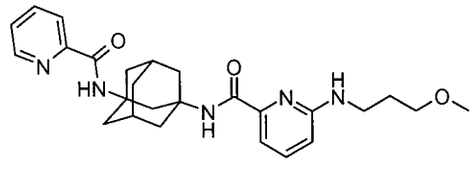
La mezcla de reacción se enfrió a temperatura ambiente. El solvente se removió en un sistema de evaporación de solvente de alto rendimiento HT–4X (Genevac Inc., *supra*). El residuo se disolvió en DCM (2 mL), se lavó con NaOH ac. 1N (2 mL) y agua (2 x 2 mL). Después de remover el solvente, el residuo se purificó en un sistema de purificación RP–HPLC/MS (Gradiente: acetonitrilo en agua con un ciclo de tiempo de 5 min. Régimen de Flujo: 100 mL/min. Aditivo de

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fase móvil: 25 mM de acetato de amonio. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um (GL Sciences, Tokyo, Japan)) para proporcionar 1,3 mg del compuesto del título, {3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–morfolin–4–il–piridin–2–carboxílico. Se verificó la calidad del producto (QC) mediante LC–EM (Gradiente: acetonitrilo en agua, 30–90%, en 1,7 minutos con un ciclo de tiempo de 2 min. Régimen de Flujo: 5.0 mL/min. Aditivo de fase móvil: 30 mM de formiato de amonio. Columna: Inertsil® C8, 50 x 4.6 mm, tamaño de partícula 3 um (GL Sciences, Tokyo, Japan)): Tiempo de retención: 1.26 min; pureza (UV_{254}): 95%; ESI–EM m/z: 462.1 $(M+H)^+$.

De manera análoga al Ejemplo 197, se sintetizaron los Ejemplos 198–203 en la Tabla 2 (siguiente) a partir del Intermediario 4 y aminas comercialmente obtenibles en escalas de 0,05–0,3 mmoles; se sintetizaron los Ejemplos 204–211 en la Tabla 2 (siguiente) a partir del Intermediario 5 y aminas comercialmente obtenibles en una escala de 0,05 mmoles; y se sintetizaron los Ejemplos 212–219 en la Tabla 2 (siguiente) a partir del Intermediario 6 y aminas comercialmente obtenibles en una escala de 0,05 mmoles.

Ejemplo 220: {3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–metoxi–propilamino)–piridin–2–carboxílico



Se sintetizó el Ejemplo 220 en la Tabla 2 (siguiente) a partir del Intermediario 4 a través del procedimiento del **Esquema 7**, *supra*, de la manera siguiente:

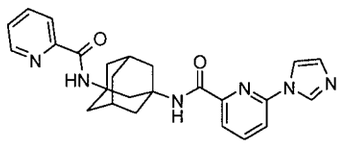
A un frasco de microondas se agregó una barra agitadora, {3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–cloro–piridin–2–carboxílico (Intermediario 4, 20 mg, 0.05 mmol), óxido de cobre (II) (20 mg, 0.2 mmole), DMA (1 mL), 3–metoxi–propilamina (0.05 mL) y carbonato de cesio (120 mg, 0.3 mmol). La mezcla se calentó a 230 °C bajo irradiación por microondas durante 30 min. El solvente se removió en Genevac. El residuo se disolvió en DCM (2 mL), se lavó con NaOH ac. 1N (2 mL), y agua (2 x 2 mL). Después de remover el solvente, se purificó el producto crudo en un sistema RP–HPLC/MS (Gradiente: acetonitrilo en agua con un ciclo de tiempo de 5 min. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 25 mM de acetato de amonio.. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um (GL Sciences, Tokyo, Japan)) para proporcionar 3,9 mg del compuesto del título, {3–[(piridin–2–carbonil)–amino]–

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adamantan–1–il}–amida de ácido 6–(3–metoxi–propilamino)–piridin–2–carboxílico. El producto se quality checked (QC) mediante LC–EM (Gradiente: acetonitrilo en agua, 30–90%, en 1,7 minutos con un ciclo de tiempo de 2 min. Régimen de Flujo: 5.0 mL/min. Aditivo de fase móvil: 30 mM de formiato de amonio. Columna: Inertsil® C8, 50 x 4.6 mm, tamaño de partícula 3 um (GL Sciences, Tokyo, Japan)): Tiempo de retención: 1.29 min; pureza (UV_{254}): 94%; ESI–EM m/z: 464.6 $(M+H)^+$.

De manera análoga al Ejemplo 220, se sintetizaron los Ejemplos 219–230 en la Tabla 2 (siguiente) a partir del Intermediario 4 y aminas comercialmente obtenibles en escalas de 0,05–0.3 mmoles; se sintetizaron los Ejemplos 231–240 en la Tabla 2 (siguiente) a partir del Intermediario 5 y aminas comercialmente obtenibles en una escala de a 0,05 mmoles; y se sintetizaron los Ejemplos 241–252 en la Tabla 2 (siguiente) a partir del Intermediario 6 y aminas comercialmente obtenibles en una escala de 0,05 mmoles.

Ejemplo 253: {3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Imidazol–1–il–piridin–2–carboxilico



Se sintetizó el Ejemplo 253 en la Tabla 2 (siguiente) a partir del Intermediario 4 a través del procedimiento del **Esquema 7**, *supra*,de la manera siguiente:

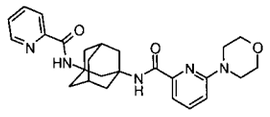
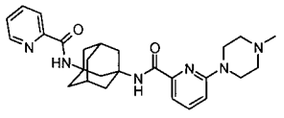
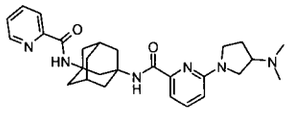
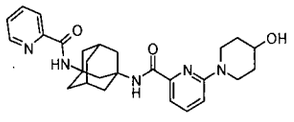
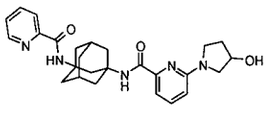
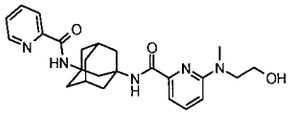
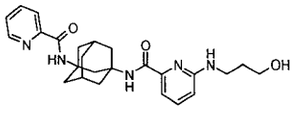
A un frasco de microondas se le agregó una barra agitadora, {3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–cloro–piridin–2–carboxílico (Intermediario 4, 20 mg, 0.05 mmol), cobre (II) acetoacetonato (20 mg), DMA (1 mL), imidazol (50 mg, 0.73 mmol) y carbonato de cesio (60 mg, 0.15 mmol). La mezcla se calentó a 180 °C bajo irradiación de microondas durante 15 minutos. El solvente se removió en un sistema de evaporación de solvente de alto rendimiento HT–4X (Genevac, Inc., *supra*). El residuo se disolvió en DCM (2 mL), se lavó con NaOH ac. 1N (2 mL), y agua (2 x 2 mL). Después de remover el solvente, el residuo se purificó en un sistema RP–HPLC/MS (Gradiente: acetonitrilo en agua con un ciclo de tiempo de 5 min. Régimen de Flujo: 100 mL/min. Aditivo de fase móvil: 25 mM de acetato de amonio. Columna: Inertsil® C8, 30 x 50 mm, tamaño de partícula 5 um (GL Sciences, Tokyo, Japan) para proporcionar 4,5 mg del compuesto del título, {3–[(piridin–2–carbonil)–amino]–

220

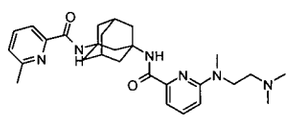
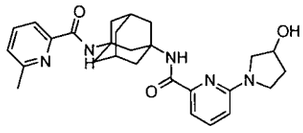
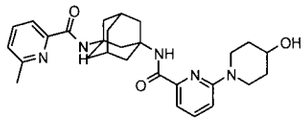
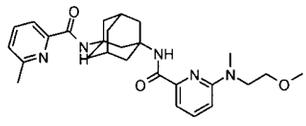
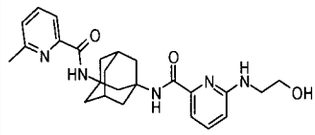
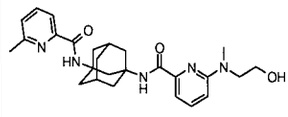
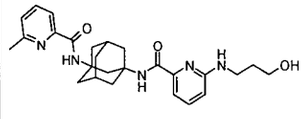
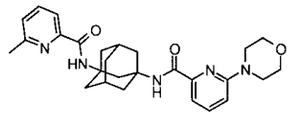
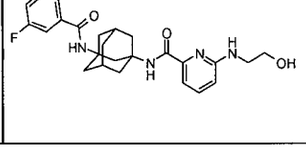
adamantan–1–il}–amida de ácido 6–imidazol–1–il–piridin–2–carboxílico. ESI–EM m/z: 443.5 $(M+H)^+$.

De manera análoga al Ejemplo 253, se sintetizaron los Ejemplos 254–255 en la Tabla 2 (siguiente) en una escala de reacción de 0,05 mmoles a partir de los Intermediarios 5 y 6, respectivamente.

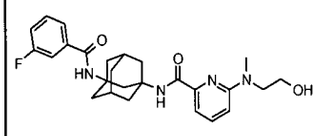
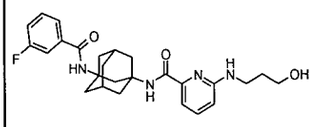
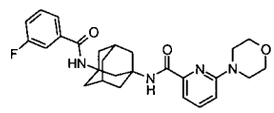
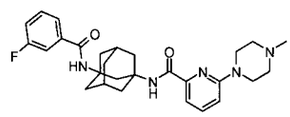
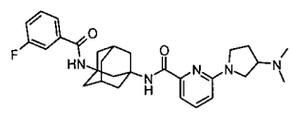
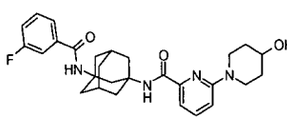
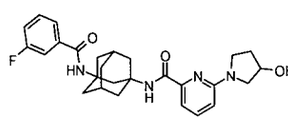
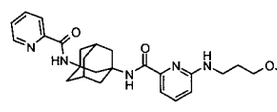
Tabla 2

EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
197		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Morfolin–4–il–piridin–2–carboxílico
198		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(4–metil–piperazin–1–il)–piridin–2–carboxílico
199		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–dimetilamin–pirrolidin–1–il)–piridin–2–carboxílico
200		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Hidroxi–3,4,5,6–tetrahidro–2H–[1,2']bipiridinil–6'–carboxílico
201		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–Hidroxi–pirrolidin–1–il)–piridin–2–carboxílico
202		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–Hidroxi–etil)–metil–amino]–piridin–2–carboxílico
203		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–Hidroxi–propilamino)–piridin–2–carboxílico

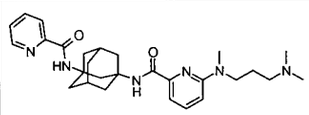
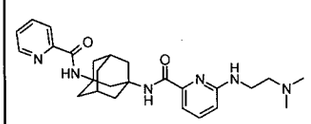
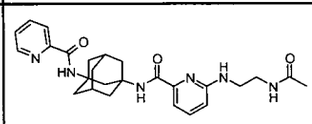
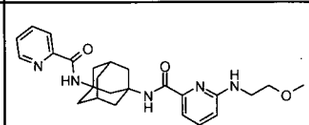
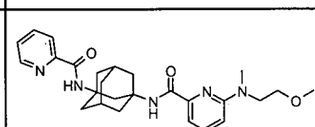
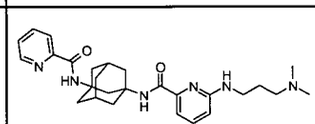
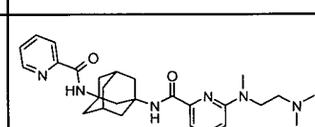
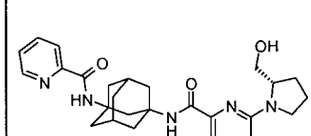
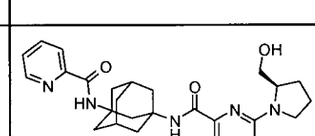
227

204		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–dimetilamin–etil)–metil–amino]–piridin–2–carboxílico
205		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–Hidroxi–pirrolidin–1–il)–piridin–2–carboxílico
206		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Hidroxi–3,4,5,6–tetrahidro–2H–[1,2']bipiridinil–6'–carboxílico
207		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–metoxi–etil)–metil–amino]–piridin–2–carboxílico
208		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–Hidroxi–etilamino)–piridin–2–carboxílico
209		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–Hidroxi–etil)–metil–amino]–piridin–2–carboxílico
210		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–Hidroxi–propilamino)–piridin–2–carboxílico
211		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–morfolin–4–il–piridin–2–carboxílico
212		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(2–Hidroxi–etilamino)–piridin–2–

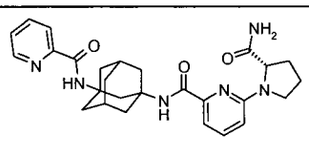
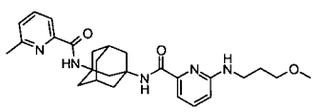
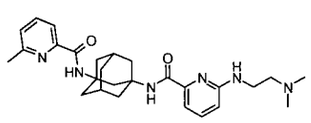
228

		carboxílico
213		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–[(2–Hidroxi–etil)–metil–amino]–piridin–2–carboxílico
214		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(3–Hidroxi–propilamino)–piridin–2–carboxílico
215		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–morfolin–4–il–piridin–2–carboxílico
216		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(4–Metil–piperazin–1–il)–piridin–2–carboxílico
217		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(3–Dimetilamin–pirrolidin–1–il)–piridin–2–carboxílico
218		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 4–Hidroxi–3,4,5,6–tetrahidro–2H–[1,2']bipiridinil–6'–carboxílico
219		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(3–Hidroxi–pirrolidin–1–il)–piridin–2–carboxílico
220		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–metoxi–propilamino)–piridin–2–carboxílico

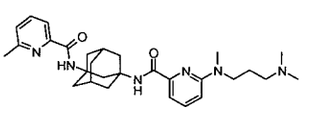
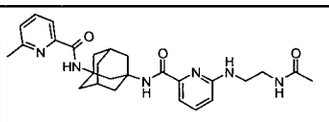
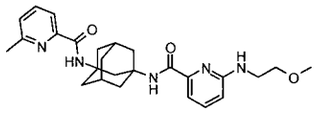
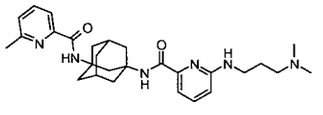
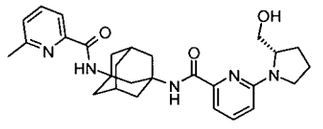
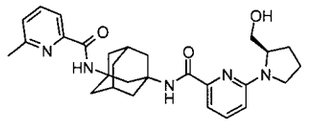
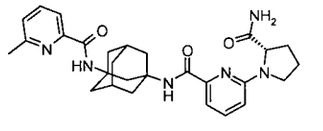
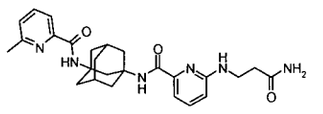
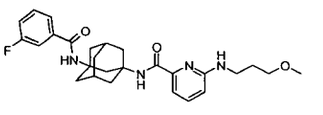
229

221		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(3–dimetilamin–propil)–metil–amino]–piridin–2–carboxílico
222		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–dimetilamin–etilamino)–piridin–2–carboxílico
223		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–acetilamin–etilamino)–piridin–2–carboxílico
224		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–metoxi–etilamino)–piridin–2–carboxílico
225		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–metoxi–etil)–metil–amino]–piridin–2–carboxílico
226		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–dimetilamin–propilamino)–piridin–2–carboxílico
227		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–dimetilamin–etil)–metil–amino]–piridin–2–carboxílico
228		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((S)–2–hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico
229		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((R)–2–hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico

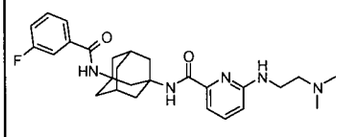
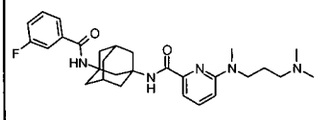
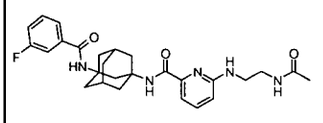
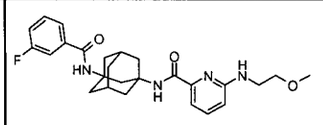
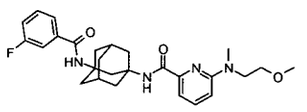
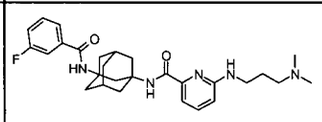
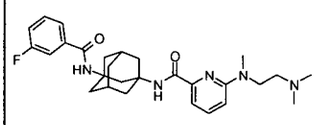
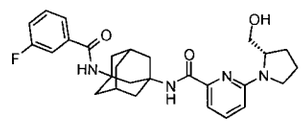
230

230		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((S)–2–carbamoil–pirrolidin–1–il)–piridin–2–carboxílico
231		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–Metoxi–propilamino)–piridin–2–carboxílico
232		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–dimetilamin–etilamino)–piridin–2–carboxílico

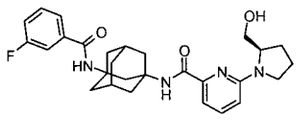
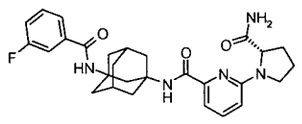
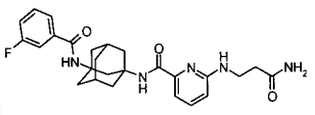
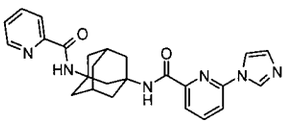
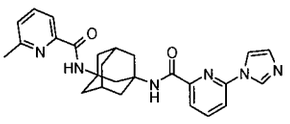
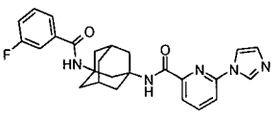
231

233		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(3–dimetilamin–propil)–metil–amino]–piridin–2–carboxílico
234		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–acetilamin–etilamino)–piridin–2–carboxílico
235		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–Metoxi–etilamino)–piridin–2–carboxílico
236		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–dimetilamin–propilamino)–piridin–2–carboxílico
237		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((S)–2–hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico
238		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((R)–2–Hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico
239		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((S)–2–Carbamoil–pirrolidin–1–il)–piridin–2–carboxílico
240		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–Carbamoil–etilamino)–piridin–2–carboxílico
241		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(3–Metoxi–

232

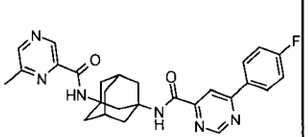
		propilamino)–piridin–2–carboxílico
242		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(2–dimetilamin–etilamino)–piridin–2–carboxílico
243		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–[(3–dimetilamin–propil)–metil–amino]–piridin–2–carboxílico
244		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(2–acetilamin–etilamino)–piridin–2–carboxílico
245		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(2–metoxi–etilamino)–piridin–2–carboxílico
246		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–[(2–metoxi–etil)–metil–amino]–piridin–2–carboxílico
247		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(3–dimetilamin–propilamino)–piridin–2–carboxílico
248		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–[(2–dimetilamin–etil)–metil–amino]–piridin–2–carboxílico
249		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–((S)–2–

233

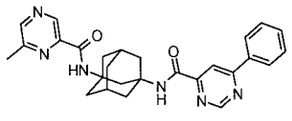
		hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico
250		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–((R)–2–hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico
251		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–((S)–2–carbamoil–pirrolidin–1–il)–piridin–2–carboxílico
252		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(2–carbamoil–etilamino)–piridin–2–carboxílico
253		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Imidazol–1–il–piridin–2–carboxílico
254		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Imidazol–1–il–piridin–2–carboxílico
255		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Imidazol–1–il–piridin–2–carboxílico

Los Ejemplos 256 y 257 en la Tabla 3 (siguiente) pueden prepararse a través del **Esquema 3** a partir del Intermediario 8 y ácido 6–(4–fluor–fenil)–pirimidin–4–carboxílico y ácido 6–fenil–pirimidin–4–carboxílico, respectivamente, en una escala de 0,05 mmoles.

Tabla 3

Ejemplo	ESTRUCTURA	NOMBRE QUIMICO
256		{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(4–fluor–fenil)–pirimidin–4–carboxílico

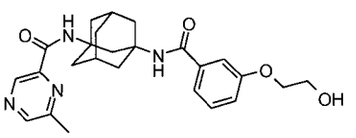
234

Ejemplo	ESTRUCTURA	NOMBRE QUIMICO
257		{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–fenil–pirimidin–4–carboxílico

4. Compuestos Hipotéticos de la Invención

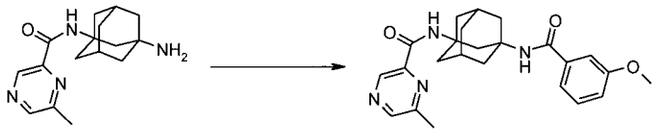
De manera similar al Ejemplo 58, pueden prepararse los Ejemplos 258–279 en la Tabla 4 (siguiente) a partir de ácidos aril o heteroaril carboxílico a través del proceso de los **Esquemas 3** y **5**. Los ácidos carboxílicos no disponibles comercialmente, tales como ácido 4–metil–pirimidin–2–carboxílico, ácido 2–metil–pirimidin–4–carboxílico, ácido 4–trifluormetil–pirimidin–2–carboxílico, ácido 2–trifluormetil–pirimidin–4–carboxílico, ácido 6–triflurometil–pirazin–2–carboxílico, y ácido 5–trifluormetil–pirazin–2–carboxílico, pueden prepararse rápidamente a partir de heteroaril–cloruro comercialmente obtenibles, tales como 2–cloro–4–metil–pirimidina, 4–cloro–2–metil–pirimidina, 2–cloro–4–trifluormetil–pirimidina, 4–cloro–2–trifluormetil–pirimidina, 2–cloro–6–triflurometil–pirazina, y 2–cloro–5–trifluormetil–pirazina, a través del proceso del **Esquema 11**, de manera similar a la síntesis del Intermediario 11, ácido 4–trifluormetil–pirimidin–2–carboxílico y del Intermediario 12, ácido 4–metil–pirimidin–2–carboxílico.

Ejemplo 280: {3–[3–(2–hidroxi–etoxi)–benzoilamino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxílico



Puede prepararse el Ejemplo 280 a través del proceso del **Esquema 9**, *supra*, de la manera siguiente:

Etapa 1: [3–(3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–pirazin–2–carboxílico

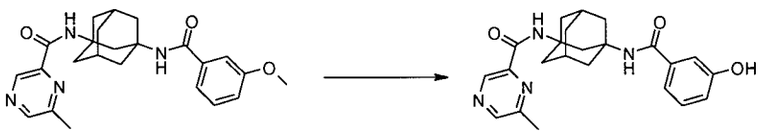


Puede prepararse [3–(3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–pirazin–2–carboxílico a partir de la amidación convencional de

235

ácido 3–metoxibenzoico comercialmente obtenible y del Intermediario 8, (3–amin–adamantan–1–il)–amida de ácido 6–metil–pirazin–2–carboxílico.

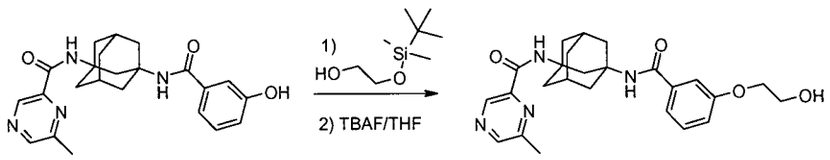
Etapa 2: [3–(3–hidroxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–pirazin–2–carboxílico



Puede prepararse rápidamente [3–(3–hidroxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–pirazin–2–carboxílico mediante tratamiento de 6–metil–pirazin–2–carboxílico [3–(3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido con BBr_3 en DCM.

2306

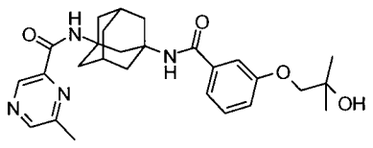
Etapa 3: {3–[3–(2–hidroxi–etoxi)–benzoilamino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico



La reacción convencional de Mitsunobu de [3–(3–hidroxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico y 2–(*t*–butildimetilsiloxi)–etanol, seguido de desprotección del grupo *t*–butildimetilsiloxi mediante tratamiento con fluoruro de tetrabutilamonio (TBAF) proporcionó el compuesto del título, {3–[3–(2–hidroxi–etoxi)–benzoilamino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxílico.

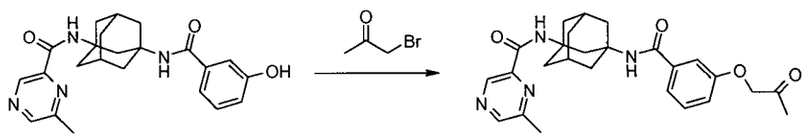
El Ejemplo 281 en la Tabla 4 (siguiente) puede prepararse de manera similar al Ejemplo 280.

Ejemplo 282: {3–[3–(2–hidroxi–2–metil–propoxi)–benzoilamino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxílico.



El Ejemplo 282 puede prepararse a partir de [3–(3–hidroxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–pirazin–2–carboxílico (Etapa 2, Ejemplo 280):

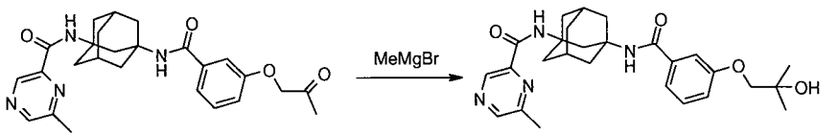
Etapa 1: {3–[3–(2–oxo–propoxi)–benzoilamino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxílico



La alquilación de [3–(3–hidroxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–pirazin–2–carboxílico (Etapa 2, Ejemplo 280) con 1–bromo–propan–2–ona en DMF bajo condiciones básicas, tales como Cs_2CO_3 a 60 °C, proporcionó el compuesto del título, {3–[3–(2–oxo–propoxi)–benzoil–amino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxílico .

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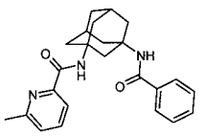
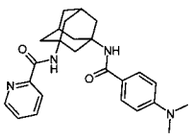
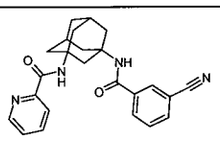
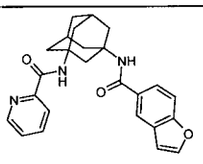
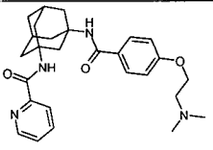
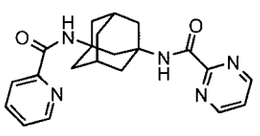
Etapa 2: {3–[3–(2–hidroxi–2–metilpropoxi)–benzoilamino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico



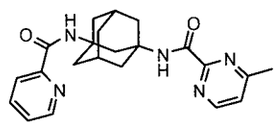
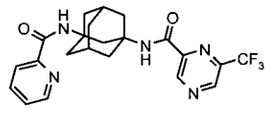
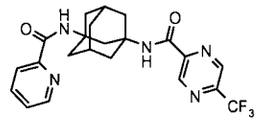
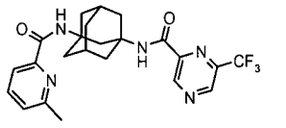
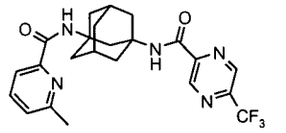
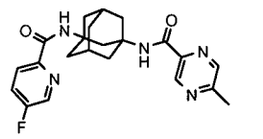
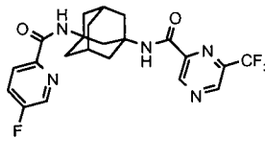
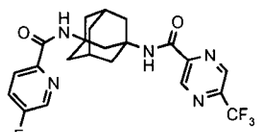
La reacción de {3–[3–(2–oxo–propoxi)–benzoil–amino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxílico con MeMgBr en THF o éter a 0 °C proporcionó el compuesto del título {3–[3–(2–hidroxi–2–metilpropoxi)–benzoilamino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxílico.

El Ejemplo 283 en la Tabla 4 (siguiente) puede prepararse de manera similar al Ejemplo 282.

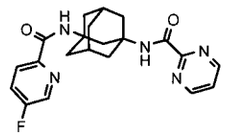
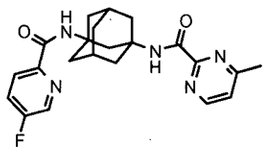
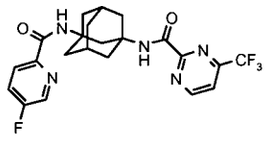
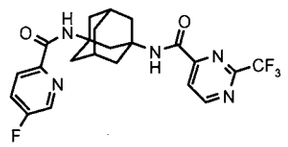
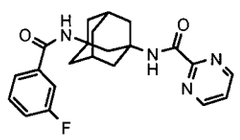
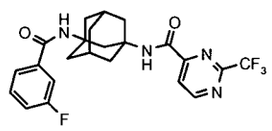
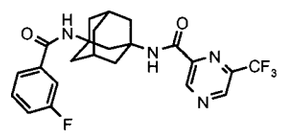
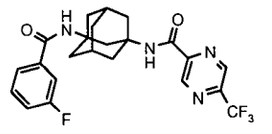
Tabla 4: Compuestos Hipotéticos

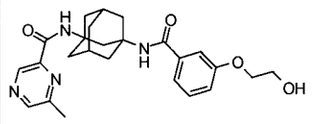
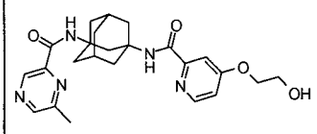
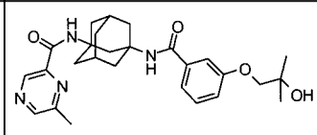
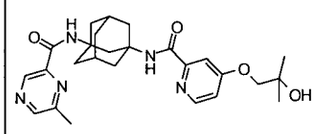
EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
258		(3–benzoilamin–adamantan–1–il)–amida de ácido 6–Metil–piridin–2–carboxílico
259		[3–(4–dimetilamin–benzoilamino)–adamantan–1–il]–amida de ácido Piridin–2–carboxílico
260		[3–(3–ciano–benzoilamino)–adamantan–1–il]–amida de ácido Piridin–2–carboxílico
261		{3–[(benzofuran–5–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2–carboxílico
262		{3–[4–(2–dimetilamin–etoxi)–benzoilamino]–adamantan–1–il}–amida de ácido Piridin–2–carboxílico
263		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2–carboxílico

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EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
264		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Metil–pirimidin–2–carboxílico
265		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–trifluormetil–pirazin–2–carboxílico
266		{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–Trifluormetil–pirazin–2–carboxílico
267		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–trifluormetil–pirazin–2–carboxílico
268		{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–Trifluormetil–pirazin–2–carboxílico
269		{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–Metil–pirazin–2–carboxílico
270		{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Trifluormetil–pirazin–2–carboxílico
271		{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–trifluormetil–pirazin–2–carboxílico

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EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
272		{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido pirimidin–2–carboxílico
273		{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–metil–pirimidin–2–carboxílico
274		{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–trifluormetil–pirimidin–2–carboxílico
275		{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–trifluormetil–pirimidin–4–carboxílico
276		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido Pirimidin–2–carboxílico
277		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 2–Trifluormetil–pirimidin–4–carboxílico
278		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–trifluormetil–pirazin–2–carboxílico
279		[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 5–Trifluormetil–pirazin–2–carboxílico

EJEMPLO	ESTRUCTURA	NOMBRE QUÍMICO
280		{3–[3–(2–hidroxi–etoxi)–benzoilamino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
281		(3–{[4–(2–hidroxi–etoxi)–piridin–2–carbonil]–amino}–adamantan–1–il)–amida de ácido 6–Metil–pirazin–2–carboxílico
282		{3–[3–(2–hidroxi–2–metil–propoxi)–benzoilamino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico
283		(3–{[4–(2–hidroxi–2–metil–propoxi)–piridin–2–carbonil]–amino}–adamantan–1–il)–amida de ácido 6–Metil–pirazin–2–carboxílico

5. Evaluación Farmacológica de los Compuestos de la Invención

Los compuestos de la presente invención han sido ensayados *in vitro* e *in vivo*, y pueden ser ensayados *in vitro* e *in vivo*, en los ensayos que se describen a continuación.

Ensayos *in vitro*

Ensayos de adición de Radioligando

Los ensayos de adición se llevaron a cabo tal como se ha descrito en [J. A. O'Brien *et al. Mol Pharmacol.*, **2003**, *64*, 731–740] con ligeras modificaciones. Resumiendo, después de descongelar, los homogeneizados de membrana se resuspendieron en 50 mM de Tris–HCl, 0,9% de buffer de adhesión NaCl a pH 7,4 hasta una concentración de ensayo final de 40 µg de proteína/ receptáculo para la adhesión de filtración de [^{3}H] metoxi–5–(2–piridiniletinil)piridina ([^{3}H] MPEP)

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(American Radiolabeled Chemicals, Inc., St. Louis, MO). Las incubaciones incluyeron 5 nM de [^{3}H] MPEP, membranas y buffer o bien concentraciones variadas de compuesto. Se incubaron muestras durante 60 minutos a temperatura ambiente con sacudimiento. La adhesión no específica se definió con 10 µM de MPEP. Después de incubación, las muestras se filtraron sobre un filtro GF/C (preremojado en 0,25% de polietilenimina (PEI)) y luego se lavaron 4 veces usando una cosechadora de células Tomtec® Harvester 96® Mach III (Tomtec, Hamden, CT) con 0,5 mL de 50 mM Tris–HCl enfriado con hielo (pH 7,4).

Los valores de CI_{50} fueron derivados a partir de la curva de inhibición y los valores K_i fueron calculados de acuerdo con la ecuación de Cheng y Prusoff de K_i = CI_{50}/ (1+ [L]/K_d) descrita en [Y. Cheng and W.H. Prusoff *Biochem. Pharmacol.* **1973**, *22*, 3099–3108] donde [L] es la concentración de radioligando y K_d es su constante de disociación en el receptor, derivada de la isoterma de saturación. El valor K_i para los Ejemplos 1 y 2 fue 6,7 y 40 nM, respectivamente. Los ejemplos 19, 42, 44, 58, 65, 67, 69, 72, 74, 79, 93, 94, 95, 96, 105, 107, 119 y 120, tienen valores Ki en el rango de desde 6 a 700 nM.

Ensayo de movilización de calcio para actividad alostérica negativa o positiva

El ADNc para el receptor glutamato metabórico 5 de rata (rmGluR5) fué un generoso obsequio de S. Nakanishi (Kyoto University, Kyoto, Japón). El rmGluR5 fue expresado establemente en la línea celular HEK 293 y cultivada en un Medio Eagle Modificado con Dulbecco's (DMEM) (Invitrogen, Carlsbad, CA) con suplementos (10% de suero de ternero bovino, 4 mM de glutamina, 100 unidades/ mL de penicilina, 100 µg/mL de estreptomicina y 0.75mM de G1418) a 37 °C, 5% de CO_2. Veinticuatro horas antes del ensayo, las células fueron sembradas dentro de placas microtituladoras de 384 receptáculos, de paredes negras, revestidas con poli–D–lisina. Justo antes del ensayo, el medio fue aspirado y las células fueron cargadas con tinte (25 µL/receptáculo) con 3 µM de Fluo–4/ 0,01% de ácido pluronic en buffer de ensayo (Solución Salina Balanceada de Hank (HBSS)): 150 mM de NaCl, 5 mM de KCl, 1 mM de $CaCl_2$, 1 mM de $MgCl_2$, más 20 mM de ácido N–2–Hidroxietil–piperacina–N'–2–etansulfónico (HEPES), pH 7.4, 0.1% de albúmina de ternero bovino (BSA) y 2.5 mM de probenicid) durante 1 hora en 5% de CO_2 a 37 °C. Después de descartar el exceso de tinte, las células fueron lavadas en buffer de ensayo y quedaron con un volumen final de 30 µL/ receptáculo. La fluorescencia basal se monitoreó en un lector de placa de formación de imagen fluorimétrica (FLIPR) (Molecular Devices, Sunnyvale, CA) con una excitación de longitud de onda de 488 nm y un rango de emisión de 500 a 560 nm. La energía de excitación laser

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se ajustó de manera que las lecturas de fluorescencia basal fueran aproximadamente 10.000 unidades fluorescentes relativas. Las células fueron estimuladas con una concentración de CE_{20} o de CE_{80} de glutamato en presencia de un compuesto a ensayar, ambas diluidas en buffer de ensayo, y las unidades fluorescentes relativas fueron medidas a intervalos definidos (exposición = 0,6 seg.) en un periodo de 3 min a temperatura ambiente. Las lecturas basales derivadas de controles negativos fueron restadas de todas las muestras. El cambio máximo de fluorescencia fue calculado para cada receptáculo. Las curvas de respuesta a la concentración, derivadas del cambio de fluorescencia máximo, fueron analizadas mediante regresión no lineal (ecuación Hill). Un modulador negativo puede ser identificado a partir de estas curvas de respuesta a la concentración, si un compuesto produce una inhibición dependiente de la concentración, de la respuesta CE_{80} de glutamato. Los compuestos ejemplificados en los Ejemplos 1–10 fueron ensayados en el ensayo anterior para la modulación alostérica negativa: la inhibición máxima FLIPR estuvo en un rango de 90% a 99% mientras que la CI_{50} de FLIPR estuvo en un rango de desde 0.9 nM a 1300 nM. Los Ejemplos 11–163 fueron también ensayados en el ensayo anterior. Para los Ejemplos 11–104, la inhibición máxima de FLIPR estuvo en un rango de desde 63% a 99% mientras que la CI_{50} de FLIPR estuvo en un rango de desde 0.7 nM a 600 nM; y para los Ejemplos 105–163, la inhibición máxima de FLIPR estuvo en un rango de desde 70% a 99%, mientras que la CI_{50} de FLIPR estuvo en un rango de desde 0.7 nM a 1800 nM. Los ejemplos 164–178, 181–182, 184–187, 189–194, 196, 197–255 fueron ensayados en el ensayo anterior para la modulación alostérica negativa: la inhibición máxima de FLIPR estuvo en un rango de desde 63% a 99% mientras que la CI_{50} de FLIPR estuvo en un rango de desde 0.4 nM a 1300 nM.

Un modulador positivo puede ser identificado a partir de estas curvas de respuesta a la concentración, si un compuesto produce un aumento dependiente de la concentración en la respuesta de CE_{20} de glutamato. Los Ejemplos 256–257 exhibieron modulación positiva, teniendo una CE_{50} de FLIPR de 300 nM y 830 nM, y una modulación máxima de 170 % y 120%, respectivamente.

Ensayos *in vivo*

Los Ejemplos 1, 2 y 58 fueron evaluados *in vivo* para los efectos ansiolíticos usando (1) métodos de enterramiento de canicas por ratones (mMB), similares a los descritos en [K. Njung'e, K. and S.L. Handley, *Pharmacology, Biochemistry and Behavior*, **1991**, *38*, 63– 67] y (2) un ensayo de conflicto de Geller–Seifter modificado, descrito en [N.A. Moore *et al. Behavioural Pharmacology*. **1994**, *5*, 196–202].

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Más específicamente, para el ensayo mMB, se usaron ratones macho adultos CD1 (Charles River Laboratories (Kingston, NY)), con un peso de 25 a 30 g. Todos los animales fueron agrupados en un espacio standard para colonias, con un ciclo de 12:12 horas de luz/ oscuridad (luces encendidas a las 6:00 am) durante por lo menos una semana antes del ensayo. Se les proporcionó comida y bebida *ad libitum*. Los animales fueron pesados, marcados en la cola y se asignaron aleatoriamente a grupos de tratamiento antes del ensayo.

Para cada ensayo, sesenta minutos después de la inyección de vehículo o compuesto de ensayo, o 30 minutos después de la inyección del control positivo, buspirona, los ratones fueron colocados individualmente en jaulas de ensayo que contenían 1,5 pulgadas (4,8 cm) de lecho Aspen (marca comercial PWI) y dos hileras de 10 canicas (20 canicas para ensayo total de jaulas). Se usaron tapas con filtro para cubrir cada jaula de ensayo. Treinta minutos más tarde, los ratones fueron sacados de las jaulas de ensayo y fueron devueltos a sus jaulas originales. La cantidad de canicas completamente visibles (2/3 de las mismas cubiertas con el material del lecho) fueron contadas y restadas de las 20, para llegar a la cantidad de canicas enterradas. Se ensayaron doce ratones por grupo.

La prueba incluyó ensayos múltiples, donde cada ensayo se llevó a cabo para evaluar el clorhidrato de buspirona (BUS; Sigma Aldrich) (control positivo) y/o un compuesto de la presente invención. Cada compuesto se disolvió inmediatamente antes del ensayo en 20% de beta–ciclodextrina (compuesto de la presente invención) o agua destilada (BUS) o bien se administró en una o más dosis (tal como 3, 10, y/o 30 mg/kg) por vía subcutánea (SC) o intraperitoneal (IP) en los tiempos de pretratamiento indicados (es decir, 30, 60 o 120 minutos de pretratamiento). Las dosis se midieron en mg de la droga (forma salina) por kg de peso corporal. Los datos se analizaron usando ANOVA de una sola vía con ensayo *post–hoc* de Dunnett.

Más específicamente para el ensayo de Conflicto Geller–Seifter, se usaron cámaras que operaban con roedores (ENV–007CT, Med Associates Inc. (Georgia, VT)) y cámaras con atenuación de sonido (ENV–018MD, Med Associates Inc.). Cada cámara estaba equipada con una luz común, alumbrado de toma de vistas, piso enrejado para liberar shocks en las patas a través de un shockeador programable y una tolva para comida. Se colocaron dos palancas en ambos lados de la tolva para comida. Las ratas fueron entrenadas para responder solamente sobre la palanca izquierda. Se usó comida de refuerzo (Dustless Precision Pellets, 45 mg, BioServ,

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(Frenchtown, NJ)). Se usó software MED–PCIV (Med Associates) para llevar a cabo las sesiones experimentales y para recoger datos.

Antes de comenzar con el procedimiento de Conflicto, los animales fueron entrenados inicialmente para presionar la palanca en programas de relación fija (FR 1, 2, 5, y 10). Una vez que los animales obtuvieron 25 recompensas en un programa FR 10 durante 2 días consecutivos, los animales comenzaron a ser entrenados en un programa de Conflicto de tres componentes. Los tres componentes fueron los siguientes: (1) un intervalo variable, sin castigo, de 30 segundos (VI30) de refuerzo de comida para reforzar la presión ejercida en la palanca en un programa de tiempo variable que promediaba los 30 segundos; este período tenía una duración de 9 minutos y fue señalado mediante iluminación con la luz de atrás solamente; (2) inmediatamente a continuación hubo un período de tiempo de 3 minutos (TO) que fue señalado por una oscuridad total; la respuesta fue registrada pero ni se premió ni se castigó; (3) un programa con castigo, de relación fija 10 (FR10) de refuerzo que presentó simultáneamente comida y shock en extremidades (0.3 mA, 500 ms) en cada décima presión de palanca durante un período de 3 minutos; este componente fue señalado por iluminación con la luz común de atrás y con alumbrado de toma de vistas arriba de cada palanca. Estos tres componentes fueron repetidos dos veces en el mismo orden durante la sesión diaria de 30 minutos.

El ensayo comenzó cuando se observaron regimenes estables de respuesta durante 5 días (ninguna tendencia significativa fluctuante). Los animales fueron sometidos a ensayo usando un diseño de cuadrado latino, los miércoles y viernes. Los animales sirvieron como sus propios controles y recibieron todos los tratamientos. Para mantener el rendimiento de base, los animales fueron también entrenados durante los tres días de la semana restantes.

El ensayo se llevó a cabo usando 12 ratas macho adultas, Sprague–Dawley, con un peso de 426–567 g (Charles River Laboratories (Kingston, NY)). Los animales fueron alojados en pares, en espacios de colonias mantenidas a temperatura controlada (68–72°F) y con un ciclo de luz/ oscuridad de 12 horas (luces encendidas a las 06:00). Se dejó que los animales tuvieran acceso libre al agua, mientras que la comida se limitó a 15 g de jamón (Bacon Lover's Treats (BioServ) después del entrenamiento/ ensayo de lunes a jueves. De viernes a domingo, los animales tuvieron acceso libre a la dieta de Lab Diet 5012 Rat Diet (PMI Nutrition International, LLC, Brentwood, MO) hasta que las jaulas fueron cambiadas y se sacó la comida el domingo.

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El ensayo incluyó ensayos múltiples en los cuales cada ensayo fue evaluado como compuesto de referencia o bien como compuesto de la presente invención. Los ansiolíticos de referencia incluyeron clordiazepóxido, diazepam y buspirona, los cuales fueron disueltos en solución salina o agua y fueron administrados por vía SC, IP, y/o PO. Los compuestos de ensayo fueron disueltos en 20% de beta–ciclodextrina, y el pH fue ajustado a 7 con $NaHCO_3$. Para cada ensayo, el compuesto fue evaluado con una o más dosis (tal como 10, 20, 30 y/o 50 mg/kg) por administración por vía p.o., 60 minutos antes del ensayo, usando una inyección de un volumen de 2 mL/kg en comparación con un grupo de vehículo de control. Las dosis se midieron en mg de droga (forma salina) por kg de peso corporal. Los datos fueron analizados usando Mediciones Repetidas ANOVA con el ensayo *post–hoc* de Dunnett.

Los compuestos de la invención tienen actividad ansiolítica significativa. Por ejemplo, el Ejemplo 1 mostró actividad significativa en ambos ensayos (mMB EDmin 3 mg/kg; Geller–Seifter EDmin 10 mg/kg). El ejemplo 2 mostró también actividad en ambos ensayos (mMB EDmin 30 mg/kg, Geller–Seifter EDmin 20 mg/kg). El ejemplo 58 mostró una actividad significativa en ambos ensayos (mMB EDmin 10 mg/kg, SC; Geller–Seifter EDmin 10 mg/kg, PO); tal como se muestra en las tablas siguientes.

Tabla 5: Dosis Activas Estadísticamente Significativas de Compuestos Representativos de la Presente Invención en el Ensayo de Enterramiento de Canicas

Ejemplo	**Dosis Activa *mg/kg (inyección SC)***	**Significado Estadístico [+]**
1	3, 10, 30	F(4,55)=19.6, p<0.01
2	30	F(4,55)=7.2, p<0.01
41	10, 30	F(4,55)=17, p<0.01
58	10, 30	F(4,55)=19, p<0.01
63	30	F(4,55)=5.7, p<0.05
93	30	F(4,54)=6.6, p<0.01
94	3, 10, 30	F(4,55)=46, p<0.01
95	10, 30	F(4,55)=18, p<0.01
96	10, 30	F(4,55)=30, p<0.01
105	30	F(4,55)=11, p<0.01
107	10	t(22)=17, p<0.01
119	10	t(22)=25, p<0.01
145	30	F(4,54)=10, p<0.01
179	10	t(22)=6, p<0.01
183	10	t(22)=4, p<0.01
185	30	F(4,55)=15, p<0.01
191	10, 30	F(4,55)=11, p<0.01

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[+] El significado estadístico se determinó usando ANOVA de una sola vía con ensayo *post–hoc* de Dunnett o t–test students emparejados

Tabla 6: Dosis Estadísticamente Activa(s) de Compuestos Representativos de la Presente Invención en el Ensayo de Geller–Seifter

Ejemplo	Dosis activa *mg/kg (inyección oral)*	Significado Estadístico [+]
1	50	t(7)=2.99, p<0.05
2	20	t(7)=2.4, p<0.05
41	30	F(3,7)=11.6, p<0.01
58	10, 20	F(3,11)=8, p<0.05
94	20	F(3,8)=2.7, p<0.05
95	10,30	F(3,9)=5.7, p<0.05

[+] El significado estadístico se determinó uando ANOVA de una vía con ensayo *post–hoc* de Dunnett o paired t–test students emparejado

Los compuestos de la presente invención fueron evaluados *in vivo* para determinar los efectos antidepresivos. Una verificación de las acciones de tipo depresivo se midió usando un ensayo de natación forzada similar al que se describe en [J.F. Cryan, *et al.* Neuroscience and Biobehavioral Reviews **2005**, *29*, 547–569.] Los animales para el ensayo de t–test fueron ratones machos NIH Swiss Webster (Harlan Laboratories (Frederick, MD)), de un peso de 22 a 24 g, los cuales fueron aclimatados y alojados tal como se describió anteriormente con respecto a los ratones que se usaron en los ensayos mMB.

Para el Ensayo de Natación Forzada (mFST), los ratones fueron colocados individualmente en cilindros claros de Pyrex® (de 11 cm de diámetro, 16.5 cm de altura) que contenían 11 cm de profundidad de agua de la canilla (23–25 °C) sesenta minutos después de la inyección de vehículo o compuesto de ensayo, o 30 minutos después de la inyección de control positivo, clorhidrato de imipramina (IMI; Sigma Aldrich, St. Louis, MO). La Imipramina se preparó con solución salina isotónica y los compuestos de ensayo se prepararon tal como se describió previamente en los ensayos mMB. Las dosis que se usaron fueron tal como las previamente descritas para los ensayos mMB. El porcentaje de tiempo que transcurrió mientras flotaban, nadaban y luchaban ("trepando") se midió durante una sesión de 6 minutos. Las

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sesiones de natación fueron monitoreadas por video y analizadas en tiempo real, usando el aparato Biobserve Automated y el software (Biobserve GmbH, Bonn, Alemania). El tamaño del grupo estaba constituido por entre doce a trece ratones. Las dosis se midieron en mg de droga (forma salina) por kg de peso corporal. Los datos fueron analizados usando ANOVA de una sola vía con el ensayo *post–hoc* de Dunnett.

Los compuestos de la presente invención tuvieron efectos antidepresivos en el mFST a 3 mg/kg, 10 mg/kg, 30 mg/kg, o una combinación de los mismos. El (Significado Estadístico ($p<0.05$) se determinó usando ANOVA de una vía con ensayo *post–hoc* de Dunnett.)

Un efecto *in vivo* de un compuesto de la presente invención puede ser también evaluado mediante el uso de los siguientes ejemplos, no limitativos, de modelos de conducta de animales *in vivo*. Los siguientes modelos de conducta no pretenden ser los únicos modelos útiles para determinar la eficacia de un compuesto de la presente invención para tratar el correspondiente trastorno o enfermedad.

Los compuestos de la invención pueden ser también evaluados *in vivo* para determinar los efectos de ansiedad, usando un método reflejo de sobresalto realzado por luz (LES) tal como el descrito por [Walker and Davis. *Biol. Psychiatry*, **1997**, *42*, 461–471]. La respuesta de sobresalto es una contracción coordinada de grupos musculares esqueletales en respuesta a un estímulo inesperado de alta intensidad. Pueden usarse la mayoría de las modalidades sensoriales, pero el sonido es el que se emplea más frecuentemente, debido a que es más fácil de controlar. Por lo tanto, cuando ocurre una corta explosión de suficiente intensidad (por ejemplo, 115 dB) ocurre una respuesta de sobresalto involuntario. Los niveles elevados de luz aumentan la respuesta de sobresalto en especies nocturnas tales como la rata y este efecto no requiere ningún pre–acondicionamiento. Los ansiolíticos – un agente que alivia la ansiedad – disminuyen el sobresalto realzado por luz.

Para el ensayo LES, puede usarse un aparato que consiste en una cámara para sobresalto, a prueba de sonidos, comercialmente obtenible (por ejemplo, SR–LAB™ Startle Response System, San Diego Instruments, San Diego, CA). Todos los eventos y datos de registro pueden ser controlados mediante un programa de computadora (por ejemplo, unidad de control SR–LAB™). Las ratas se colocan dentro de la cámara de sobresalto en un pequeño cilindro Perspex®, ligeramente más grande que la rata, el cual está unido a una placa de base que contiene un medidor de tensión. El movimiento vertical de la rata tal como ocurre durante una respuesta de sobresalto, da como resultado la deformación de la placa de base, lo cual genera

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una corriente en el medidor de tensión, que es proporcional a la dimensión del movimiento, es decir, la dimensión de la respuesta de sobresalto. Se coloca directamente un altavoz por arriba de la rata para proveer un sonido de base y estímulos. Se coloca una fuente de luz (2500 – 3500 Lux) en cada cámara de sobresalto.

El ensayo LES consiste en dos sesiones de 20 minutos (primero con las luces apagadas y luego con las luces encendidas), 5 minutos de los cuales, están destinados a la habituación, durante la cual se provee un ruido de base de 70 dB de intensidad dentro de la cámara. Al finalizar cada período de habituación, se presentan 10 estimulaciones de 110 dB para que los animales se habitúen. A continuación se presentan tres tipos de pruebas en un orden pseudo aleatorio, de 8 veces cada una. Las pruebas están separadas por 15–25 segundos. Los tipos de pruebas son 100, 105 o 110 dB sobresaltos durante los cuales se presentan 40 ms de explosiones de ruido blanco a 100, 105 o 110 dB, lo cual da como resultado una respuesta de sobresalto. Un período de 5 minutos sin luz o ruido separa las dos sesiones. Una especie de rata apropiada que puede usarse incluye ratas macho Rj: Wister (Hans) (180–280 g de peso al comienzo del ensayo con un rango de peso máximo por ensayo de 50 g) (Elevage Janvier, Le Genest–Saint–Isle, Francia). Las ratas deberían dejarse aclimatar a las condiciones de laboratorio por lo menos 5 días antes del ensayo con acceso libre a comida y agua. Las condiciones de aclimatación deberían ser comparables a aquellas descritas en la literatura científica y/o conocidas por los expertos en la materia.

El rendimiento desde la plataforma de sobresalto se registra durante 40 ms a partir del comienzo del estímulo de sobresalto. Se registran tres variables para cada prueba: la respuesta promedio de todo el período de registro, la respuesta pico y el tiempo hasta llegar a la respuesta pico. Se calcula la intensidad del sobresalto para cada rata, se promedian las 8 pruebas de cada tipo bajo condiciones de oscuridad y luz y se calcula el porcentaje de aumento de amplitud de sobresalto (valores promedio y pico) causado por la luz (LES). El tiempo hasta la respuesta pico es una medición del tiempo de reacción.

El ensayo que se lleva a cabo, es a ciegas, y se usan, por ejemplo, 12 ratas por grupo. El ensayo incluye ensayos múltiples donde cada ensayo se lleva a cabo para evaluar un compuesto de referencia (por ejemplo clordiacepóxido), un compuesto comparativo (por ejemplo, pregabalina) y/o un compuesto de la presente invención. Por ejemplo, en el ensayo 1, se usa un ansiolítico conocido, tal como clordiacepóxido y pregabalina, seguido del ensayo 2 en el que se usa el antagonista

de mGluR5, 2–metil–6–(feniletinil)–piridina (MPEP), y luego se lleva a cabo el ensayo 3, usando un compuesto de la presente invención. Alternativamente, cada compuesto de ensayo, se lleva a cabo concurrentemente, o en alguna combinación de sucesivamente y concurrentemente. Para cada ensayo, el compuesto a ser evaluado, se ensaya en una o más dosis (tales como 1, 3, 10, 30 y/o 100 mg/kg) por vía de administración p.o. 60 minutos antes del ensayo, en comparación con un vehículo o grupo de control. Antes del ensayo, los compuestos de ensayo pueden ser sometidos a ensayo para determinar la solubilidad bajo agitación en frío, de la dosis más alta propuesta para 10 min en agua destilada. Si es soluble, el agua destilada puede servir como vehículo. Si es insoluble, los compuestos de ensayo pueden suspenderse en 0,2% de hidroxi propil metilcelulosa (HPMC) en agua destilada. Las dosis pueden prepararse como soluciones de carga de peso a volumen (P/V) y luego son diluidas en forma seriada, (V/V) para los compuestos en solución o son pesados por separado (P/V) para los compuestos en suspensión.

Para cada ensayo, los datos se analizaron comparando los grupos tratados con el vehículo de control usando t tests de Student sin emparejar. LES en cada grupo será analizado comparando dentro de cada grupo tratado, la intensidad de la reacción de sobresalto bajo condiciones de oscuridad y luz usando t tests de Student emparejados.

El "Ensayo de Conflicto Vogel" descrito por Vogel et al *(Psychopharmacologia,* **1971,** *21, 1–7)* puede usarse para detectar la actividad ansiolítica de un compuesto, debido a que los ansiolíticos aumentan el castigo de privación de beber. En el ensayo, las ratas son privadas de agua durante aproximadamente 48 horas y luego son colocadas individualmente en un recinto transparente de Plexiglas® (15 x 32 x 34 cm) con un piso que consiste en barras de acero inoxidable (0.4 cm) espaciadas por una separación de 1 cm. La pared de atrás del recinto está fabricada con Plexiglas® opaco, lo cual esconde al observador del animal experimental. En el centro de la pared opuesta, a 5 cm por arriba del piso, sobresale un caño metálico de agua dentro de la jaula y está conectado a un polo de un generador de shock (Apelex: Tipo 011346). El otro polo del generador de shock está conectado con el piso metálico enrejado.

Se deja que la rata explore hasta encontrar el caño de agua. Luego, cada vez que bebe, recibe un ligero shock eléctrico (1.7 mA, 1 s) 2 segundos después que comienzan los lengüetazos. La cantidad de acciones de beber castigadas se cuenta durante un ensayo de 3 minutos.

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El ensayo se efectúa a ciegas con por ejemplo, 10 ratas por grupo. El ensayo incluye ensayos múltiples en los que se usan compuestos de referencia y compuestos de la presente invención que se preparan y administran tal como se describió previamente en el ensayo LES. Los animales de ensayo apropiados con condiciones de aclimatación son, por ejemplo las ratas macho Rj: Wistar (Hans) que han sido descritas previamente para el ensayo LES. Los datos se analizaron mediante comparación de los grupos tratados con controles apropiados, usando t tests de Student.

El efecto anti–depresivo puede ser evaluado usando la rata de Flinders Sensitive Line (FSL) en FST y el ensayo de interacción social descrito en [D.H. Overstreet and G. Griebel *Pharmacol Biochem Behav.,* **2005**, *82*, 1: 223–227]. Más específicamente, los compuestos de la invención son ensayados en dosis múltiples. (por ejemplo, 10 mg/kg, 30 mg/kg, etc.) mediante preparación de 20% de HP–beta–ciclodextrina y vehículo de control. Además de un grupo FSL de vehículo de control, se ensaya el grupo de vehículo de control de ratas Flinders Resistant Line. Los compuestos de ensayo son administrados diariamente por inyección IP (volumen de inyección de 2 mg/kg) durante 14 días. Los animales fueron ensayados en cuanto a la interacción social y con ensayos de natación forzada el día 15, 22–24 horas después de la inyección del día 14, tal como ha sido descrito en Overstreet and Griebel **2005**. Se ensayaron de seis a ocho animales por grupo.

El efecto ansiolítico y antidepresivo puede ser también evaluado usando un paradigma para la retroalimentación disminuida del eje HPA (David et al., 2007, Reunión SFN San Diego). Este modelo basado en la liberación crónica de corticosterona en agua bebible, causa conductas del tipo de ansiedad y depresión en ratones. El modelo consiste en una administración sostenida de una dosis alta (35 µg/mL), pero no de una dosis baja (7 µg/mL), de corticosterona durante cuatro a siete semanas. Dicho tratamiento indujo una conducta del tipo de ansiedad y depresión en el linaje de ratón C57Bl6/NTac, según se indica por una disminución del tiempo que tarda y del número de entradas al centro del terreno de interés, durante los 30 minutos de ensayo a campo abierto (OF), mientras que la ambulación total no fue alterada. Asimismo, la latencia a la alimentación se incrementó en los ratones tratados con corticosterona sometidos al paradigma de la novedad de comida suprimida (NSF). Como el tratamiento con corticosterona no alteró la ingestión de comida en la jaula familiar (ambiente familiar), los cambios en la latencia de comida no fueron debidos a cambios de apetito o a una anormalidad metabólica subyacente. Es importante el hecho de que la respuesta de la hormona adreno–corticotrópica

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(ACTH) y corticosterona (CORT) a un estresor agudo (ensayo de 6 minutos de natación forzada (FST)), medida como concentración en plasma, fue mitigada en ratones C57BL/6NTac. Estos resultados fueron confirmados en ratones del linaje CD1. Tres semanas de tratamiento con el antidepresivo imipramina (40 mg/kg/día ip) y fluoxetina (18 mg/kg/día ip) revertieron la ansiedad – y los efectos de tipo depresivo causados por un tratamiento de siete semanas con corticosterona en los OF, NSF y FST.

En dicho ensayo, 240 ratones macho adultos del linaje C57Bl/6Ntac (Taconic Farms (Dinamarca)), de 8–10 semanas de vida, se dejaron aclimatar a las instalaciones, durante por lo menos 1 semana antes del ensayo (por ejemplo, 5 por jaula bajo un ciclo de 12 horas (06:00–18:00) de luz–oscuridad a 22 °C) con libre acceso a comida y agua.

Un compuesto de la invención (30 o 60 mg/kg, por día en la comida), fluoxetina (18 mg/kg por día con el agua bebible) o vehículo (0.45% de β–ciclodextrina βCD en agua bebible) se administraron a ratones tratados con agua bebible con vehículo o bien con corticosterona (35 μg/mL). Después de 7 semanas de tratamiento tal como se indica a continuación, los ratones se sometieron a ensayo en los siguientes ensayos de conducta: OF, NSF, FST y ensayo de aseo de salpicaduras de sucrosa. El tratamiento se inició con cualquiera de βCD o corticosterona (35 μg/mL) administrada a través del agua bebible durante 3 semanas (n=200 ratones por grupo). A continuación, la administración con βCD o corticosterona prosigue, y los ratones se dividen en 8 grupos de 30 ratones tal como se indica a continuación para 4 semanas adicionales.

Semana 1–8	**Semana 3–7**
(vehículoβCD)	vehículo
vehículo (βCD)	fluoxetina, 18 mg/kg
vehículo (βCD)	compuesto de ensayo, 30 mg/kg
vehículo (βCD)	compuesto de ensayo, 60 mg/kg
35μg/mL/día corticosterona	vehículo
35μg/mL/día corticosterona	fluoxetina, 18mg/kg
35μg/mL/día corticosterona	compuesto de ensayo, 30 mg/kg
35μg/mL/día corticosterona	compuesto de ensayo, 60 mg/kg

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Los ratones se ensayaron en los paradigmas de conducta en este orden: OF, NSF, ensayo de aseo de sucrosa y luego el FST de ratón (15 animales/ grupo).

El ensayo de campo abierto

La actividad motora se cuantifica en cajas de Plexiglas® de campo abierto de 43 x 43 cm^2 (MED associates, Georgia, VT) en una sesión de 10 min. Se colocaron dos conjuntos de 16 foto haces infrarrojos modulados por pulso en paredes opuestas con una separación de 2,5 cm para registrar los movimientos ambulatorios x–y. Un bulbo blanco de 40–W colocado en el medio de la habitación proporcionó una iluminación de alrededor de 200–lx a nivel del piso. Las cámaras de actividad son de interfaz computadora para el muestreo de datos a una resolución de 100 ms. La computadora definió líneas de rejas que dividian cada campo abierto dentro del centro y regiones circundantes, estando cada una de cuatro líneas a 11 cm de cada pared. Las mediciones dependientes, son el tiempo total que tardan en el centro, las cantidades de entradas dentro del centro y la distancia recorrida en el centro dividida por la distancia total recorrida. La actividad motora general se cuantifica como la distancia total recorrida (cm).

La comida novedosa suprimida

La comida novedosa suprimida (NSF) es un ensayo de conflicto que provoca motivaciones competitivas: El impulso de comer y el temor de aventurarse hasta el centro del terreno de interés brillantemente iluminado. La latencia para comenzar a comer se usa como índice de la conducta de tipo ansioso debido a que las drogas ansiolíticas clásicas la disminuye. La NSF se lleva a cabo durante un período de 5 minutos tal como ha sido descrito previamente (Santarelli et al., 2003). Resumiendo, el aparato de ensayo consiste en una caja de plástico de 50x50x20 cm. El piso está cubierto con aproximadamente 2 cm de lecho de madera. Veinticuatro horas antes del ensayo de conducta, se sacó toda la comida de la jaula original. En el momento del ensayo, se colocó un solo grano de comida (comida regular) sobre una plataforma de papel blanco situada en el centro de la caja. Se colocó un animal en una esquina del laberinto e inmediatamente se puso en marcha un cronómetro. La medición de interés (masticación) se anota cuando el ratón está sentado sobre sus cuartos traseros y muerde con el uso de las patas delanteras. Inmediatamente después de este ensayo, los ratones son transferidos a su jaula original y se mide la cantidad de comida consumida en 5 minutos (consumo de alimento en la jaula original). Los ratones son sometidos a ensayo durante el período de luz. Debido a que se sabe que los antidepresores tienen varios efectos sobre el apetito, el impulso de comer es verificado devolviendo los animales a sus jaulas originales (ambiente

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familiar) inmediatamente después del ensayo. Luego, se mide la cantidad de alimento consumido en un período de 5 minutos.

Ensayo de salpicaduras

La latencia de aseo es verificada al finalizar el régimen de corticosterona (al final de la séptima semana), en presencia o ausencia de tratamiento de 3 semanas con fluoxetina. Ese ensayo consiste en arrojar 200 µl de una solución de sucrosa al 10% sobre el hocico del ratón. Luego se registra la frecuencia de aseo.

El ensayo de Natación Forzada en ratones

Se usa un procedimiento de ensayo modificado de natación forzada tal como se describe en [Dulawa et al., Neuropsychopharmcol., **2004**, *29*, 1321–1330; Holick et al., Neuropsychopharmcol., **2008**, *33*, 2: 406–417]. Los ratones se colocan individualmente dentro de cilindros de vidrio (altura: 25 cm, diámetro: 10cm) que contienen 18 cm de agua que se mantiene a 23–25 °C y se usa la videocinta de grabado durante 6 min a través de una cámara montada sobre un trípode situado directamente sobre el lado del cilindro. Un aumento de la natación y trepado ha sido relacionado con una activación del sistema serotoninérgico y noradrenérgico en ratas [ver, por ejemplo, Cryan and Lucki, Pharmcol. & Exp. Therap., **2000**, 295, 3, 1120–1126] y en ratones [ver, por ejemplo., Dulawa et al. (**2004**); Holick et al., (**2008**)], respectivamente. Por lo tanto, la conducta predominante (natación, inmovilidad o trepado) es valorada aquí durante los últimos 4 minutos del período de ensayo de 6 minutos.

Las propiedades de tipo ansiolítico pueden se también evaluadas usando estos ensayos adicionales: (1) interacción social descrita en, [S.E. File y P.Seth, *European Journal of Pharmacology*, **2003**. *463*, 35–53], y (2) laberinto plus–elevado descrito en [S.M. Korte y S.F. De Boer European Journal of Pharmacology, **2003**, *463*, 163– 175].

La enfermedad de Parkinson (PD) puede ser verificada midiendo la neurotoxicidad de MPTP en ratas, tal como se ha descrito en [E. H. Lee *et al. Chin. J. Physiol.*, **1992**, *35*, 4: 317–36]. Asimismo, la pérdida DA estriatal inducida experimentalmente en animales, es un modelo válido de Parkinsonismo, tal como ha sido descrito en [W. Schultz *Prog. Neurobiol.*, **1982**, *18*, 2–3: 121–66]. La capacidad de ciertas sustancias para dañar las neuronas catecol–aminérgicas ha sido usada extensamente para producir deficiencia DA en animales, tal como se ha descrito en [L. E. Annett *et al. Exp. Neurol.*, **1994**, *125*, 2: 228–46]. El PD puede ser también verificado midiendo la neurotoxicidad inducida por 6–hidroxidopamina (6–OHDA) tal

como se ha descrito en N. Breysse *et al. J. Neurosci.*, **2002**, *22*, 13: 5669–5678; D. Rylander *et al. J. Pharmacol. Exp. Ther.*, **2009**, 330, 1: 227–235; y L. Chen *et al. Brain Res.*, In Press, Prueba no corregida, obtenible en la red el 21 de junio de **2009**, doi:10.1016/j.brainres.2009.06.040].

El síndrome frágil X puede ser verificado usando el modelo *fmr1*^{tm1Cgr} de ratón descrito en [Q.J. Yan *et al. Neuropharmacol.*, 2005, 49, 1053–1066] así como también en ratones *Fmr1* knockout con una reducción selectiva en la expresión de mGluR5 descrita en [G. Dölen *et al. Neuron*, **2007**, *56*, 955–962].

Preclínicamente, los animales pueden ser también evaluados para el bloqueo/ atenuación de síntomas asociados con esquizofrenia. Los síntomas positivos en modelos animales de esquizofrenia pueden ser evaluados por medición de los cambios en el nivel general de actividad de dopamina (DA) con cambios paralelos concomitantes en la actividad locomotora tal como se describe en [R. Depoortere *et al. Neuropsychopharmacology,* **2003**, *28*, 11: 1889–902], D–anfetamina (AMPH) y fenilciclidina (PCP) a través de la inducción de un modelo de psicosis o fde hiperactividad locomotora, tal como se describió en [W. J. Freed *et al. Neuropharmacology,* **1984**, *23*, 2A: 175–81; F. Sams–Dodd *Neuropsychopharmacology*, **1998** *19*, 1: 18–25]. Por ejemplo, Depoortere et al., **2003**, han descrito ensayos para evaluar la actividad locomotora, catalepsia, trepado y estereotipo que se refiere a sintomatología positiva y perfil de efecto secundario, mediante la caracterización de compuestos con eficacia antipsicótica típica y atípica. La atenuación en trepado, estereotipo y catalepsia (AIC) inducidos por apomorfina puede evaluarse tal como ha sido descrito en [Y. K. Fung et al. *Pharmacol. Biochem. Behav.*, **1986**, *24*, 1: 139–41 y Y. K. Fung *et al. Steroids*, **1987**, *49*, 4–5: 287–94]. Adicionalmente, los síntomas negativos de esquizofrenia pueden ser evaluados midiendo la interacción social bajo la influencia de antagonistas de NMDA, tales como PCP, tal como se ha descrito en F. Sams–Dodd, **1998**, *supra*.

Los síntomas cognitivos de la memoria, incluyendo aquellos de la enfermedad de Alzheimer, pueden ser evaluados mediante modelos tales como el Paradigma de Condicionamiento del miedo, descrito en [T. J. Gould *et al. Behav. Pharmacol.*, **2002**, *13*, 4: 287–94, y A. O. Hamm *et al. Brain*, **2003**, *126*, Pt 2: 267–75] y el Ensayo de Brazo Radial descrito en [J. P. Aggleton *et al. Behav. Brain Res.*, **1996**, *19*, 2: 133–46], mientras que la memoria de referencia espacial y el aprendizaje pueden ser evaluados en el ensayo de laberinto de agua Morris tal como se ha descrito en [Morris. *Learn. Motiv.*, **1981**, *12*, 239–260; B. Bontempi *et al. Eur. J. Neurosci.* **1996**, *8*, 11: 2348–60]. Más específicamente, en el ensayo de laberinto de agua Morris, un

tanque de agua circular (de 150 cm de diámetro y 45 cm de altura) es llenado con aproximadamente 30 cm de agua y mantenido a 26–28 °C con una plataforma de escape (15 cm de diámemtro) a 18 cm desde el perímetro y siempre en la misma posición a 1,5 cm por debajo de la superficie del agua. El agua se torna opaca por adición de un agente colorante no tóxico (por ejemplo leche en polvo) que hace invisible a la plataforma. A los animales se les da una única sesión de entrenamiento durante un solo día. La sesión de entrenamiento consiste en 4 pruebas consecutivas en el laberinto de agua, cada una separada por 60 segundos. Para cada prueba, el animal es colocado en el laberinto de agua en uno de dos puntos de partida equidistantes de la plataforma de escape y se les deja hallar la plataforma de escape. El animal se deja en la plataforma de escape durante 60 segundos antes de iniciar una nueva prueba. Si el animal no encuentra la plataforma en el lapso de 120 segundos, dicho animal se saca del agua y se coloca en la plataforma durante 60 segundos. Durante las 4 pruebas, los animales iniciaron dos veces el laberinto desde cada punto de partida en un orden determinado aleatoriamente por animal. Los animales apropiados para el ensayo con condiciones de aclimatación son, por ejemplo, las ratas macho Rj: Wistar (Hans) descritas previamente para el ensayo LES.

Las pruebas son video–registradas y la conducta de los animales es analizada usando un sistema de seguimiento por video). (SMART, Panlab, S.L.,Cornellá (Barcelona), España). La medición principal tomada en cada prueba es la distancia recorrida para encontrar la plataforma. Las medidas secundarias tomadas son la velocidad de natación y la latencia de escape. El ensayo se llevó a cabo a ciegas, usando, por ejemplo, 12 ratas por grupo de ensayo. El ensayo, incluye ensayos múltiples en lo que se usan compuestos de referencia y los compuestos de la presente invención que se preparan y administran tal como se ha descrito previamente en el ensayo LES. Para cada ensayo, los datos fueron analizados, mediante comparación de los grupos tratados con vehículo de control usando ANOVA de una sola vía, seguido de los ensayos t tests de Dunnett. Para aumentar la comparabilidad con el ensayo de conflicto Vogel antes mencionado, en todos los ensayos, las ratas fueron sometidas a privación de agua durante aproximadamente 24 h antes del ensayo (Día 1); sin embargo, el ensayo se lleva a cabo en ratas no privadas de agua (Día 2).

Adicionalmente, con respecto a la cognición, memoria hipo–funcionamiento hipocampal pueden ser verificados por medición de la restauración de plasticidad sináptica en ratas hembra ovario–ectomizadas (OVX) tal como se describió en [M.

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Día and M. Good *Neurobiol. Learn. Mem.*, **2005**, *83*, 1: 13–21]. Además, los cambios en la función de atención, debidos a esquizofrenia, pueden ser examinados mediante el Ensayo de Tiempo de Reacción Seriado de Cinco (5) Elecciones descrito en [J. L. Muir *et al. Psychopharmacology (Berl)*, **1995**, *118*, 1: 82–92 y Robbins *et al. Ann. N. Y. Acad. Sci.*, **1998**, *846*, 222–37].

Los pacientes humanos pueden ser evaluados con relación a las enfermedades o trastornos cognitivos mediante cualquiera de los ensayos que están dentro de la pericia de los expertos en la materia.

La actividad analgésica puede ser evaluada mediante el modelo de dolor neuropático (el "modelo Chung") que se describe en [Kim and Chung, *Pain*, **1992**, *50*, 355–363]. La ligadura apretada de nervios espinales en ratas está asociada con hiperalgesia, alodinia y dolor espontáneo, y por lo tanto constituye un modelo para el dolor periférico neuropático en seres humanos. Los antihiperalgésicos reducen estos signos crónicos de hipersensibilidad al dolor. Por lo tanto, en el modelo Chung, las ratas son anestesiadas (pentobarbital de sodio 50 mg/kg i.p.) y se efectúa una incisión en el nivel L4–S2 para exponer el nervio L5 después de limpiar el flanco con clorhexidina por rociado. Un hilo de algodón (standard, de calidad no quirúrgica), desinfectado con alcohol puro, se coloca alrededor del nervio L5 y se ata una simple ligadura apretadamente alrededor del nervio. Luego la herida es suturada y rociada con CothiVet® (rocío de tintura hidrocotílica) (Neogen® Corp., Lexington, KY). Las ratas reciben una inyección s.c. de Clamoxyl (0.67 mL/kg) y se deja que se recuperen. Por lo menos 2 semanas después de la cirugía, cuando el estado de dolor crónico está completamente instalado, las ratas son sometidas consecutivamente a la estimulación táctil y térmica de ambas patas traseras.

Para estimulación táctil, el animal es colocado bajo una caja de plástico acrilico invertida (18 x 11.5 x 13 cm) sobre un piso enrejado. La punta de una sonda electrónica Von Frey (Modelo 1610, BIOSEB, Vitrolles Cedex, Francia), se aplica luego con incremento de fuerza, primero a la pata posterior no lesionada y luego a la pata trasera lesionada y la fuerza requerida para inducir el retiro de la pata es registrada automáticamente. Este procedimiento se lleva a cabo 3 veces y se calcula la fuerza media por pata.

Para la estimulación de calor, el aparato (No. 7371, Ugo Basile, Comerio VA, Italia) consiste en cajas plásticas acrílicas individuales (17 x 11 x 13 cm) colocadas sobre un piso de vidrio elevado. Se coloca una rata en la caja y se la deja libre para habituarse durante 10 minutos. Luego, una fuente radiante móvil infrarroja (96 ± 10 mW/ cm^2) es focalizada primero debajo de la pata trasera no lesionada y luego de la

lesionada y se registra automáticamente la latencia de retiro de pata. Para evitar daño en los tejidos, la fuente de calor es automáticamente apagada después de 45 segundos.

Antes de recibir tratamiento con compuesto, todos los animales son sometidos a estimulación táctil de las patas traseras y son asignados a grupos de tratamiento emparejados en base a la respuesta al dolor de la pata trasera lesionada. El ensayo se lleva a cabo, por ejemplo, en 10 ratas privadas de agua por grupo. Los animales apropiados para el ensayo son, por ejemplo, las ratas macho Rj: Wistar (Hans) descritas previamente para el ensayo LES. El ensayo incluye ensayos múltiples, en los que se usan los compuestos de referencia y compuestos de la presente invención. Además de la pregabalina y MPEP descritos previamente para el ensayo LES, puede usarse duloxetina como compuesto de referencia, debido a que es anti–hiperalgésico con respecto al dolor neuropático asociado con diabetes y fibromialgia. Los compuestos se preparan y administran tal como se ha descrito previamente en el ensayo LES. El ensayo puede llevarse a cabo usando la misma tanda de ratas tratadas repetidamente, con un mínimo descanso de 1 semana entre tratamientos. Asimismo, para aumentar la comparabilidad con el ensayo de conflicto Vogel antes mencionado, en todos los ensayos, las ratas son sometidas a privación de agua durante aproximadamente 48 horas antes de cada ensayo. Para cada ensayo de modelo Chung, los datos serán analizados comparando los grupos tratados con controles apropiados usando los t tests de Student no emparejados.

Adicionalmente, la actividad analgésica/ anti–inflamatoria puede ser evaluada *in vivo* usando el Ensayo de Pata con Formalina en el ratón, descrito por [Wheeler–Aceto et al, *Psychopharmacology,* **1991**, *104,* 35–44). Para el ensayo, los ratones reciben una inyección intraplantar de 5% de formalina (25 µl) en la pata posterior izquierda. Este tratamiento induce lamedura de pata en animales de control. El tiempo que transcurre mientras se lame, se cuenta durante 5 minutos, comenzando inmediatamente después de la inyección de formalina (fase precoz) y durante 15 minutos comenzando a los15 minutos después de la inyección de formalina (fase tardía)

En ensayo se llevó a cabo a ciegas usando, por ejemplo 10 ratones por grupo. Los animales apropiados para ensayo son, por ejemplo, ratones macho Rj: NMRI (Elevage Janvier), con un peso de 20 – 30 g (rango max. por experimento = 5 g) al comienzo del ensayo. Los animales fueron aclimatados tal como se describió para los animales que se usaron en el ensayo LES. El ensayo incluye ensayos múltiples donde se usan los compuestos de referencia (por ejemplo, morfina), compuestos

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comparativos (por ejemplo, gabapentina y duloxetina), y compuestos de la presente invención. Los compuestos de la invención pueden se evaluados en dosis múltiples tal como se ha descrito previamente en el ensayo LES, y administrarse s.c. 60 minutos antes de la formalina en comparación con un grupo de vehículo de control mientras que la morfina (64 mg/kg p.o.), gabapentina (300 mg/kg p.o.) y duloxetina (10 mg/kg p.o.) se administran p.o. 60 minutos antes de la formalina. Los datos se analizan comparando grupos tratados con grupos de vehículo de control usando ensayos no emparejados Mann–Whitney U.

La esclerosis múltiple puede ser evaluada mediante un modelo experimental de encefalomielitis autoinmune (EAE) descrito en [H. Y. Liu *et al. J. Neurosci. Res.*, **2002**, *70*, 2: 238–48].

Los expertos en la materia reconocerán que pueden efectuarse varios cambios y modificaciones en los aspectos o realizaciones de esta invención y que dichos cambios y/o modificaciones pueden efectuarse sin apartarse del espíritu y alcance de esta invención. Por lo tanto, se tiene la intención de que las reivindicaciones anexas cubran todas dichas variaciones equivalentes, que entran dentro del espíritu y alcance de esta invención.

Cada referencia citada en la presente solicitud, incluyendo las referencias de la literatura, libros, patentes y solicitudes de patente, se incorporan aquí como referencia en su totalidad.

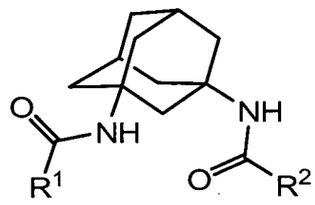
La presente solicitud es una Solicitud de Patente norteamericana No provisional que reivindica los beneficios de las solicitudes de patente norteamericanas provisionales Nos. 61/083563 y 61/160804 presentadas el 25 de julio de 2008 y el 17 de marzo de 2009, respectivamente, cada una de las cuales se incorpora aquí como referencia en su totalidad.

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REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma cómo la misma ha de ser llevada a la práctica se declara reivindicar como de propiedad y derecho exclusivo:

1) Un compuesto de fórmula (I):



(I)

donde:

R^1 y R^2 son cada uno independientemente alquilo, cicloalquilo, cetocicloalquilo, heterociclilo, arilo o heteroarilo, que está opcionalmente mono–, di–, o tri–sustituida con alquilo, alcoxi, halógeno, ciano, nitro, trifluoralquilo, amino, alquilamino, dialquilamino, acilo, arilo, heteroarilo, heterociclilo, heterociclilo–R^3, –NHR^3, –N(alquilo)R^3, –$C(O)NHR^3$, –C(O)N(alquilo)R^3, –$NHC(O)R^3$, –N(alquilo)$C(O)R^3$, –OH o –OR^3, donde:

R^3 es alquilo C_1–C_6 o cicloalquilo C_1–C_6, que está opcionalmente sustituido con halógeno, alcoxi C_1–C_3, OH, –CN, –NH_2, –NH(alquilo C_1–C_3), –N(alquilo C_1–$C_3)_2$, alquilheterociclilo C_1–$_3$, alquilcarbamato C_1–C_3, –C(O)NH(alquilo C_1–C_3), –C(O)N(alquilo C_1–$C_3)_2$, –NHC(O)–alquilo C_1–C_3, –N(alquilo C_1–C_3)–C(O)–alquilo C_1–C_3, OH, o –O–alquilo C_1–C_6;

con la condición de que el compuesto de fórmula (I) no es:

N, N'–(1,3–adamantilen)bis(3–metoxi–benzamida);

N, N'–(1,3–adamantilen)bis(4–etoxi–benzamida);

N, N'–(1,3–adamantilen)bis(4–metoxi–benzamida);

N,N'–(1,3–adamantilen)bis(3,4,5–trimetoxibenzamida);

N, N'–(1,3–adamantilen)bis(2–yodo–benzamida);

N,N'–(1,3–adamantilen)bis–benzamida;

N,N'–(1,3–adamantilen)bis(3–nitrobenzamida); y

N,N'–(1,3–adamantilen)bis–(3–piridincarboxamida); o

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o una sal farmacéuticamente aceptable del mismo.

2) El compuesto de la reivindicación 1, donde R^1 y R^2 son ambos arilo.

3) El compuesto de la reivindicación 1, donde R^1 y R^2 son ambos heteroarilo.

4) El compuesto de la reivindicación 1, donde R^1 es arilo y R^2 es heteroarilo.

5) El compuesto de la reivindicación 1, donde R^1 es arilo o heteroarilo y R^2 es cicloalquilo, cetocicloalquilo o heterociclilo.

6) El compuesto de la reivindicación 1, donde cualquiera de R^1 o R^2 es heteroarilo

7) El compuesto de la reivindicación 1, donde cualquiera de R^1 o R^2 es arilo.

8) El compuesto de la reivindicación 1, donde cualquiera de R^1 o R^2 es cicloalquilo.

9) El compuesto de la reivindicación 1, donde por lo menos un arilo es fenilo.

10) El compuesto de la reivindicación 1, donde por lo menos un heteroarilo es piridinilo, pirimidinilo, piridazinilo, tiazolilo, pirazolilo, indazolilo, tiofenilo, furanilo, benzofuranilo, benzo[c]isoxazolilo, benzoxazolilo, benzotiazolilo, dihidrotieno[3,4–b][1,4]dioxinilo, furanilo, imidazo[1,2–a]piridinilo, indazolilo, indolinilo, indolilo, isoquinolinilo, isoxazolilo, naftiridinilo, oxazolilo, pirazinilo, pirazolilo, piridazinilo, piridinilo, pirimidinilo, pirrol[3,2–c]piridinilo, quinolinilo, quinoxalinilo, tiazolilo, o tiofenilo.

11) El compuesto de la reivindicación 1, donde cicloalquilo es ciclobutilo, ciclohexilo, ciclopentilo, o ciclopropilo.

12) El compuesto de la reivindicación 1, donde por lo menos un cicloalquilo, arilo o heteroarilo está sustituido tal como se ha definido previamente.

13) El compuesto de la reivindicación 12, donde los mono–, di–, o tri–sustituyentes están independientemente seleccionados del grupo que consiste en metilo, metoxi, dimetilamin–etoxi, amino, metilamino, dimetilamino, ciano, cloro, ciano, dimetilamino, dimetilamin–etoxi, metilo, metilamino, metoxi, fluor, $–C(O)NHCH_3$, furanilo, pirrolidinilo, tiofenilo y trifluormetilo.

14) El compuesto de la reivindicación 12, donde el heteroarilo es piridinilo, y el piridinilo está mono–, di–, o tri–sustituido tal como se ha definido previamente.

15) El compuesto de la reivindicación 14, donde las mono–, di–, o tri–sustituciones son independientemente heteroarilo, heterociclilo, heterociclil–R^3, –NHR^3, –$N(alquilo)R^3$, donde R^3 es tal como se ha definido previamente.

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16) El compuesto de la reivindicación 8, donde el cicloalquilo está tetra–sustituido con flúor.

17) El compuesto de la reivindicación 1, donde el compuesto es:

N,N'–(1,3–adamantilen)bis(6–metil–piridin–2–carboxamida);

N,N'–(1,3–adamantilen)bis(2–piridincarboxamida);

N,N'–(1,3–adamantilen)bis(3–cloro–benzamida);

N,N'–(1,3–adamantilen)bis(4–piridincarboxamida);

N,N'–(1,3–adamantilen)bis(3–ciano–benzamida);

[3–(3–cloro–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico ;

[3–(3–ciano–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico;

{3–[(1–metil–5–tiofen–2–il–1H–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico;

{3–[(5–furan–2–il–1–metil–1H–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–metil–2H–indazol–3–carboxílico;

(3–benzoilamin–adamantan–1–il)–amida de ácido 6–Metil–piridin–2–carboxílico;

[3–(4–dimetilamin–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico;

[3–(4–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico;

[3–(3–ciano–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico;

{3–[(benzofuran–5–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico;

{3–[4–(2–dimetilamin–etoxi)–benzoilamin]–adamantan–1–il}–amida de ácido piridin–2–carboxílico;

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{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

N,N'–(1,3–adamantilen)bis(4–metil–piridin–2–carboxamida);

N,N'–(1,3–adamantilen)bis(quinolin–2–carboxamida);

N,N'–(1,3–adamantilen)bis(quinoxalin–2–carboxamida);

N,N'–(1,3–adamantilen)bis(tiofen–2–carboxamida);

N,N'–(1,3–adamantilen)bis(3–fluorbenzamida);

N,N'–(1,3–adamantilen)bis(3–metilbenzamida);

N,N'–(1,3–adamantilen)bis(1–metil–1*H*–pirazol–3–carboxamida);

{3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–metil–pirazin–2–carboxílico;

{3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido tiazol–2–carboxílico;

{3–[(1–metil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–amida de ácido 6–morfolin–4–il–piridin–2–carboxílico ;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–trifluormetil–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido piridazin–3–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–cianometil–piridin–2–carboxílico;

{3–[(5–ciclopropil–isoxazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido [1,8]naftiridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–metil–piridin–2–carboxílico;

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{3–[(2–metil–oxazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico;

{3–[(isoxazol–5–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

[3–(3–ciano–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico;

{3–[(benzofuran–5–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido quinoxalin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido pirimidin–4–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido benzotiazol–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 1–metil–1*H*–indazol–3–carboxílico;

{3–[(2,3–dihidro–tieno[3,4–b][1,4]dioxin–5–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

{3–[(5–metil–isoxazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

{3–[(tiazol–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido pirazin–2–carboxílico;

{3–[(1–etil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

[3–(3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico;

[3–(3–pirimidin–2–il–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico;

[3–(3–clorometil–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–piridin–2–carboxílico;

[3–(ciclobutancarbonil–amino)–adamantan–1–il]–amida de ácido 6–metil–piridin–2–carboxílico;

{3–[(3,3–difluor–ciclobutancarbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

{3–[(2–metil–ciclopropancarbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–metil–2*H*–indazol–3–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–cloro–imidazo[1,2–a]piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–7–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–6–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–imidazo[1,2–a]piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–metil–imidazo[1,2–a]piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 7–metil–imidazo[1,2–a]piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–cloro–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–pirazin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido pirimidin–4–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–pirrolidin–1–il–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido benzo[c]isoxazol–3–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–metil–pirazin–2–carboxílico;

2–metilamida 6–({3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2,6–dicarboxílico);

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–metil–benzoxazol–6–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 1*H*–pirrol[3,2–b]piridin–5–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2,3–dihidro–1*H*–indol–5–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metoxi–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 1–Metil–1*H*–indol–5–carboxílico;

Ester ter–butílico de ácido 6–{3–[(piridin–2–carbonil)–amino]–adamantan–1–il–carbamoil}–3,4–dihidro–1*H*–isoquinolina–2–carboxílico;

(3–benzoilamin–adamantan–1–il)–amida de ácido piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(5–metil–isoxazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2–carboxílico;

{3–[(tiazol–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2–carboxílico;

{3–[(tiofen–2–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico;

{3–[(1–metil–1H–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico;

{3–[(isoxazol–5–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico;

{3–[(3–metil–isoxazol–5–carbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–metil–2*H*–indazol–3–carboxílico;

[3–(3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico;

[3–(4–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico;

[3–(ciclobutancarbonil–amino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico;

{3–[(2,2–difluor–ciclopropancarbonil)–amino]–adamantan–1–il}–amida de ácido piridin–2–carboxílico;

[3–(ciclohexancarbonil–amino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico;

[3–(ciclopentancarbonil–amino)–adamantan–1–il]–amida de ácido piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–cloro–imidazo[1,2–a]piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–7–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Imidazo[1,2–a]piridin–6–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–metil–imidazo[1,2–a]piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 7–metil–imidazo[1,2–a]piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–metil–imidazo[1,2–a]piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido pirimidin–4–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 5–Metil–pirazin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido pirazin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 1–Metil–1*H*–pirazol–3–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–cloro–imidazo[1,2–a]piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido Imidazo[1,2–a]piridin–7–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido Imidazo[1,2–a]piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido Imidazo[1,2–a]piridin–6–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–metil–imidazo[1,2–a]piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 5–metil–imidazo[1,2–a]piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 7–metil–imidazo[1,2–a]piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–morfolin–4–il–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(4–Metil–piperazin–1–il)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–dimetilamin–pirrolidin–1–il)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–hidroxi–3,4,5,6–tetrahidro–2*H*–[1,2']bipiridinil–6'–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–hidroxi–pirrolidin–1–il)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–hidroxi–etil)–metil–amino]–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–hidroxi–propilamino)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–dimetilamin–etil)–metil–amino]–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–Hidroxi–pirrolidin–1–il)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Hidroxi–3,4,5,6–tetrahidro–2*H*–[1,2]bipiridinil–6–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–Metoxi–etil)–metil–amino]–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–Hidroxi–etilamino)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–Hidroxi–etil)–metil–amino]–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–Hidroxi–propilamino)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–morfolin–4–il–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(2–Hidroxi–etilamino)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–[(2–Hidroxi–etil)–metil–amino]–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(3–hidroxi–propilamino)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–morfolin–4–il–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(4–Metil–piperazin–1–il)–piridin–2–carboxílico;

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[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(3–dimetilamin–pirrolidin–1–il)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 4–Hidroxi–3,4,5,6–tetrahidro–2H–[1,2']bipiridinil–6'–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(3–Hidroxi–pirrolidin–1–il)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–Metoxi–propilamino)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(3–dimetilamin–propil)–metil–amino]–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–dimetilamin–etilamino)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–Acetilamin–etilamino)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–Metoxi–etilamino)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–Metoxi–etil)–metil–amino]–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–dimetilamin–propilamino)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(2–dimetilamin–etil)–metil–amino]–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((S)–2–hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((R)–2–hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((S)–2–carbamoil–pirrolidin–1–il)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–Metoxi–propilamino)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–dimetilamin–etilamino)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–[(3–dimetilamin–propil)–metil–amino]–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–acetilamin–etilamino)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–metoxi–etilamino)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(3–dimetilamin–propilamino)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((S)–2–hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((R)–2–hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–((S)–2–carbamoil–pirrolidin–1–il)–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(2–carbamoil–etilamino)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(3–metoxi–propilamino)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(2–dimetilamin–etilamino)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–[(3–dimetilamin–propil)–metil–amino]–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(2–acetilamin–etilamino)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(2–Metoxi–etilamino)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–[(2–metoxi–etil)–metil–amino]–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(3–dimetilamin–propilamino)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–[(2–dimetilamin–etil)–metil–amino]–piridin–2–carboxílico;

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[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–((S)–2–hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–((R)–2–hidroximetil–pirrolidin–1–il)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–((S)–2–carbamoil–pirrolidin–1–il)–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–(2–carbamoil–etilamino)–piridin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Imidazol–1–il–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Imidazol–1–il–piridin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Imidazol–1–il–piridin–2–carboxílico;

{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–(4–fluor–fenil)–pirimidin–4–carboxílico;

{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–fenil–pirimidin–4–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido pirimidin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Metil–pirimidin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–trifluorometil–pirimidin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–Metil–pirimidin–4–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–trifluormetil–pirimidin–4–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–trifluormetil–pirazin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–trifluormetil–pirazin–2–carboxílico;

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{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirimidin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–metil–pirimidin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–trifluormetil–pirimidin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–metil–pirimidin–4–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–trifluormetil–pirimidin–4–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–trifluormetil–pirazin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–trifluormetil–pirazin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–fluor–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–fluor–piridin–2–carboxílico;

{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirazin–2–carboxílico;

{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–Metil–pirazin–2–carboxílico;

{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–trifluormetil–pirazin–2–carboxílico;

{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 5–trifluormetil–pirazin–2–carboxílico;

{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirimidin–2–carboxílico;

{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Metil–pirimidin–2–carboxílico;

{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Trifluormetil–pirimidin–2–carboxílico;

{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–Trifluormetil–pirimidin–4–carboxílico;

{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–Metil–pirimidin–4–carboxílico;

{3–[(5–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirimidin–4–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido pirimidin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 4–Metil–pirimidin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 4–Trifluormetil–pirimidin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 2–Metil–pirimidin–4–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 2–Trifluormetil–pirimidin–4–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Trifluormetil–pirazin–2–carboxílico;

[3–(3–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 5–Trifluormetil–pirazin–2–carboxílico;

{3–[3–(2–hidroxi–etoxi)–benzoilamino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

(3–{[4–(2–hidroxi–etoxi)–piridin–2–carbonil]–amino}–adamantan–1–il)–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[3–(2–hidroxi–2–metil–propoxi)–benzoilamino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

(3–{[4–(2–hidroxi–2–metil–propoxi)–piridin–2–carbonil]–amino}–adamantan–1–il)–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirazin–2–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2,6–Dimetil–pirimidin–4–carboxílico;

{3–[(piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Fluor–piridin–2–carboxílico;

{3–[(1,5–dimetil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2–carboxílico;

{3–[(2–metil–tiazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2–carboxílico;

[3–(3–dimetilamin–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(piridin–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(6–aminopiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2,6–dimetil–pirimidin–4–carboxílico;

{3–[(tiazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido benzoxazol–5–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido [1,6]naftiridin–2–carboxílico;

{3–[(2,3–dihidro–benzo[1,4]dioxin–6–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(4–fluorpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4,6–dimetil–piridin–2–carboxílico;

{3–[(1,5–dimetil–1*H*–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

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{3–[(4–metoxipiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(3–fluorpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(5–metilpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(4–hidroxipiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

6–({3–[(6–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2,6–dicarboxílico 2–amida de ácido);

{3–[(6–hidroximetilpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Piridin–2,6–dicarboxílico 2–amida de ácido;

{3–[(6–fluorpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(2–metil–tiazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(4–bromopiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

Ester metílico de ácido 6–{3–[(6–Metil–piridin–2–carbonil)–amino]–adamantan–1–ilcarbamoil}–piridin–2–carboxílico;

{3–[(6–acetilpiridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(6–(1–hidroxi–etil)–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

{3–[(6–(1–hidroxi–1–metil–etil)–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–piridin–2–carboxílico;

N,N'–(1,3–adamantilen)bis(6–metil–pirazin–2–carboxamida);

[3–(3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(3–etoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(2,5–difluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(3–cloro–4–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(2–fluor–3–trifluormetil–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(6–metoxi–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(3–cloro–2–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(4–metoxi–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(2–metoxi–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(2–etoxi–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(2–metil–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(2–metil–tiazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(3–fluor–5–metil–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(4–fluor–3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(2–fluor–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(5–cloro–2–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(3–difluormetoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(3–cloro–5–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

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{3–[(6–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(5–metil–piridin–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(4–fluor–3–metil–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(2–fluor–3–metoxi–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(3–metil–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(2–fluor–5 trifluormetil–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(5–cloro–piridin–3–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(4–fluor–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirimidin–2–carboxílico;

{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–Metil–pirimidin–4–carboxílico;

{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido [1,6]naftiridin–2–carboxílico;

{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido Benzoxazol–5–carboxílico;

{3–[(4–bromo–piridin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

[3–(4–fluor–benzoilamino)–adamantan–1–il]–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(2–bromo–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 6–Metil–pirazin–2–carboxílico;

{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–trifluormetil–pirimidin–4–carboxílico;

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{3–[(6–metil–pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–trifluormetil–pirimidin–2–carboxílico;

{3–[(2–bromo–piridin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirazin–2–carboxílico;

{3–[(2–metil–tiazol–4–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirazin–2–carboxílico;

{3–[(5–ciclopropil–2H–pirazol–3–carbonil)–amino]–adamantan–1–il}–amida de ácido Pirazin–2–carboxílico;

{3–[(pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Metil–pirimidin–2–carboxílico;

{3–[(pirazin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–Trifluormetil–pirimidin–4–carboxílico;

{3–[(2–metil–pirimidin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Trifluormetil–pirimidin–2–carboxílico;

{3–[(4–metil–pirimidin–2–carbonil)–amino]–adamantan–1–il}–amida de ácido 2–Metil–pirimidin–4–carboxílico;

{3–[(pirimidin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Metil–pirimidin–2–carboxílico;

{3–[(pirimidin–4–carbonil)–amino]–adamantan–1–il}–amida de ácido 4–Trifluormetil–pirimidin–2–carboxílico; o

una sal farmacéuticamente aceptable de los mismos.

18) Una composición farmacéutica que comprende por lo menos un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo, y por lo menos un portador farmacéuticamente aceptable.

19) Un método para tratar una enfermedad o trastorno, el método comprende administrar una cantidad terapéuticamente eficaz de por lo menos un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo a un mamífero que lo necesita, donde la enfermedad o trastorno es una enfermedad o trastorno del sistema nervioso central.

20) El método de la reivindicación 19, donde el mamífero es un ser humano.

21) El método de la reivindicación 19, donde la enfermedad o trastorno del sistema nervioso central es una enfermedad o trastorno cognitivo, neurodegenerativo, psiquiátrico o neurológico.

22) El método de la reivindicación 21, donde la enfermedad o trastorno cognitivo o neurodegenerativo está seleccionado del grupo que consiste en trastorno del talante, ansiedad, esquizofrenia, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis múltiple, corea de Huntington, esclerosis lateral amiotrófica, enfermedad de Creutzfeld–Jakob, neurodegeneración inducida por trauma, encefalopatía inducida por SIDA, encefalopatía no inducida por SIDA. síndrome X Frágil, trastorno dentro del espectro de autismo, y una combinación de los mismos.

23) El método de la reivindicación 22, donde el trastorno del talante es depresión.

24) El método de la reivindicación 23, donde la depresión está seleccionada del grupo que consiste en depresión atípica, depresión bipolar, depresión unipolar, depresión principal, depresión endógena, depresión involucional, depresión reactiva, depresión post–parto, depresión primaria, depresión psicótica, depresión secundaria, y una combinación de los mismos.

25) El método de la reivindicación 22, donde la enfermedad o trastorno de ansiedad está seleccionada del grupo que comprende trastorno de ansiedad generalizada, ansiedad por pánico, trastorno obsesivo compulsivo, fobia social, ansiedad por estado general, trastorno por estrés post–traumático, reacción de estrés agudo, trastorno de ajuste, trastorno hipocondríaco, un trastorno de ansiedad por separación, agorafobia, una fobia específica, un trastorno de ansiedad debido a una afección médica general, trastorno de ansiedad inducida por una sustancia, ansiedad inducida por abstinencia de alcohol y una combinación de los mismos.

26) El método de la reivindicación 19, donde la enfermedad o trastorno del sistema nervioso central es una enfermedad o trastorno por dolor seleccionada del grupo que consiste en dolor inflamatorio, dolor neuropático y dolor por migraña.

27) El método de la reivindicación 26, donde la enfemedad o trastorno por dolor a causa de migraña o dolor neuropático está seleccionado del grupo que consiste en alodinia, dolor hiperalgésico, dolor fantasma, dolor neuropático relacionado con neuropatía diabética, dolor neuropático relacionado con migraña, y una combinación de los mismos.

28) El método de la reivindicación 19, donde la enfermedad o trastorno del sistema nervioso central es una enfermedad o trastorno causado por un estado de hiperexitación neuronal.

29) El método de la reivindicación 28, donde el estado o trastorno de hiperexitación neuronal es un estado de hiperexitación neuronal por retiro de medicamento, un estado de hiperexitación neuronal en intoxicaciones, o una combinación de los mismos.

30) El método de la reivindicación 21, donde se trata por lo menos un síntoma de la enfemedad o trastorno.

31) El método de la reivindicación 30, donde la enfermedad o trastorno es una depresión.

32) El método de la reivindicación 32, donde por lo menos un síntoma de la depresión es sensación de depresión, talante deprimido, pérdida de interés o placer en alguna o todas las actividades, cambios en el apetito, cambios en el peso, cambios en los patrones del sueño, falta de energía, fatiga, baja autoestima, capacidad disminuida para pensar, concentrarse o decidir, sentimientos de desilución o inutilidad, agitación o retardo psicomotores, auto–reproche, culpamiento inapropiado, frecuentes pensamientos de muerte o suicidio, planes o intentos para cometer suicidio o una combinación de los mismos.

33) El método de la reivindicación 30, donde la enfermedad o trastorno es ansiedad.

34) El método de la reivindicación 33, donde por lo menos un síntoma de la ansiedad es aprehensión, miedo, temblor, dolores musculares, insomio, malestares abdominales, mareos, irritabilidad, pensamientos persistentes, recurrentes, compulsiones, palpitaciones cardíacas, dolor torácico, molestia torácica, transpiración, sensaciones de hormigueo, sensación de ahogo, miedo a la pérdida de control, retrocesos, pesadillas, pensamientos intrusivos, recuerdos intrusivos, comportamientos de evitación, aturdimiento emocional e incapacidad de dormir, sentimientos de ansiedad, respuesta hiperactiva de sobresaltos, hipervigilia, explosión de cólera, lipotimia, sonrojo, transpiración profusa o una combinación de los mismos.

35) El método de la reivindicación 30, donde la enfermedad o trastorno es esquizofrenia.

36) El método de la reivindicación 35, donde por lo menos un síntoma de la esquizofrenia es un síntoma positivo seleccionado del grupo que consiste en alucionación, desilución, paranoia, y una combinación de los mismos.

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37) El método de la reivindicación 35, donde por lo menos un síntoma de esquizofrenia es un síntoma negativo seleccionado del grupo que consiste en retraimiento social, sentimiento de abatimiento, anhedonia, motivación disminuida y una combinación de los mismos.

38) El método de la reivindicación 35, donde el síntoma de esquizofrenia es un síntoma cognitivo seleccionado del grupo que consiste en déficit grave de atención, déficit grave en la denominación de objetos, grave déficit en el funcionamiento de la memoria, grave déficit en el alamacenamiento a largo término en la memoria, grave déficit en el funcionamiento ejecutivo, un enlentecimiento en el proceso de información, un enlentecimiento de la actividad neural, depresión a largo término y una combinación de los mismos.

39) El método de la reivindicación 30, donde la enfermedad o trastorno es la enfermedad de Parkinson.

40) El método de la reivindicación 39, donde por lo menos un síntoma de la enfermedad de Parkinson es es disquinecia inducida por levodopa, falta de equilibria, paso lento parkinsoniano, bradiquinesia, rigidez, temblor, cambios en el habla, pérdida de la expresión facial, micrografía, dificultad para tragar, babeo, dolor, demencia, confusión, disturbio del sueño, constipación, problemas de piel, depresión, temor, ansiedad, dificultad de la memoria, raciocinio lento, disfunción sexual, problema urinario, fatiga, dolor, pérdida de energía o una combinación de los mismos.

41) El método de la reivindicación 30, donde la enfermedad o trastorno es la enfermedad de Alzheimer.

42) El método de la reivindicación 41, donde por lo menos un síntoma de la enfermedad de Alzheimer es la alteración de la memoria, la alteración de la atención, la alteración del juicio, la alteración en la toma de decisiones, la alteración en la orientación de contornos físicos, alteración del lenguaje, la alteración de las actividades que dependenden del habla, alteración del razonamiento abstracto, alteración en las capacidades visoespaciales, alteración en el funcionamiento ejecutivo, alteración en los trastornos de comportamiento, desinterés y pasividad, apatía, acicalamiento inapropiado, autocuidado defectuoso, agitación, explosión violenta, agresión, depresión, ansiedad, alucinación, delirio, cambios en la personalidad, cambios en el talante, demencia o combinación de los mismos.

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43) El método de la reivindicación 30, donde la enfermedad o trastorno cognitivo o neurodegenerativo es la esclerosis múltiple.

44) El método de la reivindicación 43, donde por lo menos un síntoma de la esclerosis múltiple es visión borrosa por neuritis óptica, dolor en los ojos, pérdida del color de la visión, ceguera, visión doble por dipoplia, movimientos de nistagmus rítmico oculares, dismetría ocular, movimientos oculares sub– o hiperfulgurantes, oftalmoplejía internuclear, nistagmus, diplopia, fosfenos con movimiento y sonido, diplopia, defecto pupilar aferente, paresia motora, monoparesia, paraparesia, hemiparesia, cuadraparesia plejía, paraplejía, hemiplejía, tetraplejía, cuadraplejía, espasiticidad, disartria, atrofia muscular, espasmos, calambres, hipotonia, clono, mioclono, mioquimia, síndrome de pierna inquieta, reflejos disfuncionales de pie extendido (MRSs, Babinski's, Hoffman's, Chaddock's), parestesia, anestesia, neuralgia, dolor neuropático, dolor neurogénico, l'hermitte's, disfunción propioceptiva, neuralgia trigeminal, ataxia, temblor intencional, dismetria, ataxia vestibular, vértigo, ataxia del habla, distonia, disdiadocoquinesia, micción frecuente, espasticidad de la vejiga, vejiga fláccida, disinergia de esfínter detrusor, disfunción eréctil, anorgasmo, eyaculación retrograda, frigidez, constipación, urgencia fecal, depresión, disfunción cognitiva, demencia, cambios de talante, labilidad emocional, euforia, síndrome bipolar, ansiedad, afasia, disfagia, fatiga, síntoma de uhthoffs, reflujo gastroesofágico, trastorno del sueño, o una combinación de los mismos.

45) Un método para tratar reflujo gastroesofágico, el método comprende administrar una cantidad terapéuticamente eficaz de por lo menos un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo a un mamífero que lo necesita.

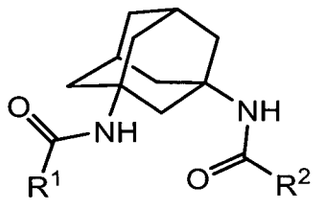
46) Un método para tratar la dependencia al alcohol, el método comprende administrar una cantidad terapéuticamente eficaz de por lo menos un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo a un mamífero que lo necesita.

p.de: H. LUNDBECK A/S

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RESUMEN

La presente invención provee derivados adamantil–diamida de fórmula (I):



(I)

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donde R^1 y R^2 son tal como se han definido aquí, o una sal farmacéuticamente aceptable del mismo, y composiciones farmacéuticas y métodos de uso del mismo.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/050934

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C233/79 A61K31/4412 A61K31/444 A61P25/00 C07C233/00
C07D213/81 C07D215/48 C07D231/14 C07D241/44 C07D333/38
C07D401/12 C07D401/14 C07D403/12 C07D405/12 C07D405/14

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)
A61K A61P C07D C07C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/73283 A (NPS PHARMA INC [US]; WAGENEN BRADFORD C VAN [US]; MOE SCOTT T [US]; SM) 7 December 2000 (2000-12-07) the whole document	1-46
A	BACH ET AL.: "Metabotropic glutamate receptor 5 modulators and their potential therapeutic applications" EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 17, no. 4, 1 April 2007 (2007-04-01), pages 371-384, XP002552836 cited in the application the whole document	1-46

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[X] Further documents are listed in the continuation of Box C. [X] 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
30 October 2009	16/11/2009

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	Lécaillon, Jennifer

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/050934

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 897 747 A (DAICEL CHEM [JP]; ISHII YASUTAKA [JP] DAICEL CHEM [JP]) 24 February 1999 (1999-02-24) example 83	1
A	claim 1	2-17
X	WO 2006/090244 A (GLENMARK PHARMACEUTICALS SA [CH]; GOPALAN BALASUBRAMANIAN [IN]; THOMAS) 31 August 2006 (2006-08-31) *example 20 step 2 page 54*	1
A	claim 1	2-17
X	STETTER, H. AND WULFF, C.: "über die Bromierung des Adamantans" CHEMISCHE BERICHTE, vol. 93, 1960, pages 1366-1371, XP002552837 compound (V)	1
X	BEWICK ET AL.: "Electrochemical Difunctionalisation of Adamantane and further Oxidation of Substituted Adamantanes" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1: ORGANIC AND BIO-ORGANIC CHEMISTRY (1972-1999), vol. 16, 1977, pages 1831-1834, XP009124892 compound (5)	1
X	SEINO ET AL.: "Synthesis of Aliphatic Polyimides Containing Adamantyl Units" JOURNAL OF POLYMER SCIENCE, PART A: POLYMER CHEMISTRY, vol. 37, no. 18, 1999, pages 3584-3590, XP002552838 *compound DAAA scheme 2*	1
X	BEWICK ET AL.: "The Electrochemical Difunctionalisation of Saturated Hydrocarbons" TETRAHEDRON LETTERS, no. 8, 1976, pages 631-364, XP002552839 *compound (ii) Table 2)*	1
X	WO 03/068726 A (DAICEL CHEM [JP]; TATSUMI ATSUO [JP]; KUWANA JUN [JP]) 21 August 2003 (2003-08-21) *compound of formula (3b)*	1
X	JP 2003 050441 A (KONISHIROKU PHOTO IND) 21 February 2003 (2003-02-21) *compound 2(t)*	1

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/050934

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BETTAYEB, KARIMA ET AL: "Meriolins, a New Class of Cell Death-Inducing Kinase Inhibitors with Enhanced Selectivity for Cyclin -Dependent Kinases" XP002553042 retrieved from STN Database accession no. 2007:996096 abstract & CANCER RESEARCH , 67(17), 8325-8334 CODEN: CNREA8; ISSN: 0008-5472, 2007,	1
A	US 3 053 907 A (WILLIAM SMITH GEORGE ET AL) 11 September 1962 (1962-09-11) *example 1 step B pages 2-3*	1
A	GEORGE W. SMITH AND HARRY D.WILLIAMS: "Reactions of adamantane and adamantane derivatives" JOURNAL OF ORGANIC CHEMISTRY, vol. 26, 1961, pages 2207-2212, XP002553041 page 2211	1
X,P	DATABASE CHEMCATS [Online] CHEMCATS ABSTRACTS SERVICES, COLUMBUS, OHIO, US; XP002552840 retrieved from STN Order Numbers: M-993259 M-993260 M-993263 X-072338 POD_70/0518 abstract	1
P,X	& "Scientific Exchange Product List" 27 May 2009 (2009-05-27), SCIENTIFIC EXCHANGE, INC. , CENTER OSSIPEE, NH, 03814 USA	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/050934

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0073283	A	07-12-2000	AT	302194 T	15-09-2005
			AU	778063 B2	11-11-2004
			AU	5178000 A	18-12-2000
			AU	2005200633 A1	17-03-2005
			CA	2376024 A1	07-12-2000
			CH	1196397 H1	31-05-2007
			CN	1361768 A	31-07-2002
			CN	1789246 A	21-06-2006
			DE	60022050 D1	22-09-2005
			DE	60022050 T2	14-06-2006
			DK	1196397 T3	02-01-2006
			EP	1196397 A1	17-04-2002
			ES	2249272 T3	01-04-2006
			JP	2003500480 T	07-01-2003
			MX	PA01012445 A	10-09-2003
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EP 0897747	A	24-02-1999	DE	69834077 T2	24-08-2006
			WO	9830329 A1	16-07-1998
			US	6468487 B1	22-10-2002
WO 2006090244	A	31-08-2006	NONE		
WO 03068726	A	21-08-2003	NONE		
JP 2003050441	A	21-02-2003	NONE		
US 3053907	A	11-09-1962	NONE		

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*** (32) ***Fecha*** (33) ***País***
61/083,563 **25/07/2008** **US**
61/160,804 **17/03/2009** **US**

(51) Int Cl: **C07C 233/079**

(71)Solicitante(s) **H. LUNDBECK A/S**

(72) Inventor(es) **HERMOGENES N. JIMÉNEZ Y OTROS**

(74) Apoderado: **LUZ CLEMENCIA DE PAEZ**

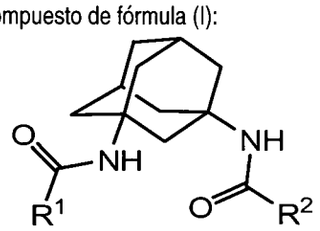
(85) Fecha limite inicio fase nacional: 25/02/2011
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 17/07/2009
No. de solicitud PCT/US2009/050934

(87) Publicación internacional
Fecha: 28/01/2010
N° publicación: ***WO 2010/011570 A1***

(54) Titulo: **DERIVADOS ADAMANTIL DIAMIDA Y USOS DE LOS MISMOS**

Reivindicación(es):

1) Un compuesto de fórmula (I):



(I)

donde:
R^1 y R^2 son cada uno independientemente alquilo, cicloalquilo, cetocicloalquilo, heterociclilo, arilo o heteroarilo, que está opcionalmente mono–, di–, o tri–sustituida con alquilo, alcoxi, halógeno, ciano, nitro, trifluoralquilo, amino, alquilamino, dialquilamino, acilo, arilo, heteroarilo, heterociclilo, heterociclilo–R^3, –NHR^3, –N(alquilo)R^3, –C(O)NHR^3, –C(O)N(alquilo)R^3, –NHC(O)R^3, –N(alquilo)C(O)R^3, –OH o –OR^3, donde:

R^3 es alquilo C_1–C_6 o cicloalquilo C_1–C_6, que está opcionalmente sustituido con halógeno, alcoxi C_1–C_3, OH, –CN, $–NH_2$, –NH(alquilo C_1–C_3), –N(alquilo C_1–$C_3)_2$, alquilheterociclilo C_1–$_3$, alquilcarbamato C_1–C_3, –C(O)NH(alquilo C_1–C_3), –C(O)N(alquilo C_1–$C_3)_2$, –NHC(O)–alquilo C_1–C_3, –N(alquilo C_1–C_3)–C(O)–alquilo C_1–C_3, OH, o –O–alquilo C_1–C_6;
con la condición de que el compuesto de fórmula (I) no es:
N, N'–(1,3–adamantilen)bis(3–metoxi–benzamida);
N, N'–(1,3–adamantilen)bis(4–etoxi–benzamida);
N, N'–(1,3–adamantilen)bis(4–metoxi–benzamida);
N,N'–(1,3–adamantilen)bis(3,4,5–trimetoxibenzamida);
N, N'–(1,3–adamantilen)bis(2–yodo–benzamida);
N,N'–(1,3–adamantilen)bis–benzamida;
N,N'–(1,3–adamantilen)bis(3–nitrobenzamida); y
N,N'–(1,3–adamantilen)bis–(3–piridincarboxamida); o
o una sal farmacéuticamente aceptable del mismo.

2) El compuesto de la reivindicación 1, donde R^1 y R^2 son ambos arilo.

3) El compuesto de la reivindicación 1, donde R^1 y R^2 son ambos heteroarilo.

4) El compuesto de la reivindicación 1, donde R^1 es arilo y R^2 es heteroarilo.

5) El compuesto de la reivindicación 1, donde R^1 es arilo o heteroarilo y R^2 es cicloalquilo, cetocicloalquilo o heterociclilo.

6) El compuesto de la reivindicación 1, donde cualquiera de R^1 o R^2 es heteroarilo

7) El compuesto de la reivindicación 1, donde cualquiera de R^1 o R^2 es arilo.

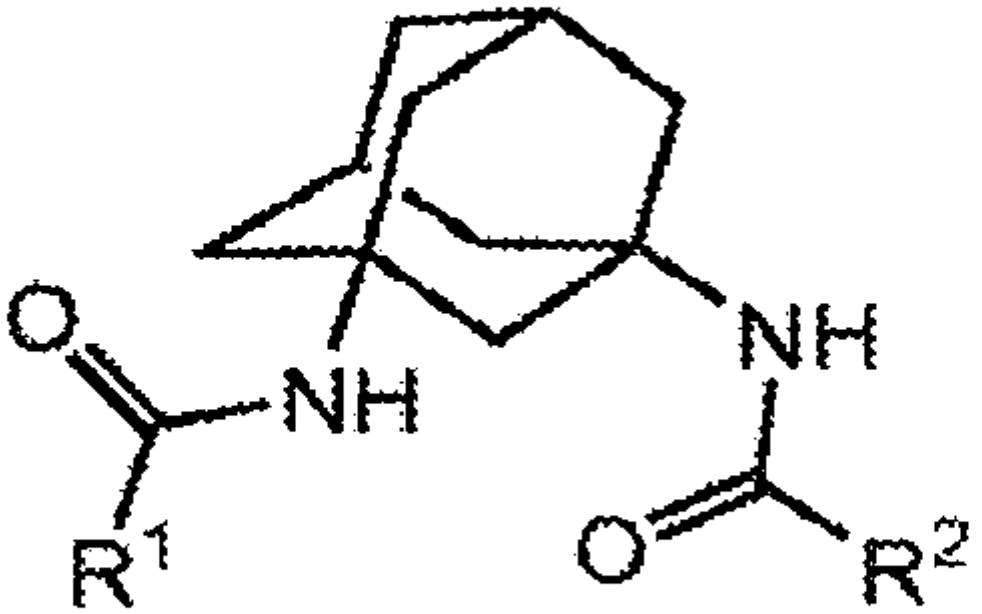
8) El compuesto de la reivindicación 1, donde cualquiera de R^1 o R^2 es cicloalquilo.

9) El compuesto de la reivindicación 1, donde por lo menos un arilo es fenilo.

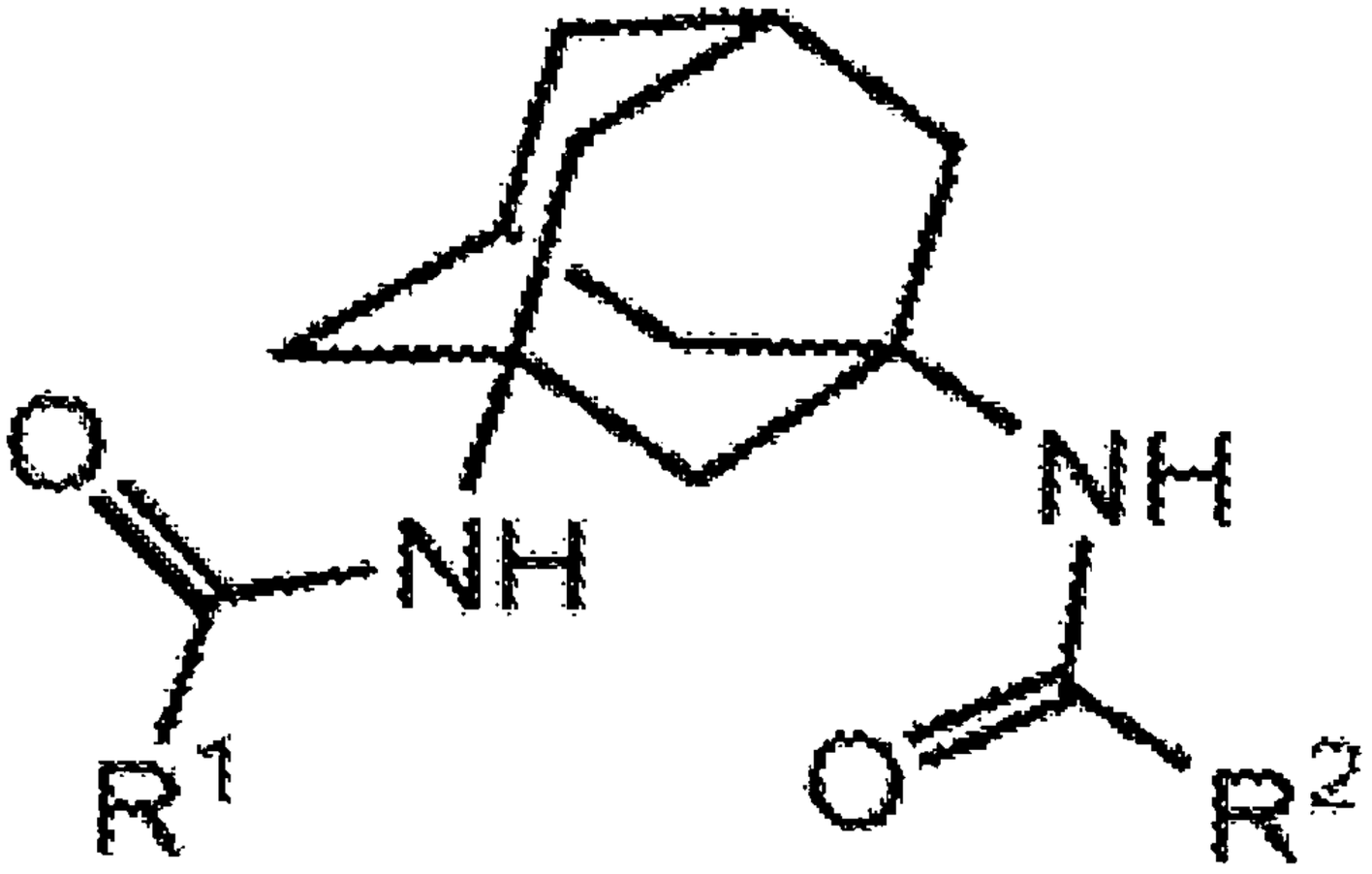
10) El compuesto de la reivindicación 1, donde por lo menos un heteroarilo es piridinilo, pirimidinilo, piridazinilo, tiazolilo, pirazolilo, indazolilo, tiofenilo, furanilo, benzofuranilo, benzo[c]isoxazolilo, benzoxazolilo, benzotiazolilo, dihidrotieno[3,4–b][1,4]dioxinilo, furanilo, imidazo[1,2–a]piridinilo, indazolilo, indolinilo, indolilo, isoquinolinilo, isoxazolilo, naftiridinilo, oxazolilo, pirazinilo, pirazolilo, piridazinilo, piridinilo, pirimidinilo, pirrol[3,2–c]piridinilo, quinolinilo, quinoxalinilo, tiazolilo, o tiofenilo.

11) El compuesto de la reivindicación 1, donde cicloalquilo es ciclobutilo, ciclohexilo, ciclopentilo, o ciclopropilo.

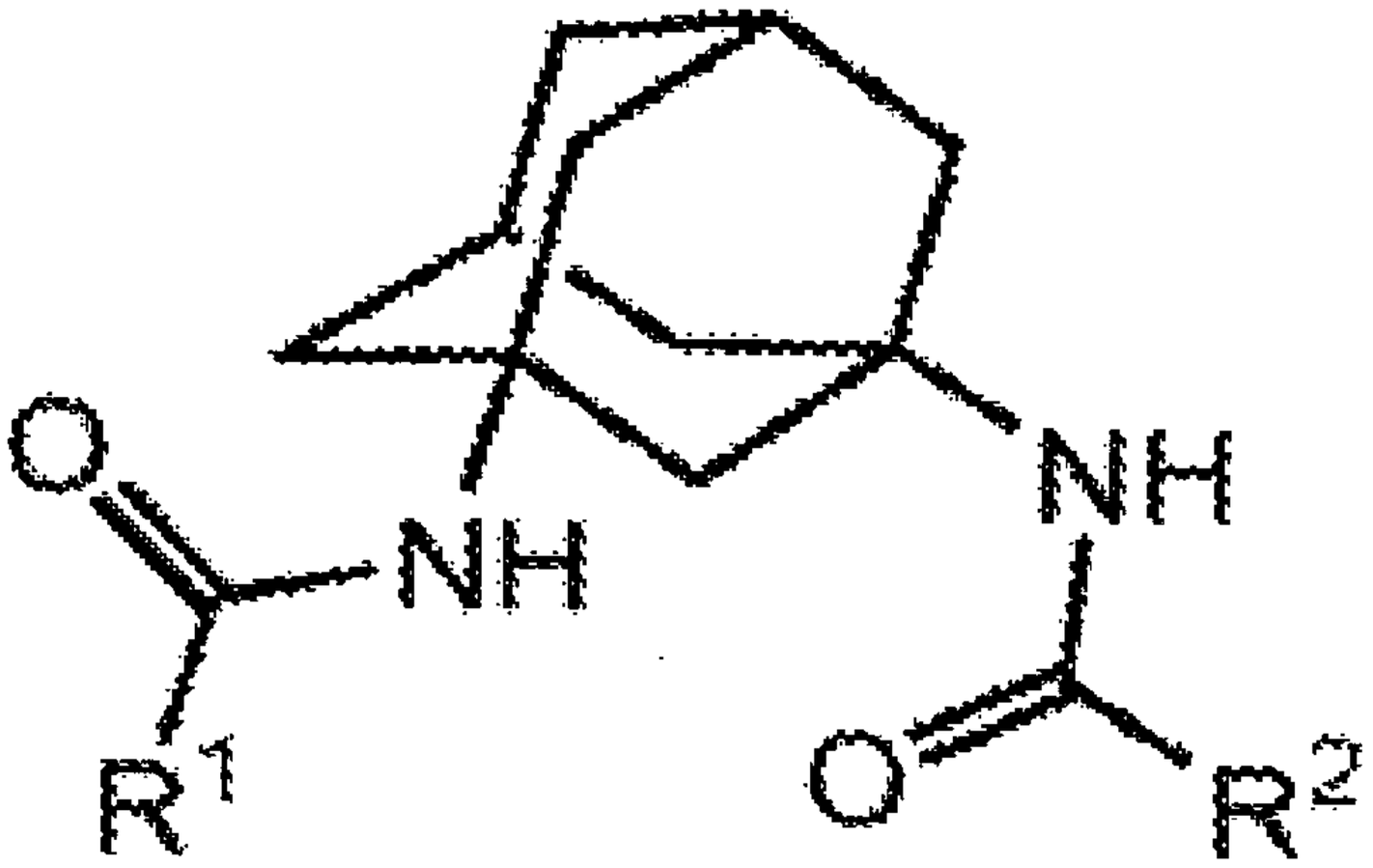
12) El compuesto de la reivindicación 1, donde por lo menos un cicloalquilo, arilo o heteroarilo está sustituido tal como se ha definido previamente.



(I)



(I)



(I)

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-159479- -00000-0000

Fecha: 2010-12-20 11:46:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 294

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 104,309
FECHA : DICIEMBRE 7 DE 2010

***** 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	146320775	06/12/2010	63,501,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	5,000.00
		TOTAL : $	5,000.00

SON: CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Colo: 03003-841-106-9

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

291

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT :

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-159479- -00000-0000
Fecha: 2010-12-20 11:46:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 294

RECIBO OFICIAL DE CAJA : 10 - 106,127
FECHA : DICIEMBRE 13 DE 2010

***** 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	146326854	13/12/2010	40,289,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	*** REIVINDICACION UNITARIA ADICIONAL	26,000.00
		TOTAL : $	26,000.00

SON: VEINTISEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo: 03003-841-106-9

292

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 8(

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-159479- -00000-0000
Fecha: 2010-12-20 11:46:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 294

RECIBO OFICIAL DE CAJA : 10 - 106,151
FECHA : DICIEMBRE 13 DE 2010

***** 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	146326854	13/12/2010	40,299,000.00

***** 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._____

Cob: 03003 - 841 - 106 - 9

293

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 106,196
FECHA : DICIEMBRE 13 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-159479- -00000-0000
Fecha: 2010-12-20 11:46:04 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 294

***** 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	146326854	13/12/2010	40,288,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	*** TASA ANUAL AÑOS 17 a 20 PARA MANT	907,000.00

****

TOTAL : $ 907,000.00

SON: NOVECIENTOS SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Colo: 03003-841-106-9

295

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-159479- -00000-0000
Fecha: 2010-12-20 11:46:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 294

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐

- ☐ 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 ☐