Industria y Comercio

SUPERINTENDENCIA

PCT

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 03-67869.

54 **TÍTULO** Inhibidores Heterocíclicos de ERK 2 y usos de los mismos

51 **CLASIFICACIÓN INTERNACIONAL** C07D 403/04, 401/14 413/14, 405/14, 403/14, A61K 31/506, A61P 35/00

71 **SOLICITANTE** Vertex Pharmaceuticals Incorporated

DOMICILIO Estados Unidos de América

74 **APODERADO** Ernesto Cavelier Franco

22. **BOGOTÁ, D. C.,** 8 agosto de 2003.

(FORMA P-10)

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

03 087869 00

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Radicacion : 03087869 00000000 Folios: 381
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Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

① **SOLICITUD DE**

[X] Patente de Invención [ ] Patente de Modelo de Utilidad

[ ] Capítulo I [X] Capítulo II

② **SOLICITANTE (71)**	Nombre Vertex Pharmaceuticals Incorporated Dirección 130 Waverly Street, Cambridge, MA 02139-4242, U.S.A. Nacionalidad o Domicilio Estados Unidos de América Lugar de Constitución Estados Unidos de América Teléfono Fax E-mail	**IDENTIFICACIÓN** CC [ ] NIT [ ] CE [ ] Otro [X] Cual_____ Número _____
③ **REPRESENTANTE O APODERADO**	Nombre Ernesto Cavelier Franco Dirección Carrera 9 No. 74-08 Of. 504 Teléfono 3764200 Fax 3761707 E-mail ernesto.cavelierapre-laws.com	**IDENTIFICACIÓN** CC [X] NIT [ ] CE [ ] Otro [ ] Cual_____ Número 19.081.620 TP 11519
④ **INVENTOR (ES) (72)**	Nombre Ver Anexo folio 12 Dirección Nacionalidad o Domicilio	

⑤ **PCT (86)**

Solicitud Internacional No PCT/US02/03791 Fecha 08/02/2002

Publicación Internacional No WO 02/064586A2 Fecha 22/08/2002

⑥ **Título (54)** Inhibidores Heterocíclicos de ERK2 y usos de los mismos.

⑦ **Clasificación Internacional (51)** C07D 403/04, 401/14, 413/14, 405/14, 403/14, A61K 31/506, A61P 35/00

⑧ **Prioridad**	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] NO [ ]	US	09/02/01 (Febr)	60/267,918
	US	12/10/01 (dr.)	60/328,768

⑨ **Comprobante de pago No.** 55204 **Fecha** [illegible] 2003

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

2 f

(10) ANEXOS

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [X] Arte Final 12X12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional
- [ ] Otros

(11) FIGURA CARACTERISTICA:

(12) Solicito la concesión de la patente,

NOMBRE Ernesto Cavelier Franco

Ernesto Cavelier

FIRMA _____

C C 19.081.620 T P 11519

TRADUCCION OFICIAL No 009/2003 de un documento escrito en Inglés, el cual para su identificación se sella con el sello de la Traductora lo mismo que la presente ----

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Traducción de un Poder escrito en Inglés, y sus respectivas autenticaciones

PODER

La organización **VERTEX PHARMACEUTICALS INC.**, que actualmente cumple con su objeto, actuando por medio de su representante legal, formada y existente de conformidad con las leyes de los Estados Unidos de América, con oficinas registradas en el número 130 Waverly Street, Cambridge, Massachusetts, Estados Unidos de América, por medio del presente nombra a Ernesto Cavelier, con TPA 11 519, Bernardo Rodríguez Ossa, con TPA 41.858, Alvaro Parra Gómez, con TPA 47 452 y Helena Camargo Williamson, con TPA 76 985, todos ellos con oficinas situadas en la Carrera 9 No 74-08, Oficina 504, Bogotá, D C , Colombia, en el mismo [illegible] como sus apoderados reales y verdaderos, para representarla ante [illegible] entidades administrativas o judiciales, árbitros, mediadores, [illegible] corte de arbitramento o conciliación, o ante cualquier autoridad con el objeto de obtener el mantenimiento la protección de los derechos de propiedad industrial y la acción [illegible] de dichos derechos, estando facultados para ese objeto para

1 Solicitar, seguir los respectivos procesos y obtener [illegible] registrar patentes de invención, modelos de utilidad, diseños industriales, variedades vegetales, marcas, lemas, nombres y signos y denominaciones de origen, y su renovación y prórroga, cesión de los mismos, registro de cambio de nombre y domicilio, y de contratos y licencias sobre los mismos, y para el registro de la cesión de contratos de tecnología,

REPUBLICA DE COLOMBIA
CIRCULO DE BOGOTA
SANTA FE DE BOGOTA
NOTARIA
15 MAYO 2003
Certifico que el presente coincide con el ORIGINAL que tengo a la vista

TRADUCCION OFICIAL No. 004/2003
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INTERPRETE OFICIAL
RESOLUCION No 2165 ABRIL 17 1998

2 Solicitar la protección de los derechos de autor, y sus secretos y conocimientos industriales, seguir los procesos respectivos, obtenerlos, y registrarlos,

3 Solicitar, seguir los procesos respectivos, y obtener el registro sanitario y los permisos para sus productos, y licencias de operación, así como las renovaciones o prórrogas de los mismos, su cesión, el registro del cambio de nombre o domicilio, y el registro de contratos y licencias con relación a los mismos,

4 Registrar oposiciones, observaciones, demandas, peticiones de reposición o reconsideración, apelaciones, acciones de cancelación administrativas o judiciales, acciones de nulidad, acciones de protección del consumidor, protección de secretos industriales y demás acciones relacionadas con los derechos derivados de los asuntos antes mencionados y contra la competencia desleal y la restricción de comercio, acciones relacionadas con la obtención o explotación de licencias, así como la intervención en procesos civiles, comerciales, criminales, contencioso administrativos, y policivos, todos con relación a las acciones o procesos iniciados por el otorgante o por terceros contra el otorgante o con relación al

5 Conciliar, cancelar, dirimir, transigir, desistir, recibir y to[illegible] del asunto de litigio y renunciar o desistir de los derechos [illegible] en proceso de ser otorgados, y admitir los hechos en los procesos legales

6 Ratificar o no, los actos a que se haya comprometido el agente aquí nombrado

7 Recibir notificaciones de procesos y nombrar apoderados, [illegible] y sustituir el presente poder y revocar sustituciones

El otorgante pagará a cada uno de los apoderados por los costos, demandas, gastos y obligaciones de cualquier naturaleza, en que cada uno de los apoderados haya incurrido

209/2003

TRADUCCION OFICIAL No.
ALICIA GROOT
INTERPRETE OFICIAL
RESOLUCION No 2198 ABRIL 17 1989
DEL MINISTERIO DE JUSTICIA

con relación a este poder y ratificará y confirmará todos los actos a que se hayan comprometido los apoderados con relación a este poder, con excepción de los casos de incumplimiento, negligencia o actos que hayan sido llevados a cabo en oposición a las instrucciones expresas del otorgante

Este poder estará regido e interpretado por las leyes de la República de Colombia, que lo rigen en su totalidad.

Dado y firmado en Cambridge, Massachusetts, el día 3 de abril del 2003

Por (firmado) (firma ilegible)

Kenneth S Boger

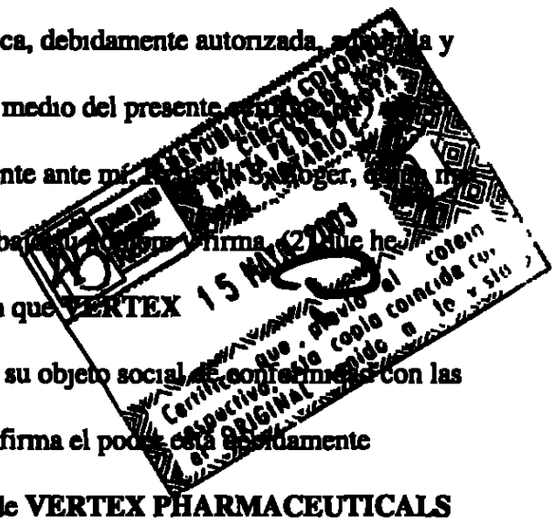
Vicepresidente Principal y Asesor Legal General

Vertex Pharmaceuticals, Inc

Hay un Certificado Notarial, que dice así

CERTIFICADO DE NOTARIO PUBLICO

Yo, Victoria M Clifford, suscrita Notaria Pública, debidamente autorizada, [illegible] y habiendo prestado juramento , en ejercicio, por medio del presente [illegible] día 3 de abril del 2003, compareció personalmente ante mí, [illegible] Boger, [illegible] presentó el anterior poder y quien lo identificó [illegible] firma, [illegible] he tenido a mi vista los documentos que atestiguan que **VERTEX PHARMACEUTICALS INC.** existe y ejerce su objeto social de conformidad con las leyes de Massachusetts; (3) que la persona que firma el poder está debidamente autorizada para ello, como representante legal de **VERTEX PHARMACEUTICALS INC.**



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ALICIA GROOT
INTERPRETE OFICIAL
RESOLUCION No 2193 ABRIL 17 1989
DEL MINISTERIO DE JUSTICIA

Firma y Sello

(firmado) Victoria M Clifford

Mi comisión vence el 6 de marzo del 2009

Hay un sello en relieve que dice VICTORIA M CLIFFORD - Notaria Pública - Massachusetts

Hay un sello en relieve del ESTADO DE MASSACHUSETTS

(Este documento deberá ser debidamente legalizado hasta por un Cónsul colombiano o por Apostilla)

Adjunto se halla un Certificado que dice

ESTADO DE MASSACHUSETTS

William Francis Galvin

Secretario del Estado

APOSTILLA

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

1 País Estados Unidos de América

Este documento público

2 ha sido firmado por la Sra Victoria M Clifford

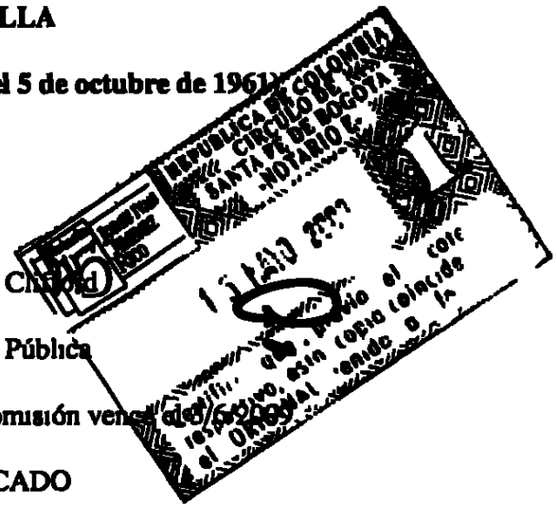
3 quien ha actuado en calidad de Notaria Pública

4 en el Estado de Massachusetts, cuya comisión vence el 6/6/2009

CERTIFICADO

5 en Boston, Massachusetts

6 el 4/23/2003 a las 3 06 14 PM



TRADUCCION OFICIAL No. 009/2003
ALICIA GROOT
INTERPRETE OFICIAL
RESOLUCION No 2158 ABRIL 17 1980
DEL MINISTERIO DE JUSTICIA

7 por el Secretario del Estado

8 **44638**

9 firmado bajo el Gran Sello del Estado

10 Firma

(firmado) William Francis Galvin

Secretario del Estado

En relieve, Gran Sello del Estado de Massachusetts

ES TRADUCCION FIEL Y COMPLETA

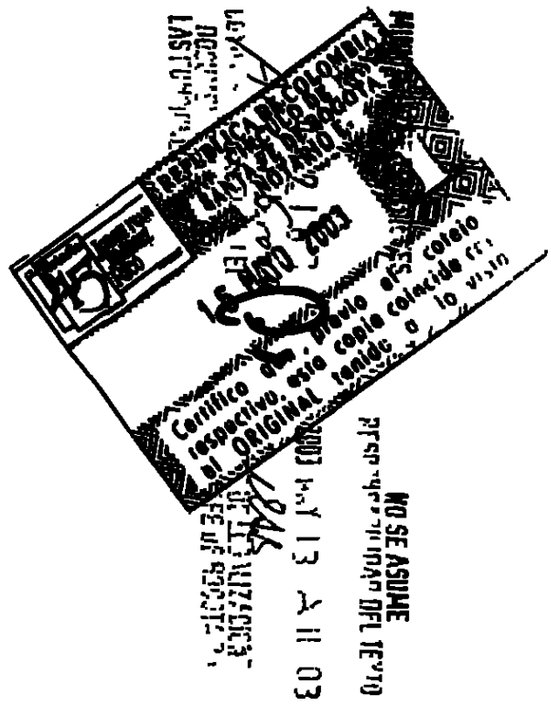
Bogotá, Mayo 12 del 2003

AG

Alicia Ariza

009/2003

INTERPRETE OFICIAL
RESOLUCION NO 2193 ABRIL 17 1998
DEL MINISTERIO DE JUSTICIA



POWER OF ATTORNEY

The organization **VERTEX PHARMACEUTICALS INC.**, at present carrying out its purpose, acting through its legal representative, formed and existing according to the laws of United States of America, with registered offices at 130 Waverly Street, Cambridge, Massachusetts, United States of America, hereby appoints Ernesto Caveller, with TPA 11 519, Bernardo Rodriguez Osan, with TPA 41.858, Alvaro Parra Gómez, with TPA 47.452 and Helena Camargo Williamson with TPA 76.985, all of them with offices at Cra. 9 No. 74-08 Of. 504, Bogotá DC, Colombia, in this same order, as its true and lawful attorneys, to represent it before any person, administrative or judicial entities, arbitrator, mediator, court or board of arbitration or conciliation, or before any authority for the purpose of obtaining and maintaining the protection of its industrial property rights and acting in the defense of such rights, being empowered for such purpose to:

1. Apply for, follow the respective proceedings and obtain or register patents of invention, utility models, industrial designs, plant varieties, trademarks, slogans, names and signs and denominations of origin, and their renewal and extension, assignment thereof, registration of change of name and domicile, and of agreements and licenses thereon, and for registration of transfer of technology contracts;

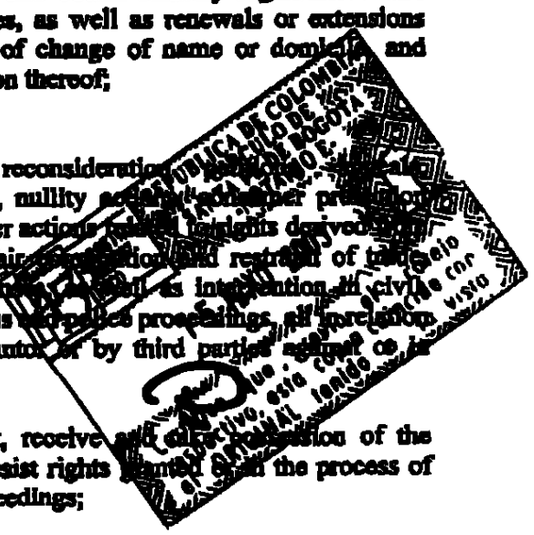
2. Apply for protection of its authors rights, and its industrial secrets and know-how, follow the respective proceedings, obtain, and register them,

3. Apply for, follow the respective proceedings, and obtain sanitary registrations and permits for its products, and operating licences, as well as renewals or extensions thereof, assignment of the same, registration of change of name or domicile and registration of agreements and licences in relation thereof;

4. File oppositions, observations, claims, reconsideration [illegible] administrative or judicial cancellation actions, nullity [illegible] actions, protection of industrial secrets and other actions [illegible] the above mentioned matters and against unfair [illegible] actions related to obtaining or exploiting licenses [illegible] commercial, criminal, administrative contentious [illegible] to actions or proceedings initiated by the grantor or by third parties against or in relation to the grantor;

5. Conciliate, cancel, settle, compromise, desist, receive and [illegible] subject matter of litigation and renounce or desist rights [illegible] being granted, and admit the facts in legal proceedings;

6. Ratify or not the acts undertaken by a self-appointed agent;



TRADUCCION OFICIAL 009/2003
ALICIA GROOT
INTERPRETE OFICIAL
RESOLUCION No 2198 ABRIL 17 1968
DEL MINISTERIO DE JUSTICIA

9

7. Receive service of process and appoint attorneys, resign and substitute the present power of attorney and revoke the substitutions.

The grantor shall pay each and every one of the attorneys for the costs, claims, expenses and liabilities of any nature, incurred by each one of the attorneys in relation with this power of attorney and shall ratify and confirm all acts undertaken by the attorneys in relation with this power of attorney, except in the cases of default, negligence or acts carried out in contradiction to the express instructions of the grantor.

This power of attorney shall be ruled and interpreted by the laws of the Republic of Colombia, which governs it in its entirety.

Given and signed at CAMBRIDGE, MA today, the 3rd of APRIL of 2003

By: _____

Kenneth S. Boger
Senior Vice President and General Counsel
Vertex Pharmaceuticals, Inc.

NOTARY PUBLIC CERTIFICATE

I Victoria M. Clifford the undersigned Notary Public, duly authorized admitted and sworn, practicing in do hereby certify: (1) that on the 3rd day of APRIL 2003, personally appeared before me Kenneth S. Boger who did present to me the preceding power of attorney and did identify to me under his name and signature; (2) that I have seen the documents that attest that VERTEX PHARMACEUTICALS INC. exists and exercises its legal purpose according to the laws of Massachusetts; (3) that the person who signs the power of attorney is duly authorized to do it, as legal representative of VERTEX PHARMACEUTICALS INC.

Signature and seal: _____

(*This document should be duly legalized up to a Colombian Consul or Vice-Consul*)

15 MAYO 2003 ... previo el cotejo ... esta copia coincide co... el ORIGINAL tenido a la vista ...

009/2003
ALICIA CROOT
INTERPRETE OFICIAL
RESOLUCION NO 2195 ABRIL 17 1980
DEL MINISTERIO DE JUSTICIA

1 de 2

The Commonwealth f Massachusetts

William Francis Galvin
Secretary of the Commonwealth
APOSTILLE

(Convention de la Haye du 5 octobre 1961)

1 Country United States of America

This public document...

2 has been signed by Ms. Victoria M Clifford

3. acting in the capacity Notary Public

4 in the state of Massachusetts, whose commission expires on

3/6/2009

CERTIFIED

5. at Boston, Massachusetts

6. on 4/23/2003 3:06:14 PM

7 by the secretary of the Commonwealth

8. 44638

9 signed under the

Great Seal of the Commonwealth

10. Signature

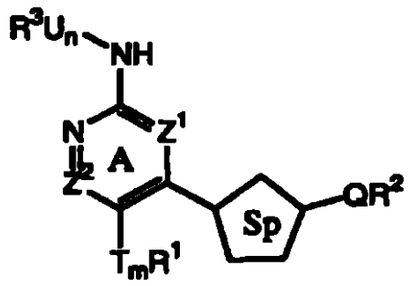
William Francis Galvin
Secretary of the Commonwealth

REPUBLICA DE COLOMBIA
CIRCULO DE SANTA FE DE BOGOTA D.C.
NOTARIA 5
MAYO 2003
Certifico que previo el cotej... respectivo, esta copia coincide con el ORIGINAL tenido a la vist...

TRADUCIDO 09/20/03
ALICE KROUT
INTERPRETE OFICIAL
RESOLUCION NO 2105 ABRIL 17 1986
DEL MINISTERIO DE JUSTICIA

Título: INHIBIDORES HETEROCICLICOS DE ERK2 Y USOS DE LOS MISMOS

Resumen: Aquí se describen compuestos que son útiles como inhibidores de proteína cinasa que tienen la fórmula (I)



I

en donde Z^1 y Z^2 son cada uno de manera independiente nitrógeno o CH y el anillo A, T_mR^1, QR^2, U_nR^3, y Sp son como se describen en la descripción. Los compuestos son especialmente útiles como inhibidores de la ERK2 y para el tratamiento de enfermedades en mamíferos que son aliviadas por medio de un inhibidor de proteína cinasa, particularmente enfermedades tales como el cáncer, los trastornos inflamatorios, la restenosis, la diabetes, y la enfermedad cardiovascular.

ANEXO INVENTORES

CAO, Jingrong, un ciudadano canadiense, domiciliado en 15 Madison Avenue, Newton, MA 02460, Estados Unidos de América, **GREEN, Jeremy**, un ciudadano de la Gran Bretaña, domiciliado en 21 Greyston Court, Burlington, MA 01803, Estados Unidos de América, **HALE, Michael**, un ciudadano de los Estados Unidos de América, domiciliado en 42 Sunset Road, Bedford, MA 01730, Estados Unidos de América, **MALTAIS, Francois**, un ciudadano canadiense, domiciliado en 24 Randolph Drive, Tewksbury, MA 10876, Estados Unidos de América, **STRAUB, Judy**, una ciudadana de los Estados Unidos de América, domiciliada en 70 Kinnaird Street, Cambridge, MA 01235, Estados Unidos de América, **TANG, Quing**, un ciudadano canadiense, domiciliado en 2377 Massachusetts Avenue, Cambride, MA, 02140, Estados Unidos de América, **ARONOV, Alex**, un ciudadano ruso, domiciliado en 13 Circuit Lane, Watertown, MA 02472, Estados Unidos de América

INHIBIDORES HETEROCICLICOS DE ERK2 Y USOS DE LOS MISMOS

REFERENCIA CRUZADA A SOLICITUDES RELACIONADAS

Esta solicitud reivindica prioridad de la Solicitud de Patente Provisional US 60/267,818 presentada el 9 de Febrero de 2001 y la Solicitud de Patente Provisional US 60/328,768 presentada el 12 de Octubre de 2001 Los contenidos de dichas solicitudes son incorporados aquí como referencia

CAMPO DE LA INVENCION

La presente invención es en el campo de la química medicinal y se relaciona con compuestos pirazol que son inhibidores de proteína cinasa, especialmente inhibidores de ERK, las composiciones que contienen tales compuestos y métodos de uso. Los compuestos son útiles para el tratamiento del cáncer y otras enfermedades que son aliviadas por medio de inhibidores de proteína cinasa.

ANTECEDENTES DE LA INVENCIÓN

Las proteínas cinasas activadas por mitógenos de mamíferos (MAP)1 son serina/treonina cinasas que sirven de intermediarias en las rutas de transducción de señales

intracelulares (Cobb y Goldsmith, 1995, *J Biol. Chem.*, **270**, 14843, Davis, 1995, *Mol. Reprod. Dev.* **42**, 459) Los miembros de la familia de las MAP cinasas comparten similaridad en la secuencia y dominios estructurales conservados, e incluyen la ERK2 (cinasa regulada por una señal extracelular), JNK (cinasa Jun N-terminal), y cinasas p38. Las cinasas JNKs y p38 son activadas en respuesta a las citoquinas pro-inflamatorias TNF-alfa e interleucina-1, y por medio de tensión celular tal como choque térmico, hiperosmolaridad, radiación ultravioleta, lipopolisacáridos e inhibidores de síntesis de proteínas (Derijard y otros, 1994, *Célula* **76**, 1025, Han y otros, 1994, *Science* **265**, 808, Raingeaud y otros, 1995, *J Biol. Chem.* **270**, 7420, Shapiro y Dinarello, 1995, *Proc. Natl. Acad. Sci USA* **92**, 12230) Por el contrario, las ERKs son activadas por medio de mitógenos y factores de crecimiento (Bokemeyer y otros. 1996, *Kidney Int.* **49**, 1187).

La ERK2 es una proteína cinasa ampliamente distribuida que alcanza la actividad máxima cuando tanto Thr183 como Tyr185 son fosforidadas por medio de la MAP cinasa cinasa de la parte ascendente, MEK1 (Anderson y otros, 1990, *Nature* **343**, 651, Crews y otros, 1992, *Science* **258**, 478). Con la activación, la ERK2 fosforila muchas proteínas reguladoras, que incluyen las proteínas cinasas Rsk90 (Bjorbaek y otros, 1995, *J. Biol. Chem.* **270**, 18848) y MAPKAP2 (Rouse y otros, 1994, *Célula* **78**, 1027), y factores de transcripción tales como ATF2 (Raingeaud y

otros, 1996, *Mol Célula Biol.* 16, 1247), Elk-1 (Raingeaud y otros 1996), c-Fos (Chen y otros, 1993 *Proc Natl. Acad Sci. USA* 90, 10952), y c-Myc (Oliver y otros, 1995, *Proc. Soc Exp. Biol. Med.* 210, 162) La ERK2 también es un objetivo de la parte descendente de las rutas dependientes Ras/Raf dependent rutas (Moodie y otros, 1993, *Science* 260, 1658) y puede ayudar a transmitir las señales de estas porteínas potencialmente oncogénicas. La ERK2 ha demostrado que juega un papel en el control negativo del crecimiento de las células de cáncer de seno (Frey y Mulder, 1997, *Cáncer Res.* 57, 628) y se ha reportado la hiperexpresión de la ERK2 en el cáncer humano de seno (Sivaraman y otros, 1997, *J Clin. Invest* 99, 1478). La ERK2 activada también ha sido implicada en la proliferación de la células de músculos lisos para el paso de aire estimuladas por la endotelina, sugiriendo un papel para esta cinasa en el asma (Whelchel y otros, 1997, *Am. J. Respir. Célula Mol. Biol.* 16, 589).

La Aurora-2 es una proteína serina/treonina cinasa que ha sido implicada en el cáncer humano, tal como de colon, de seno y otros túmores sólidos. Se cree que esta cinasa se encuentra involucrada en los eventos de fosforilación de proteínas que regulan el ciclo celular. Específicamente, la Aurora-2 puede jugar un papel en el control de la correcta segregación de los cromosomas durante la mitosis. La regulación erróena del ciclo celular puede conducir a la proliferación celular y otras anormalidades. En el tejido de cáncer de colon humano, se

encontró que la proteína aurora-2 estaba sobreexpresada. Ver Bischoff y otros, *EMBO J.*, 1998, **17**, 3052 - 3065, Schumacher y otros, *J. Célula Biol.*, 1998, **143**, 1635 - 1646, Kimura y otros, *J. Biol. Chem.*, 1997, **272**, 13766 - 13771

La glicógeno sintasa cinasa-3 (GSK-3) es una proteína serina/treonina cinasa compuesta por las isoformas α y β que son cada una codificadas por genes distintos [Coghlan y otros, *Chemistry & Biology*, **7**, 793 - 803 (2000); Kim y Kimmel, *Curr Opinion Genetics Dev* , **10**, 508 - 514 (2000)]. La GSK-3 ha sido implicada en varias enfermedades que incluyen la diabetes, la enfermedad de Alzheimer, los trastornos del SNC tales como el trastorno maniaco depresivo y las enfermedades neurodegenerativas, y la hipertrofia del cardiomiocito [WO 99/65897, WO 00/38675, y Haq y otros, *J. Célula Biol.* (2000) **151**, 117]. Estas enfermedades pueden ser causadas por, o resultar en, la operación anormal de ciertas rutas de señalización celular en las cuales la GSK-3 juega un papel Se ha encontrado que la GSK-3 fosforila y modula la actividad de una cantidad de proteínas reguladoras Estas proteíncomo encluyen la glicógeno sintasa, la cual es la enzima limitante de la velocidad necesaria para la síntesis del glicógeno, la proteína Tau asociada al microtúbulo, el factor β-catenina de transcripción de genes, el factor eIF2B de iniciación de la traducción, al igual que la ATP citrato liasa, la axina, el factor-1 de choque térmico, la c-Jun, la C-Myc, la C-Myb, la CREB, y

la CEPBα Estas diversas proteínas objetivo implican a la GSK-3 en muchos aspectos del metabolismo celular, la proliferación, la diferenciación y el desarrollo.

En una ruta mediada por la GSK-3 que es relevante para el tratamiento de la diabetes tipo II, la señal inducida por la insulina conduce a la captación de glucosa celular y a la síntesis del glicógeno. A lo largo de esta ruta, la GSK-3 es un regulador negativo de la señal inducida por la insulina. Normalmente, la presencia de la insulina ocasiona la inhibición de la fosforilación mediada por la GSK-3 y la desactivación de la glicógeno sintasa. La inhibición de la GSK-3 conduce a la síntesis incrementada de glicógeno y la captación de glucosa [Klein y otros, *PNAS*, **93**, 8455 - 9 (1996), Cross y otros, *Biochem. J.*, **303**, 21 - 26 (1994), Cohen, *Biochem. Soc Trans.*, **21**, 555 - 567 (1993); Massillon y otros, *Biochem J.* **299**, 123 - 128 (1994)] Sin embargo, en un paciente diabético en donde la respuesta a la insulina está deteriorada, la síntesis del glicógeno y la captación de la glucosa fallan en incrementarse a pesar de la presencia de niveles sanguíneos de insulina relativamente altos. Esto conduce a niveles sanguíneos anormalmente altos de glucosa con efectos agudos y a largo plazo que pueden resultar a la larga en enfermedad cardiovascular, falla renal y ceguera. En tales pacientes, la inhibición normal inducida por la insulina de la GSK-3 falla en ocurrir También se ha reportado que en pacientes con diabetes del tipo II, la GSK-3 se encuentra sobreexpresada [WO

00/38675] Los inhibidores terapéuticos de GSK-3 son, por lo tanto, considerados como útiles para el tratamiento de los pacientes diabéticos que sufren de una respuesta deteriorada a la insulina.

La actividad de la GSK-3 también ha sido asociada con la enfermedad de Alzheimer Esta enfermedad se caracteriza por el bien conocido péptido β-amiloide y la formación de nudos neurofibrilares intracelulares. Los nudos neurofibrilares contienen la proteína Tau hiperfosforilada, estando la proteína Tau fosforilada en sitios anormales Se ha demostrado que la GSK-3 fosforila estos sitios anormales en modelos celulares y animales Además, se ha demostrado que la inhibición de la GSK-3 previene la hiperfosforilación de la proteína Tau en las células [Lovestone y otros, *Current Biology* 4, 1077 - 86 (1994); Brownlees y otros, *Neuroreport* 8, 3251 - 55 (1997)] Por lo tanto, se cree que la actividad de la GSK-3 puede promover la generación de los nudos neurofibrilares y la progresión de la enfermedad de Alzheimer.

Otro substrato de la GSK-3 es la β-catenina que es degradada después de la fosforilación por la GSK-3 Se han reportado niveles reducidos de β-catenina en pacientes esquizofrénicos y también han sido asociados con otras enfermedades relacionadas con el incremento en la muerte de las células neuronales [Zhong y otros,

Nature, 395, 698 - 702 (1998), Takashima y otros, *PNAS*, 90, 7789 - 93 (1993); Pei y otros, *J. Neuropathol. Exp*, 56, 70 - 78 (1997)]

Como un resultado de la importancia biológica de la GSK-3, hay un interés actual en los inhibidores de la GSK-3 terapéuticamente efectivos Recientemente se han reportado pequeñas moléculas que inhiben la GSK-3 [WO 99/65897 (Chiron) y WO 00/38675 (SmithKline Beecham)]

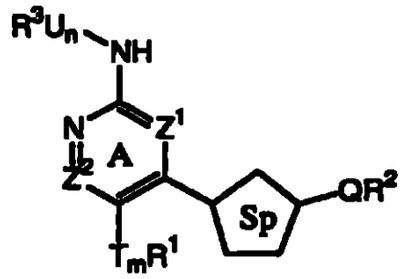
Los pirroles aril substituídos son conocidos en la literatura En particular, los tri-aril pirroles (US 5,837,719) han sido descritos como poseedores de una actividad antagonista del glucagón. Los 1,5-diarilpirazoles han sido descritos como inhibidores p38 (WO 9958523).

Hay una gran necesidad médica sin satisfacer de desarrollar nuevos tratamientos terapéuticos que sean útiles para tratar las diversas condiciones asociadas con la activación de la ERK2. Para muchas de estas condiciones, las opciones de tratamiento disponibles en la actualidad son inadecuadas

Por consiguiente, hay un gran interés en inhibidores nuevos y efectivos de proteína cinasa, que incluyen a los inhibidores de ERK2, que son útiles en el tratamiento de diversas condiciones asociadas con la activación de la proteína cinasa

DESCRIPCION DE LA INVENCIÓN

Se ha encontrado ahora que los compuestos de esta invención y las composiciones farmacéuticas de los mismos son efectivos como inhibidores de las proteínas cinasas, especialmente como inhibidores de la ERK2. Estos compuestos tienen la fórmula general I.



I

o un derivado farmacéuticamente aceptable de los mismos, en donde

Sp es un grupo espaciador que comprende un anillo heteroaromático de 5 miembros, en donde el Anillo A y QR^2 se encuentran unidos a Sp en posiciones no adyacentes; y en donde Sp tiene hasta dos substituyentes R^6, con la condición de que dos átomos de carbono substituibles del anillo en Sp no son substituidos de manera simultanea por R^6;

Z^1 y Z^2 son cada uno seleccionados de manera independiente a partir de N o CH,

T y Q son cada uno un grupo ligante seleccionado de manera independiente;

U es seleccionado a partir de $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, o $-SO_2-$,

m y n son cada uno seleccionados de manera independiente a partir de cero o uno,

R^1 es seleccionado a partir de hidrógeno, CN, halógeno, R, $N(R^7)_2$, OR, o OH;

R^2 es seleccionado a partir de $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, $-(CH_2)_yCH(R^6)CH(R^5)_2$, $-N(R^4)_2$, o $-NR^4(CH_2)_yN(R^4)_2$;

y es 0 - 6,

R^3 es seleccionado a partir de R^7, R, $-(CH_2)_yCH(R^6)R$, CN, $-(CH_2)_yCH(R^6)CH(R^5)_2$, o $-(CH_2)_yCH(R^6)N(R^4)_2$;

cada R es seleccionado de manera independiente a partir de un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, arilo C_{6-10}, un anillo heteroarilo que tiene 5 - 10 átomos en el anillo, o un anillo heterociclilo que tiene 3 - 10 átomos en el anillo,

cada R^4 es seleccionado de manera independiente a partir de R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, o $-(CH_2)_yCH(R^5)_2$;

cada R^5 es seleccionado de manera independiente a partir de R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$,

cada R^6 es seleccionado de manera independiente a partir de R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7,

$NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$,

cada R^7 es seleccionado de manera independiente a partir de hidrógeno o un grupo alifático C_{1-6} substituido de manera opcional, o dos R^7 en el mismo nitrógeno son tomados junto con el nitrógeno para formar un anillo heterocíclilo o heteroarilo de 5 - 8 miembros,

R^8 es seleccionado a partir de R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, o $(CH_2)_wSR^7$;

y

cada w es seleccionado de manera independiente a partir de 0 - 4

Tal como se emplean aquí, las siguientes definiciones se aplicarán a menos que se indique otra cosa. La frase "substituido de manera opcional" es empleada de manera intercambiable con la frase "substituido o no substituido" o con el término "(no) substituido". A menos que se indique otra cosa, un grupo substituido de manera opcional puede tener un substituyente en cada posición substituible del grupo, y cada substitución es independiente de la otra.

El término "alifático" o "grupo alifático" tal como se emplea aquí significa una cadena de hidrocarburo C_1-C_{12} de cadena recta o ramificada que se encuentra completamente saturada o que contiene una o más unidades de insaturación, o un hidrocarburo C_3-C_8 monocíclico o un hidrocarburo C_8-C_{12} bicíclico que se encuentra

completamente saturada o que contiene una o más unidades de insaturación, pero que no es aromático (también referido aquí como "carbociclo" o "cicloalquilo"), que tiene un solo punto de unión al resto de la molécula, en donde cualquier anillo individual en dicho sistema de anillo bicíclico tiene 3 - 7 miembros. Por ejemplos, los grupos alifáticos adecuados incluyen, pero no se limitan a, lineales o ramificados, o grupos alquilo, alquenilo, alquinilo e híbridos de los mismo tales como (cicloalquil)alquilo, (cicloalquenil)alquilo o (cicloalquil)alquenilo.

Los términos "alquilo", "alcoxi", "hidroxialquilo", "alcoxialquilo", y "alcoxicarbonilo", empleados solos o como parte de un radical más grande incluyen cadenas tanto rectas como ramificadas que contienen de uno a doce átomos de carbono Los términos "alquenilo" y "alquinilo" empleados solos o como parte de un radical más grande incluirán cadenas tanto rectas como ramificadas que contienen de dos a doce átomos de carbono

Los términos "haloalquilo", "haloalquenilo" y "haloalcoxi" significan alquilo, alquenilo o alcoxi, según el caso, substituido con uno más atomos de halógeno. El término "halógeno" significa F, Cl, Br, o I.

El término "heteroátomo" significa nitrógeno, oxígeno, o azufre e incluye cualquier forma oxidada de nitrógeno y azufre, y la forma cuaternizada de cualquier nitrógeno

básico El término "nitrógeno" también incluye un nitrógeno substituible de un anillo heterocíclico Como un ejemplo, en un anillo saturado o parcialmente insaturado que tiene 0 - 3 heteroátomos seleccionados a partir de oxígeno, azufre o nitrógeno, el nitrógeno puede ser N (como en 3,4-dihidro-2*H*-pirrolilo), NH (como en pirrolidinil) o NR^+ (como en pirrolidinilo N-substituido).

El término "arilo" empleado solo o como parte de un radical más grande como en "aralquilo", "aralcoxi", o "ariloxialquilo", hace referencia a sistemas de anillo monocíclico, bicíclico y tricíclico que tienen un total de cinco a catorce miembros en el anillo, en donde al menos un anillo en el sistema es aromático y en donde cada anillo en el sistema contiene de 3 a 7 miembros en el anillo. El término "arilo" puede ser empleado de manera intercambiable con el término "anillo arilo".

[0001] El término "heterociclo", "heterociclilo", o "heterocíclico", tal como se emplean aquí, hacen referencia a sistemas de anillo monocíclico, bicíclico o tricíclico no aromáticos que tienen de cinco a catorce miembros en el anillo, en los cuales uno o más miembros en el anillo es un heteroátomo, en donde cada anillo en el sistema contiene de 3 a 7 miembros en el anillo

[0002] El término "heteroarilo", empleado solo o como parte de un radical más grande como en "heteroaralquilo"

o "heteroarilalcoxi", hace referencia a sistemas de anillo monocíclico, bicíclico o tricíclico que tienen un total de cinco a catorce miembros en el anillo, en donde al menos un anillo en el sistema es aromático, al menos un anillo en el sistema contiene uno o más heteroátomos, y en donde cada anillo en el sistema contiene de 3 a 7 miembros en el anillo. El término "heteroarilo" puede ser empleado de manera intercambiable con el término "anillo heteroarilo" o con el término "heteroaromático"

Un grupo arilo (que incluye el aralquilo, el aralcoxi, el ariloxialquilo y otros por el estilo) o heteroarilo (que incluye heteroaralquilo y heteroarilalcoxi y otros por el estilo) puede contener uno o más substituyentes. Los substituyentes adecuados en el átomo de carbono insaturado de un grupo arilo, heteroarilo, aralquilo, o heteroaralquilo son seleccionados a partir de halógeno, -R°, -O°, -SR°, 1,2-metileno-dioxi, 1,2-etilenodioxi, OH protegido (tal como aciloxi), fenilo (Ph), Ph substituido con R°, -O(Ph), O-(Ph) substituido con R°, -CH_2(Ph), -CH_2(Ph) substituido con R°, -CH_2CH_2(Ph), -CH_2CH_2(Ph) substituido con R°, -NO_2, -CN, -$N(R^{\circ})_2$, -$NR^{\circ}C(O)R^{\circ}$, -$NR^{\circ}C(O)N(R^{\circ})_2$, -$NR^{\circ}CO_2R^{\circ}$, -$NR^{\circ}NR^{\circ}C(O)R^{\circ}$, -$NR^{\circ}NR^{\circ}C(O)N(R^{\circ})_2$, -$NR^{\circ}NR^{\circ}CO_2R^{\circ}$, -$C(O)C(O)R^{\circ}$, -$C(O)CH_2C(O)R^{\circ}$, -$CO_2R^{\circ}$, -$C(O)R^{\circ}$, -$C(O)N(R^{\circ})_2$, -$OC(O)N(R^{\circ})_2$, -$S(O)_2R^{\circ}$, -$SO_2N(R^{\circ})_2$, -$S(O)R^{\circ}$, -$NR^{\circ}SO_2N(R^{\circ})_2$, -$NR^{\circ}SO_2R^{\circ}$, -$C(=S)N(R^{\circ})_2$, -$C(=NH)-N(R^{\circ})_2$, -$(CH_2)_yNHC(O)R^{\circ}$, o -$(CH_2)_yNHC(O)CH(V-R^{\circ})(R^{\circ})$, en donde cada R° es seleccionado de manera independiente a partir de hidrógeno, alifático

C_{1-6} substituido de manera opcional, un anillo heteroarilo o heterocíclico no substituido de 5 - 6 miembros, fenilo (Ph), -O(Ph), o $-CH_2(Ph)-CH_2(Ph)$, en donde y es 0 - 6, y V es un grupo ligante

Los substituyentes sobre el grupo alifático de R° son seleccionados a partir de NH_2, NH(alifático C_{1-4}), N(alifático C_{1-4})$_2$, halógeno, alifático C_{1-4}, OH, O-(alifático C_{1-4}), NO_2, CN, CO_2H, CO_2(alifático C_{1-4}), -O(halo alifático C_{1-4}), o halo alifático C_{1-4}

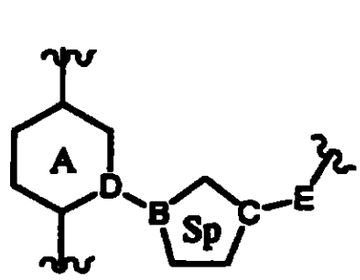
Un grupo alifático o un anillo heterocíclico no aromático puede contener uno o más substituyentes. Los substituyentes adecuados sobre el carbono saturado de un grupo alifático o de un anillo heterocíclico no aromático son seleccionados a partir de aquellos listados anteriormente para el carbono insaturado de un grupo arilo o heteroarilo y los siguientes. =O, =S, $=NNHR^*$, $=NN(R^*)_2$, =N-, $=NNHC(O)R^*$, $=NNHCO_2$(alquilo), $=NNHSO_2$(alquilo), o $=NR^*$, en donde cada R^* es seleccionado de manera independiente a partir de hidrógeno o un alifático C_{1-6} substituido de manera opcional. Los substituyentes en el grupo alifático de R^* son seleccionados a partir de NH_2, NH(alifático C_{1-4}), N(alifático C_{1-4})$_2$, halógeno, alifático C_{1-4}, OH, O-(alifático C_{1-4}), NO_2, CN, CO_2H, CO_2(alifático C_{1-4}), -O(halo alifático C_{1-4}), o halo alifático C_{1-4}

Los substituyentes en el nitrógeno de un anillo heterocíclico no aromático son seleccionados a partir de $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, o $-NR^+SO_2R^+$, en donde R^+ es hidrógeno, un alifático C_{1-6} substituido de manera opcional, fenilo (Ph) substituido de manera opcional, -O(Ph) substituido de manera opcional, $-CH_2$(Ph) substituido de manera opcional, $-CH_2CH_2$(Ph) substituido de manera opcional, o un anillo heteroarilo o heterocíclico sin substituir de 5 - 6 miembros. Los substituyentes en el grupo alifático o en el anillo fenilo de R^+ son seleccionados a partir de NH_2, NH(alifático C_{1-4}), N(alifático C_{1-4})$_2$, halógeno, alifático C_{1-4}, OH, O-(alifático C_{1-4}), NO_2, CN, CO_2H, CO_2(alifático C_{1-4}), -O(halo alifático C_{1-4}), o halo alifático C_{1-4}

El término "cadena de alquilideno" hace referencia a una cadena de carbono recta o ramificada, substituida de manera opcional, que puede encontrarse completamente saturada o tener una o más unidades de insaturación Los substituyentes opcionales son como se describieron anteriormente para un grupo alifático.

El término "grupo espaciador" hace referencia a un grupo que separa y orienta las otras partes de la molécula unidas a ella, de manera que el compuesto interactúa de manera favorable con los grupos funcionales en el sitio activo de una enzima Tal como se emplea aquí, grupo espaciador separa y orienta el anillo A y QR^2 dentro del

sitio activo de forma tal que ellos pueden formar interacciones favorables con los grupos funcionales que existen dentro del sitio activo de la enzima ERK2. Cuando el grupo espaciador es un anillo heteroaromático de 5 miembros, el anillo A y QR^2 son unidos a posiciones no adyacentes "B" y "C", y el anillo de 5 miembros es unido al anillo A en el punto "D" y a QR^2 en el punto "E", tal como se ilustra a continuación



De manera preferible, la distancia entre "D" y "C" es 3.7Å, la distancia entre "D" y "C" es 5 OÅ, la distancia entre "B" y "C" es 2.2Å, y la distancia entre "B" y "E" es 3.5Å, en donde cada una de las distancias anteriormente descritas es más/menos 0.2 Å

The grupo espaciador por sí mismo también puede formar interacciones adicionales dentro del sitio activo para incrementar adicionalmente la actividad inhibidora de los compuestos. Por ejemplo, cuando Sp es un pirrol, el pirrol-NH puede formar un puente de hidrógeno adicional dentro del sitio activo de la Enzima ERK2.

El término "grupo ligante" significa un radical orgánico que conecta dos partes de un compuesto. Los ligantes se encuentran típicamente compuestos por un átomo tal como oxígeno o azufre, una unidad tal como -NH-, -CH_2-, -CO-, o una cadena de átomos, tal como una cadena de alquilideno La masa molecular de un ligante se encuentra típicamente en el rango de aproximadamente 14 a 200

Los ejemplos de ligantes incluyen una cadena de alquilideno C_{1-6} saturada o insaturada, la cual se encuentra substituida de manera opcional, y en donde hasta dos carbonos saturados de la cadena son reemplazados de manera opcional por -C(O)-, -C(O)C(O)-, -$CONR^7$-, -$CONR^7NR^7$-, -CO_2-, -OC(O)-, -NR^7CO_2-, -O-, -NR^7CONR^7-, -OC(O)NR^7-, -NR^7NR^7-, -NR^7CO-, -S-, -SO-, -SO_2-, -NR^7-, -SO_2NR^7-, o -NR^7SO_2-.

Tal como se emplea aquí, el grupo ligante Q connecta a Sp con R^2 Q también puede formar interacciones adicionales con el sitio de unión de ERK2 para incrementar adicionalmente la actividad inhibidora del compuesto. Cuando Q es un radical que contiene carbonilo tal como -C(O)-, -CO_2-, -OC(O)-, -C(O)C(O)-, -CONH-, -CO_2NH-, -CONHNH-, -NHCO-, -OC(O)NH-, o -$NHCO_2$-, o un radical que contiene sulfonilo tal como -SO_2-, -SO_2NH-, o -$NHSO_2$-, el oxígeno del carbonilo o del sulfonilo forma un puente de hidrógeno con la lisina 54 en el sitio de unión de la ERK2 Cuando Q es un radical que contiene NH tal como -CH_2NH- o -NHNH-, el grupo NH forma un puente de hidrógeno

con el residuo de ácido aspártico 167 en el sitio de unión de la ERK2. Cuando Q es un grupo hidrofóbico tal como una cadena alquilo, -O-, o -S-, Q forma interacciones hidrofóbicas adicionales dentro del sitio de unión de la ERK2

R^2 forma interacciones hidrofóbicas dentro del sitio de unión de la ERK2, especialmente con los carbonos de la cadena lateral de la lisina 54 y del ácido aspártico 167. R^2 también puede formar interacciones hidrofóbicas con el bucle rico en glicina que se encuentra integrado por los residuos de aminoácido 33-38. Cuando R^2 se encuentra substituido, los substituyentes pueden formar interacciones adicionales dentro del sitio de unión para incrementar la actividad inhibidora del compuesto Por ejemplo, cuando un subsituyente en R^2 es un donador en un puente de hidrógeno o un aceptor en un puente de hidrógeno, dicho substituyente forma un puente de hidrógeno con las moléculas de agua unidas a la enzima que existen en el sitio de unión

Tal como se emplea aquí, el grupo ligante T, cuando se encuentra presente, conecta Sp con R^1 T también puede formar interacciones adicionales dentro del sitio de unión de la ERK2 para incrementar adicionalmente la actividad inhibidora del compuesto. Cuando T contiene carbonilo tal como -CO-, -CO_2-, -OCO-, -COCO-, -CONH-, -CO_2NH-, -CONHNH-, -NHCO-, o -NHCO_2-, o contiene sulfonilo tal como -SO_2-, -SO_2NH-, o -NHSO_2-, el oxígeno del

carbonilo o del sulfonilo forma un puente de hidrógeno con el NH de la glutamina 105 en el sitio de unión de la ERK2 Cuando T contiene NH tal como -CH_2NH- o -NHNH-, el grupo NH forma un puente de hidrógeno con el carbonilo de la glutamina 105 Cuando T es un grupo hidrofóbico tal como una cadena alquilo, -O-, o -S-, T forma interacciones hidrofóbicas adicionales con los carbonos de la cadena lateral de la glutamina 105 al igual que con la isoleucina 84

Las interacciones de unión descritas aquí entre los compuestos de esta invención y el sitio de unión de la ERK2 han sido determinadas por medio de programas de modelado molecular que son conocidos por aquellas personas versadas en la materia. Estos programas de modelado molecular incluyen QUANTA [Molecular Simulations, Inc., Burlington, Mass , 1992] y SYBYL [Programa de Modelado Molecular, Tripos Associates, Inc , St Louis, Mo , 1992] Tal como se emplea aquí, la numeración de los aminoácidos para la enzima ERK2 corresponde a la entrada de acceso #P28482 de la base de datos Swiss-Prot La base de datos Swiss-Prot es una base de datos internacional de de secuencia de proteínas distribuida por el Instituto Europeo de Bioinformática (EBI) en Ginebra, Suiza. La base de datos puede ser encontrada en el sitio www ebi ac.uk/swissprot.

Los compuestos de esta invención se encuentran limitados a aquellos que son químicamente factibles y estables Por

lo tanto, una combinación de substituyentes o variables en los compuestos descritos anteriormente es permisible solo si tal combinación resulta en un compuesto estable o químicamente factible Un compuesto estable o un compuesto químicamente factible es aquel en el cual la estructura química no es sustancialmente alterada cuando se mantiene a una temperatura de 40 °C o menos, en la ausencia de humedad u otras condiciones químicamente reactivas, por al menos una semana

A menos que se indique de otra forma, las estructuras aquí descritas también tienen la intención de incluir todas las formas estereoquímicas de la estructura, esto es, las configuraciones R y S para cada centro asimétrico. Por lo tanto, los isómeros estereoquímicos sencillos al igual que las mezclas enantioméricas y diastereoméricas de los compuestos de la presente solicitud están dentro del alcance de la invención. A menos que se establezca de otra forma, las estructuras aquí descritas también tienen la intención de incluir los compuestos que solo difieren en la presencia de uno o más átomos isotópicamente enriquecidos. Por ejemplo, los compuestos que tienen las estructuras de la presente solicitud excepto por el reemplazo de un hidrógeno por un deuterio o tritio, o el reemplazo de un carbono por un carbono enriquecido ^{13}C- o ^{14}C- se encuentran dentro del alcance de esta invención

Los compuestos de la fórmula I o las sales de los mismos pueden estar fórmulados en composiciones En una realización preferida, la composición es una composición farmacéuticamente aceptable. En una realización, la composición comprende una cantidad del inhibidor de proteína cinasa efectiva para inhibir una proteína cinasa, particularmente la ERK-2, en una muestra biológica o en un paciente. En otra realización, los compuestos de esta invención y las composiciones farmacéuticas de los mismos, que comprenden una cantidad del inhibidor de proteína cinasa efectiva para tratar o prevenir una condición mediada por la ERK-2 y un portador, coadyuvante o vehículo farmacéuticamente aceptables, pueden estar fórmulados para la administración a un paciente.

El término "paciente" incluye sujetos humanos y veterinarios

El término "muestra biológica", tal como se usa aquí, incluye, sin limitación, cultivos de células o extractos de los mismos; preparaciones de una enzima adecuada para ensayos *in vitro*, material de biopsia obtenido de un mamífero o extractos del mismo; y sangre, saliva, orina, heces, semen, lágrimas, u otros fluidos corporales o extractos de los mismos

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la ERK-

2, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I o una farmacéuticamente aceptable que comprende dicho compuesto.

El término "enfermedad mediada por la ERK-2" o "condición mediada por la ERK-2", tal como se usa aquí, significa cualquier enfermedad u otra condición nociva en la cual se sabe que la ERK-2 juega un papel. El término "enfermedad mediada por la ERK-2" o "condición mediada por la ERK-2" también significa aquellas enfermedades o condiciones que son aliviadas por el tratamiento con un inhibidor de la ERK-2. Tales condiciones incluyen, sin limitación, el cáncer, el ataque, la diabetes, la hepatomegalia, la enfermedad cardiovascular incluyendo la cardiomegalia, la enfermedad de Alzheimer, la fibrosis quística, la enfermedad viral, las enfermedades autoinmunes, la aterosclerosis, la restenosis, la psoriasis, los trastornos alérgicos que incluyen el asma, la inflamación, los trastornos neurológicos y las enfermedades relacionadas con las hormonas El término "cáncer" incluye, pero no se limita a, los siguientes cánceres: de seno, de ovario, cervical, de prostata, de testículo, del tracto genitourinario, de esófago, de laringe, glioblastoma, neuroblastoma, de estomago, de piel, queratoacantoma, de pulmón, carcinoma epidermoide, carcinoma de grandes células, carcinoma de pequeñas células, adenocarcinoma de pulmón, de hueso, de colon,

adenoma, de páncreas, adenocarcinoma, de tiroides, carcinoma folicular, carcinoma no diferenciado, carcinoma papilar, seminoma, melanoma, sarcoma, carcinoma de vejiga, carcinoma de hígado y pasajes biliares, carcinoma de riñón, trastornos mieloides, trastornos linfoides, células pilosas de Hodgkin, de cavidad bucal y faringe (oral), de labios, de lengua, de boca, de faringe, de intestino delgado, de colon-recto, de intestino grueso, de recto, de cerebro y del sistema nervioso central, y leucemia.

El método de la presente invención es especialmente putil para el tratamiento de una enfermedad que es aliviada por medio del uso de un inhibidor de ERK2 u otras proteínas cinasas Aunque los compuestos de la presente invención fueron diseñados como inhibidores de la ERK2, se ha encontrado que ciertos compuestos de esta invención también inhiben otras proteínas cinasas tales como GSK3, Aurora2, Lck, CDK2, y AKT3

Otro aspecto de la invención se relaciona con la inhibición de la actividad de la ERK-2 en una muestra biológica, método que comprende contactar la muestra biológica con un compuesto de la fórmula I, o una composición farmacéuticamente aceptable que comprende dicho compuesto.

Otro aspecto de esta invención se relaciona con un método de inhibir la actividad de la ERK-2 en un paciente,

método que comprende la administración al paciente de un compuesto de la fórmula I o una composición farmacéuticamente aceptable que comprende dicho compuesto

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la Aurora-2, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I o una farmacéuticamente aceptable que comprende dicho compuesto

El término "enfermedad mediada por la Aurora-2" o "condición mediada por la Aurora-2", tal como se usa aquí, significa cualquier enfermedad o condición nociva en las cuales se sabe que la Aurora juega un papel. El término "enfermedad mediada por la Aurora-2" o "condición mediada por la Aurora-2" también significa aquellas enfermedades o condiciones que son aliviadas por el tratamiento con un inhibidor de la Aurora-2 Tales condiciones incluyen, sin limitación, el cáncer El término "cáncer" incluye, pero no se limita a los siguientes cánceres: de colon, de seno, de estómago y de ovario.

Otro aspecto de la invención se relaciona con la inhibición de la actividad de la Aurora-2 en una muestra biológica, método que comprende contactar la muestra

biológica con un compuesto de la fórmula I, o una composición farmacéuticamente aceptable que comprende dicho compuesto.

Otro aspecto de esta invención se relaciona con un método de inhibir la actividad de la Aurora-2 en un paciente, método que comprende la administración al paciente de un compuesto de la fórmula I o una composición farmacéuticamente aceptable que comprende dicho compuesto

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la GSK-3, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I o una composición farmacéuticamente aceptable que comprende dicho compuesto.

El término "enfermedad mediada por la GSK-3" o "condición mediada por la GSK-3", tal como se usa aquí, significa cualquier enfermedad u otra condición o estado nocivos en los cuales se sabe que la GSK-3 juega un papel Tales enfermedades o condiciones incluyen, sin limitación, la diabetes, la enfermedad de Alzheimer, la enfermedad de Huntington, la enfermedad de Parkinson, la demencia asociada con el SIDA, la esclerosis amiotrófica lateral (AML), la esclerosis múltiple (MS), la esquizofrenia, la

hipertrofia del cardiomiocito, la reperfusión/isquemia, y la calvicie.

Un aspecto de esta invención se relaciona con un método para incrementar la síntesis de glicógeno y/o disminuir los niveles sanguíneos de glucosa en un paciente con necesidad del mismo, método que comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de la fórmula I o una farmacéuticamente aceptable del mismo Este método es especialmente útil para pacientes diabéticos Otro método se relaciona con la inhibición de la producción de la proteína Tau hiperfosforilada, el cual es útil en detener o hacer más lento el progreso de la enfermedad de Alzheimer Otro método se relaciona con la inhibición de la fosforilación de la β-catenina, el cual es útil para el tratamiento de la esquizofrenia.

Otro aspecto de la invención se relaciona con la inhibición de la actividad de la GSK-3 en una muestra biológica, método que comprende contactar la muestra biológica con un compuesto de la fórmula I.

Otro aspecto de esta invención se relaciona con un método de inhibir la actividad de la GSK-3 en un paciente, método que comprende la administración al paciente de un compuesto de la fórmula I o una composición farmacéuticamente aceptable que comprende dicho compuesto.

La inhibición de la actividad cinasa de ERK2, Aurora2, CDK2, GSK-3, Lck, o AKT3 en una muestra biológica es útil para una variedad de propósitos que son conocidos por una persona versada en la materia. Los ejemplos de tales propósitos incluyen, pero no se limitan a, la transfusión de sangre, el transplante de órganos, el almacenamiento de especímenes biológicos, y los ensayos biológicos.

El término "portador, coadyuvante, o vehículo farmacéuticamente aceptables" hace referencia a un portador, coadyuvante, o vehículo no tóxicos que pueden ser administrados a un paciente, junto con un compuesto de esta invención, y que no destruye la actividad farmacológica del mismo

La cantidad efectiva para inhibir la proteína cinasa, por ejemplo, la Aurora-2 y la GSK-3, es aquella que inhibe de manera medible la actividad de la cinasa cuando se compara con la actividad de la enzima en ausencia de un inhibidor. Cualquier método puede ser empleado para determinar la inhibición, tal como, por ejemplo, los Ejemplos de Pruebas Biológicas descritos más adelante.

Los portadores farmacéuticamente aceptables que pueden ser empleados en estas composiciones farmacéuticas incluyen, pero no se limitan a, intercambiadores iónicos, alumina, estearato de aluminio, lecitina, proteínas de suero, tales como la albumina sérica humana, las

sustancias tampón tales como los fosfatos, la glicina, el ácido sórbico, el sorbato de potasio, las mezclas de glicéridos parciales de ácidos grasos vegetales saturados, el agua, las sales o electrolitos, tales como el sulfato de protamina, el fosfato ácido disódico, el fosfato ácido de potasio, el cloruro de sodio, las sales de zinc, la silica coloidal, el trisilicato de magnesio, la polivinil pirrolidona, las sustancias basadas en celulosa, el polietilen glicol, la carboximetilcelulosa de sodio, los poliacrilatos, las ceras, los polímeros en bloque de polietileno-polioxipropileno, el polietilen glicol y la grasa de lana

Las composiciones de la presente invención pueden ser administradas oralmente, parenteralmente, mediante spray de inhalación, tópicamente, rectalmente, nasalmente, bucalmente, vaginalmente o mediante un reservorio implantado. El término "parenteral" tal como se emplea aquí, incluye inyección subcutánea, intravenosa, intramuscular, intra-articular, intra-sinovial, intrasternal, intratecal, intrahepática, intralesional e intracraneal o técnicas de infusión Preferiblemente, las composiciones son administradas oralmente, intraperitonealmente o intravenosamente.

Las formas inyectables estériles de las composiciones de esta invención pueden ser suspensiones acuosas u oleaginosas Estas suspensiones puede ser fórmuladas de acuerdo con las técnicas conocidas en el arte empleando

agentes dispersantes o humectantes adecuados y agentes de suspensión. La preparación inyectable estéril puede también ser una solución o suspensión inyectables estériles en un diluyente o solvente parenteralmente aceptable no tóxico, por ejemplo como una solución en 1,3-butanodiol. Entre los vehículos y solventes aceptables que pueden ser empleados se encuentran el agua, la solución de Ringer y la solución de cloruro de sodio isotónico. Además, los aceites fijos estériles son convencionalmente empleados como un solvente o medio de suspensión Para este propósito, cualquier aceite fijo suave puede ser empleado incluyendo mono- o di-glicéridos sintéticos Los ácidos grasos, tales como el ácido oleico y sus derivados glicérido son útiles en la preparación de inyectables, dado que son aceites naturales farmacéuticamente aceptables, tales como el aceite de oliva o el aceite de ricino, especialmente en sus versiones polioxietiladas Estas soluciones o suspensiones oleosas pueden también contener un diluyente o dispersante de alcohol de cadena larga, tal como la carboximetil celulosa o agentes dispersantes similares que son normalmente empleados en la fórmulación de formas de dosificación farmacéuticamente aceptables que incluyen las emulsiones y las suspensiones. Otros surfactantes normalmente empleados, tales como los Tweens, Spans y otros agentes emulsificantes o mejoradores de biodisponibilidad que son normalmente empleados en la fabricación de sólidos, líquidos u otras formas de

dosificación farmacéuticamente aceptables, pueden también ser empleados para los propósitos de fórmulación.

Las composiciones farmacéuticas de esta invención pueden ser oralmente administradas en cualquier forma de dosificación oralmente aceptable incluyendo, pero no limitándose a, cápsulas, tabletas, suspensiones o soluciones acuosas. En el caso de las tabletas para uso oral, los portadores normalmente empleados incluyen la lactosa y el almidón de maíz Los agentes lubricantes, tales como el estearato de magnesio, son también típicamente adicionados Para la administración oral en una forma de cápsula, los diluyentes útiles incluyen la lactosa y el almidón de maíz secado Cuando las suspensiones acuosas son requeridas para uso oral, el ingrediente activo es combinado con agentes emulsificantes y de suspensión Si se desea, también pueden ser adicionados ciertos agentes endulzantes, saborizantes o colorantes

De manera alternativa, las composiciones farmacéuticas de esta invención pueden ser administradas en la forma de supositorios para administración rectal Estos pueden ser preparados mezclando el agente con un excipiente no irritante adecuado, el cual es sólido a temperatura ambiente pero líquido a la temperatura rectal y, por lo tanto, se fundirá en el recto para liberar el medicamento Tales materiales incluyen la mantequilla de cacao, la cera de abejas y los polietilen glicoles.

Las composiciones farmacéuticas de esta invención también pueden ser administradas tópicamente, especialmente cuando el objetivo del tratamiento incluye áreas u órganos fácilmente accesibles por aplicación tópica, incluyendo enfermedades del ojo, la piel, o el tracto intestinal inferior. Las fórmulaciones tópicas adecuadas son fácilmente preparadas para cada una de estas áreas u órganos

La aplicación tópica para el tracto intestinal inferior puede ser efectuada en una fórmulación de supositorio rectal (ver anteriormente) o en una fórmulación de enema adecuada Los parches tópicamente transdérmicos también pueden ser empleados.

Para aplicaciones tópicas, las composiciones farmacéuticas pueden ser fórmuladas en un ungüento adecuado que contiene el componente activo suspendido o disuelto en uno o más portadores. Los portadores para la administración tópica de los compuestos de esta invención incluyen, pero no están limitados a, aceite mineral, petrolato líquido, petrolato blanco, propilen glicol, polioxietileno, compuesto de polioxipropileno, cera emulsificante y agua. De manera alternativa, las composiciones farmacéuticas pueden ser fórmuladas en una loción o crema adecuadas que contienen los componentes activos suspendidos o disueltos en uno o más portadores farmacéuticamente aceptables Los portadores adecuados

incluyen, pero no están limitados a, el aceite mineral, el monoestearato de sorbitan, el polisorbato 60, la cera de cetil ésteres, el alcohol cetearílico, el 2-octildodecanol, el alcohol bencílico y el agua.

Para uso oftálmico, las composiciones farmacéuticas pueden ser fórmuladas como suspensiones micronizadas en salina estéril de pH ajustado, isotónica, o preferiblemente, como soluciones en salina estéril de pH ajustado, isotónica, ya sea con o sin un conservante tal como el cloruro de bencilalconio De manera alternativa, para usos oftálmicos, las composiciones farmacéuticas pueden ser fórmuladas en un ungüento tal como el petrolato.

Las composiciones farmacéuticas de esta invención también pueden ser administradas mediante aerosol nasal o inhalación Tales composiciones son preparadas de acuerdo con técnicas bien conocidas en el arte de la fórmulación farmacéutica y pueden ser preparadas como soluciones en salina, empleando alcohol bencílico u otros conservantes adecuados, promotores de absorción para incrementar la biodisponibilidad, fluorocarbonos, y/u otros agentes solubilizantes o dispersantes convencionales

Además de los compuestos de esta invención, los derivados farmacéuticamente aceptables de los compuestos de esta invención también pueden ser empleados en las

composiciones para tratar o prevenir las enfermedades o trastornos anteriormente identificados.

Un "derivado farmacéuticamente aceptable" significa cualquier sal, éster, sal de un éster u otro derivado farmacéuticamente aceptables de un compuesto de esta invención que, con la administración a un receptor, es capaz de proveer, ya sea directamente o indirectamente, un compuesto de esta invención o un metabolito o residuo del mismo con una capacidad inhibidora activa Los derivados particularmente favorecidos son aquellos que incrementan la biodisponibilidad de los compuestos de esta invención cuando tales compuestos son administrados a un paciente (por ejemplo, permitiendo que un compuesto oralmente administrado sea más rápidamente absorbido en la sangre) o que incrementan el envío del compuesto precursor a un compartimento biológico (por ejemplo, el cerebro o el sistema linfático) relativo a las especies precursoras

Las sales farmacéuticamente aceptables de los compuestos de esta invención incluyen aquellas derivadas de ácidos y bases inorgánicos y orgánicos farmacéuticamente aceptables. Los ejemplos de sales ácidas adecuadas incluyen acetato, adipato, alginato, aspartato, benzoato, benzensulfonato, bisulfato, butirato, citrato, camforato, camforsulfonato, ciclopentanopropionato, digluconato, dodecilsulfato, etanosulfonato, formato, fumarato, glucoheptanoato, glicerofosfato, glicolato, hemisulfato,

heptanoato, hexanoato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxietanosulfonato, lactato, maleato, malonato, metanosulfonato, 2-naftalenosulfonato, nicotinato, nitrato, oxalato, palmoato, pectinato, persulfato, 3-fenilpropionato, fosfato, picrato, pivalato, propionato, salicilato, succinato, sulfato, tartrato, tiocianato, tosilato y undecanoato Otros ácidos, tales como oxálico, aunque no son por sí mismos farmacéuticamente aceptables, pueden ser empleados en la preparación de sales útiles como intermediarios en la obtención de los compuestos de la invención y sus sales de adición ácida farmacéuticamente aceptables.

Las sales derivadas de bases apropiadas incluyen sales de metales alcalinos (por ejemplo, sodio y potasio), de metales alcalinotérreos (por ejemplo, magnesio), de amonio y de N^+(alquilo C_{1-4})$_4$. Esta invención también prevé la quaternización de cualesquiera grupos básicos que contienen nitrógeno de los compuestos aquí revelados. Los productos solubles o dispersables en agua o en aceite pueden ser obtenidos por medio de tal quaternización

La cantidad de inhibidor de proteína cinasa que puede ser combinada con los materiales portadores para producir una forma de dosificación sencilla variará dependiendo del paciente tratado y el modo particular de administración Preferiblemente, las composiciones deben ser fórmuladas de manera que una dosificación de entre 0.01 - 100 mg/kg

de peso corporal/día del inhibidor pueda ser administrada a un paciente que recibe estas composiciones.

También debe entenderse que una dosificación y régimen de tratamiento específicos para cualquier paciente particular dependerá de una variedad de factores, incluyendo la actividad del compuesto específico empleado, la edad, el peso corporal, la salud general, el sexo, la dieta, el tiempo de administración, la velocidad de excreción, la combinación de medicamentos, y el juicio del médico tratante y la severidad de la enfermedad particular a ser tratada La cantidad del inhibidor dependerá también del compuesto particular en la composición

Los inhibidores de cinasa de esta invención o las composiciones farmacéuticas de los mismos también pueden ser incorporadas en composiciones para el cubrimiento de un dispositivo medico implantable, tales como las prótesis, las válvulas artificiales, los injertos vasculares, los stents, y los catéteres Los stents vasculares, por ejemplo, han sido empleados para superar la restenosis (re-angostando la pared del vaso después de la herida) Sin embargo, los pacientes que emplean los stents u otros dispotivos implantables corren el riesgo de la formación de un coágulo o de la activación de las plaquetas. Estos efectos indeseados pueden ser prevenidos o mitigados por medio del pre-cubrimiento del dispositivo con una composición farmacéuticamente aceptable que

comprende un inhibidor de cinasa Los cubrimientos adecuados y la preparación general de los dispositivos implantables recubiertos son descritos en las patentes estadounidenses 6,099,562; 5,886,026; y 5,304,121 Los cubrimientos son típicamente materiales poliméricos biocompatibles tales como un polímero de hidrogel, el polimetildisiloxano, la policaprolactona, el polietilen glicol, el ácido polilláctico, el acetato de etilen vinilo, y las mezclas de los mismos Los cubrimientos pueden de manera opcional ser adicionalmente recubiertos por medio de una cubierta superior adecuada de fluorosilicona, polisacáridos, polietilen glicol, fosfolípidos o combinaciones de los mismos para otorgar características de liberación controlada en la composición. Los dispositivos implantables recubiertos con un inhibidor de cinasa de esta invención son otra realización de la presente invención.

Dependiendo de la condición particular mediada por la proteína cinasa a ser tratada o prevenida, agentes terapéuticos adicionales, que son normalmente administrados para tratar o prevenir esa condición, pueden ser administrados junto con los inhibidores de esta invención. Por ejemplo, en el tratamiento del cáncer, otros agentes quimoterapéuticos u otros agentes anti-proliferativos pueden ser combinados con los compuestos de la presente invención para tratar el cáncer. Estos agentes incluyen, sin limitación, la adriamicina, la dexametasona, la vincristina, la

ciclofosfamida, el fluorouracilo, el topotecan, el taxol, los interferones, y los derivados de platino

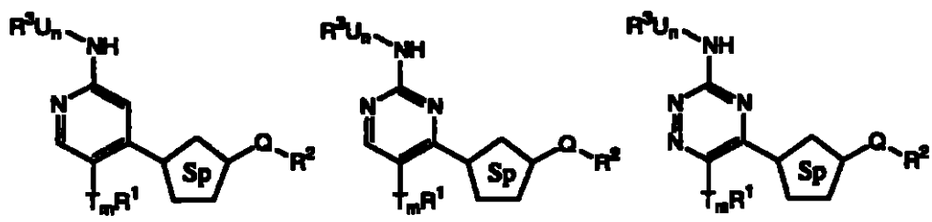
Otros ejemplos de agentes que pueden ser también combinados con los inhibidores de esta invención incluyen, sin limitación, agentes para tratar la diabetes tales como la insulina o los análogos de insulina, en forma inyectable o de inhalación, las glitazonas, los inhibidores alfa glucosidasa, las biguanidas, los sensibilizadores de la insulina, y las sulfonil ureas; agentes anti-inflamatorios tales como los corticosteroides, los bloqueadores del TNF, la IL-1 RA, la azatioprina, la ciclofosfamida, y la sulfasalazina; agentes inmunomoduladores e inmunosupresores tales como la ciclosporina, el tacrolimus, la rapamicina, el micofenolato mofetil, los interferones, los corticosteroides, la ciclofosfamida, la azatioprina, y la sulfasalazina, factores neurotróficos tales como los inhibidores de la acetilcolinesterasa, los inhibidores de la MAO, los interferones, los anti-convulsivos, los bloqueadores de canales iónicos, el riluzol, y los agentes anti-Parkinson; agentes para tratar enfermedad cardiovascular tales como los bloqueadores beta, los inhibidores de ACE, los diuréticos, los nitratos, los bloqueadores del canal de calcio, y las estatinas; agentes para el tratamiento de la enfermedad del hígado tales como los corticosteroides, la colestiramina, los interferones, y los agentes anti-virales, agentes para el tratamiento de trastornos sanguíneos tales como los

corticosteroides, los agentes anti-leucémicos, y los factores de crecimiento, y los agentes para el tratamiento de trastornos de inmunodeficiencia tales como la gama globulina

Esos agentes adicionales pueden ser administrados de manera separada de la composición que contiene el inhibidor de la proteína cinasa, como parte de un régimen de dosis múltiple. De manera alternativa, esos agentes pueden ser parte de una forma de dosificación única, mezclados junto con el inhibidor de proteína cinasa de esta invención en una composición única.

Los compuestos de esta invención pueden existir en formas tautoméricas alternativas. A menos que se indique otra cosa, la representación de cualquier tautómero quiere decir que incluye al otro.

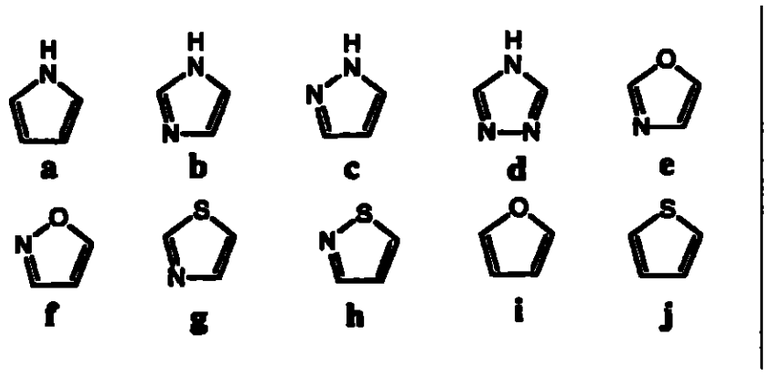
Por consiguiente, la presente invención se relaciona con los compuestos de la fórmula I en donde el Anillo A es un anillo piridina (II), pirimidina (III), o triazina (IV) como se muestra a continuación:



II III IV

o un derivado farmacéuticamente aceptable de los mismos, en donde Sp, T_mR^1, R^2, U_nR^3, Q, y T son como se describieron anteriormente.

Los ejemplos de los grupos Sp adecuados de la fórmula I incluyen el pirrol (a), el imidazol (b), el pirazol (c), el triazol (d), el oxazol (e), el isoxazol (f), el 1,3-tiazol (g), el 1,2-tiazol (h), el furano (i), y el tiofeno (j), como se muestra a continuación



en donde cada uno de a a j es substituido de manera opcional con R^6

Los grupos T_mR^1 preferidos de la fórmula I son seleccionados a partir de hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros. Cuando R^1 es un grupo fenilo o alifático substituidos de manera opcional, los substituyentes preferidos en el grupo fenilo o alifático son R^7, halógeno, nitro, alcoxi, y amino Los grupos T_mR^1 preferidos son metilo, etilo,

propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, y CH_2NHCH_3. Los grupos T_mR^1 más preferidos de la fórmula I son aquellos listados en la Tabla 1 que se encuentra más adelante.

Los grupos R^3 preferidos de la fórmula I son hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros Los ejemplos de tales grupos incluyen metilo, etilo, propilo, ciclopropilo, ciclohexilo, bencilo, isoxazolilo, tetrahidrofuranilo, e isopropilo. Cuando R^3 es fenilo substituido de manera opcional, los substituyentes preferidos en el anillo fenilo son halógeno, alquilo, alcoxi, haloalquilo, Obencil, Ofenil, OCF_3, OH, SO_2NH_2, y metileno dioxi. Cuando R^3 es $-CH(R^8)R$, los ejemplos de tales grupos incluyen $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, y $-CH(CH_2OH)CH_2$ciclopropilo. Los grupos U_n preferidos, cuando se encuentran presentes, son $-CH_2-$, $-O-$, $-NR^7-$, $-NHCO-$, y $-NHCO_2-$. Los grupos U_nR^3 más preferidos de la fórmula I son aquellos listados en la Tabla 1 que se encuentra más adelante.

Cuando R^2 es R^5, los grupos R^5 preferidos son pirrolidin-1-il, morfolin-4-il, piperidin-1-il, y piperazin-1-il, 4-metil[1,4]diazepan-1-il, 4-fenil-piperazin-1-il, en donde cada grupo se encuentra substituido de manera opcional Cuando R^2 es $(CH_2)_yR^5$, $(CH_2)_yCH(R^5)_2$, o $-N(R^4)_2$, los grupos

R^5 preferidos son además seleccionados a partir de piridin-3-il, piridin-4-il, imidazolilo, furan-2-il, 1,2,3,4-tetrahidroisoquinolina, tetrahidrofuran-2-il, ciclohexilo, fenilo, bencilo, $-CH_2OH$, $-(CH_2)_2OH$, e isopropilo, en donde cada grupo es substituido de manera opcional. Los substituyentes preferidos en R^5 son -OH, piridilo, piperidinilo, y fenilo substituido de manera opcional. Cuando R^2 es $-(CH_2)_yCH(R^6)CH(R^5)_2$, los grupos R^6 preferidos son R^7 y OR^7 tal como OH y CH_2OH y los R^5 preferidos son como se describieron anteriormente. Los grupos $-(CH_2)_yCH(R^6)CH(R^5)_2$ preferidos de la fórmula I son -CH(OH)CH(OH)fenil y -CH(Me)CH(OH)fenil Otros grupos $-QR^2$ preferidos son aquellos listados en la Tabla 1 que se encuentra más adelante.

Los compuestos preferidos de la fórmula I son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de:

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^6)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_nR^1 es hidrógeno, amino, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros;

(c) Q es -CO-, -CO_2-, -CONH-, -SO_2-, -SO_2NH-, -OC(O)NH-, -C(O)ONH-, o -CONHNH-,

(d) R^2 es -$NR^4(CH_2)_yN(R^4)_2$, -$(CH_2)_yR^5$, -$(CH_2)_yCH(R^5)_2$, o -$(CH_2)_yCH(R^8)CH(R^5)_2$,

(f) R^4 es R, R^7 o -$(CH_2)_yCH(R^5)_2$; y

(g) R^5 es un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, fenilo, heteroarilo de 5 - 6 miembros, o heterociclilo de 5 - 6 miembros

Los compuestos más preferidos de la fórmula I son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de:

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, -CH(CH_2OH)fenilo, -CH(CH_2OH)etilo, -$CH(CH_2OH)_2$, -CH(CH_2OH)isopropilo, -CH(CH_2OH)CH_2ciclopropilo, o un grupo fenilo, bencilo, o isoxazolilo substituidos de manera opcional;

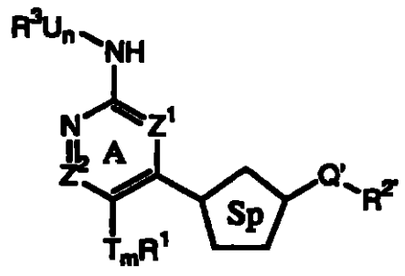
(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, NHC(O)$NHCH_3$, o CH_2NHCH_3;

(c) Q es -CO-, -CONH-, -SO_2-, o -SO_2NH-;

(d) R^2 es -$(CH_2)_yR^5$, -$(CH_2)_yCH(R^5)_2$, o -$(CH_2)_yCH(R^8)CH(R^5)_2$, en donde R^8 es OH o CH_2OH; y

(e) R^5 es $-CH_2OH$, $-(CH_2)_2OH$, isopropilo, o un grupo substituido de manera opcional seleccionado a partir de pirrolidin-1-il, morfolin-4-il, piperidin-1-il, piperazin-1-il, 4-metil[1,4]diazepan-1-il, 4-fenil-piperazin-1-il, piridin-3-il, piridin-4-il, imidazolilo, furan-2-il, 1,2,3,4-tetrahidroisoquinolina, tetrahidrofuran-2-il, ciclohexilo, fenilo, o bencilo

Una realización preferida de esta invención se relaciona con los compuestos de la fórmula I':



I'

o un derivado farmacéuticamente aceptable de los mismos, en donde

Sp es un grupo espaciador que comprende un anillo heteroaromático de 5 miembros, en donde el Anillo A y $Q'R^{2'}$ se encuentran unidos a Sp en posiciones no adyacentes, y en donde Sp tiene hasta dos substituyentes R^6, con la condición de que dos átomos de carbono en el anillo sustituibles en Sp no se encuentran simultáneamente substituidos por R^6,

Z^1 y Z^2 son cada uno seleccionados de manera independiente a partir de N o CH,

Q' es seleccionado a partir de $-CO_2-$, $-C(O)NR^7-$ o $-SO_2NR^7-$;

T es un grupo ligante;

U es seleccionado a partir de $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, -O-, $-CONR^7-$, -CO-, $-CO_2-$, -OC(O)-, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, o $-SO_2-$,

m y n son cada uno seleccionados de manera independiente a partir de cero o uno,

R^1 es seleccionado a partir de hidrógeno, CN, halógeno, R, $N(R^7)_2$, OR, u OH,

$R^{2'}$ es seleccionado a partir de $-(CH_2)_yCH(R^5)_2$ o $-(CH_2)_yCH(R^6)CH(R^5)_2$;

y es 0 - 6 ,

R^3 es seleccionado a partir de R^7, R, $-(CH_2)_yCH(R^6)R$, CN, $-(CH_2)_yCH(R^6)CH(R^5)_2$, o $-(CH_2)_yCH(R^6)N(R^4)_2$;

cada R es seleccionado de manera independiente a partir de un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, arilo C_{6-10}, un anillo heteroarilo que tiene 5 - 10 átomos en el anillo, o un anillo heterociclilo que tiene 3 - 10 átomos en el anillo,

cada R^4 es seleccionado de manera independiente a partir de R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, o $-(CH_2)_yCH(R^5)_2$;

cada R^5 es seleccionado de manera independiente a partir de R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7,

$NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$;

cada R^6 es seleccionado de manera independiente a partir de R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$;

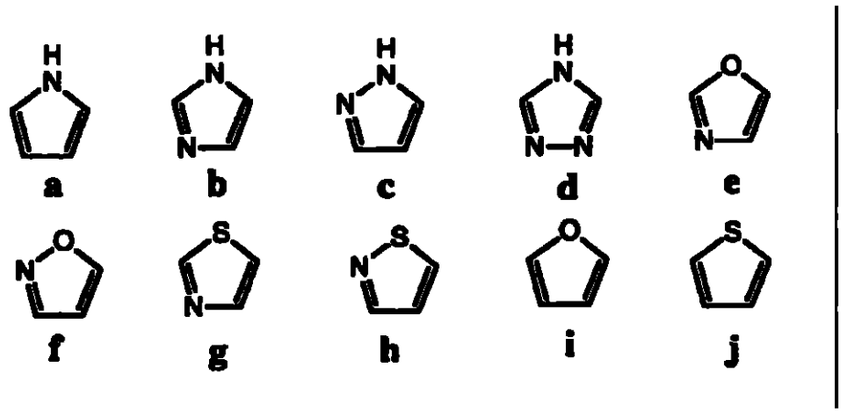
cada R^7 es seleccionado de manera independiente a partir de hidrógeno o un grupo alifático C_{1-6} substituido de manera opcional, o dos R^7 en el mismo nitrógeno son tomados junto con el nitrógeno para formar un anillo heterocíclilo o heteroarilo de 5 - 8 miembros;

R^8 es seleccionado a partir de R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, o $(CH_2)_wSR^7$;

y

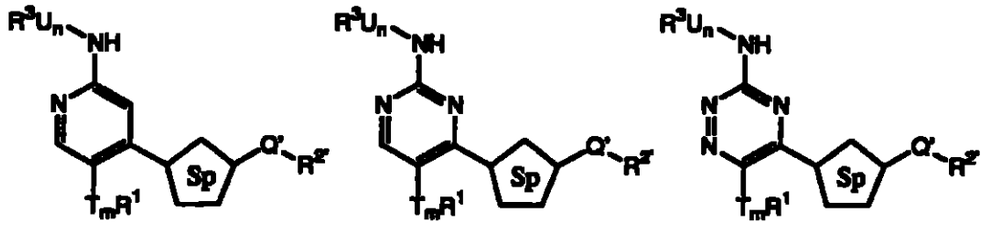
cada w es seleccionado de manera independiente a partir de 0 - 4.

Los ejemplos de grupos Sp adecuados de la fórmula I' incluyen pirrol (a), imidazol (b), pirazol (c), triazol (d), oxazol (e), isoxazol (f), 1,3-tiazol (g), 1,2-tiazol (h), furano (i), y tiofeno (j), como se muestra a continuación.



en donde cada uno de a a j es substituido de manera opcional con R^6.

Por consiguiente, la presente invención se relaciona con los compuestos de la fórmula I' en donde el Anillo A es un anillo piridina (II'), pirimidina (III'), o triazina (IV') como se muestra a continuación:



o un derivado farmacéuticamente aceptable de los mismos, en donde Sp, T_mR^1, $Q'R^{2'}$, y U_nR^3 son como se describieron anteriormente.

Los grupos R^5 preferidos de la fórmula I' son R u OR^7 Los ejemplos de tales grupos incluyen OH, CH_2OH, carbocíclico, o anillos arilo o heteroarilo de 5 o 6

miembros substituidos de manera opcional, tal como fenilo, piridilo, y ciclohexilo

Los grupos R^8 preferidos de la fórmula I' son R y OR^7, en donde R es un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros Los ejemplos de tales grupos incluyen fenilo, metilo, etilo, OH, y CH_2OH Los substituyentes preferidos en el anillo arilo o heteroarilo R^5 son halógeno, haloalquilo, OR^o, y R^o.

Los grupos T_mR^1 preferidos de la fórmula I' son hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros Cuando R^1 es un grupo fenilo o alifático substituidos de manera opcional, los substituyentes preferidos en el grupo fenilo o alifático son R^7, halógeno, nitro, alcoxi, y amino Los grupos T_mR^1 preferidos incluyen metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, y CH_2NHCH_3. Los grupos T_mR^1 más preferidos de la fórmula I' son aquellos listados en la Tabla 1 que se encuentra más adelante

Los grupos R^3 preferidos de la fórmula I' son hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4},

heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros Los ejemplos de tales grupos incluyen metilo, etilo, propilo, ciclopropilo, ciclohexilo, bencilo, isoxazolilo, tetrahidrofuranilo, e isopropilo. Cuando R^3 es fenilo substituido de manera opcional, los substituyentes preferidos en el anillo fenilo son halógeno, alquilo, alcoxi, haloalquilo, Obencil, Ofenil, OCF_3, OH, SO_2NH_2, y metileno dioxi. Cuando R^3 es $-CH(R^8)R$, ejemplos de tales grupos incluyen $-CH(CH_2OH)$fenil, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropil, y $-CH(CH_2OH)CH_2$ciclopropil. Los grupos U_n preferidos, cuando se encuentran presentes, son $-CH_2-$, $-O-$, $-NR^7-$, $-NHCO-$, y $-NHCO_2-$. Los grupos U_nR^3 más preferidos de la fórmula I' son aquellos listados en la Tabla 1 que se encuentra más adelante.

Los compuestos preferidos de la fórmula I' son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros,

(b) T_mR^1 es hidrógeno, amino, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros, y

(c) R^5 es R o OR^7, en donde R es carbocíclico, o un anillo arilo o heteroarilo de 5 o 6 miembros substituido de manera opcional.

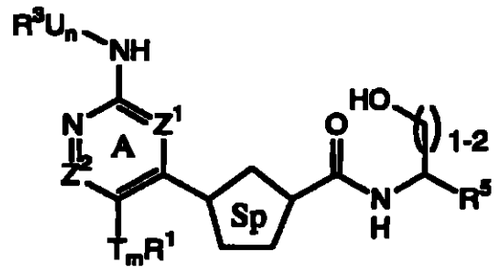
Los compuestos más preferidos de la fórmula I' son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, $-CH(CH_2OH)CH_2$ciclopropilo, o un grupo fenilo, bencilo, o isoxazolilo substituidos de manera opcional,

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, o CH_2NHCH_3; y

(c) R^5 es OH, CH_2OH, carbocíclico, o un anillo fenilo o piridilo substituido de manera opcional, y Q' es $C(O)NH$

Otra realización preferida de esta invención se relaciona con los compuestos de la fórmula I"



I^s

o un derivado farmacéuticamente aceptable de los mismos, en donde

Sp es un grupo espaciador que comprende un anillo heteroaromático de 5 miembros, en donde el Anillo A y $C(O)NHCH[(CH_2)_{1-2}OH]R^5$ se encuentran unidos a Sp en posiciones no adyacentes, y en donde Sp tiene hasta dos substituyentes R^6, con la condición de que dos átomos de carbono en el anillo sustituibles en Sp no se encuentran simultáneamente substituidos por R^6,

Z^1 y Z^2 son cada uno seleccionados de manera independiente a partir de N o CH,

T es un grupo ligante,

U es seleccionado a partir de $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, o $-SO_2-$;

m y n son cada uno seleccionados de manera independiente a partir de cero o uno;

R^1 es seleccionado a partir de hidrógeno, CN, halógeno, R, $N(R^7)_2$, OR, u OH;

R^3 es seleccionado a partir de R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, o $-(CH_2)_yCH(R^8)N(R^4)_2$;

cada R es seleccionado de manera independiente a partir de un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, arilo C_{6-10}, un anillo heteroarilo que tiene 5 - 10 átomos en el anillo, o un anillo heterociclilo que tiene 3 - 10 átomos en el anillo,

cada R^4 es seleccionado de manera independiente a partir de R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, o $-(CH_2)_yCH(R^5)_2$,

cada R^5 es seleccionado de manera independiente a partir de R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$;

cada R^6 es seleccionado de manera independiente a partir de R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$;

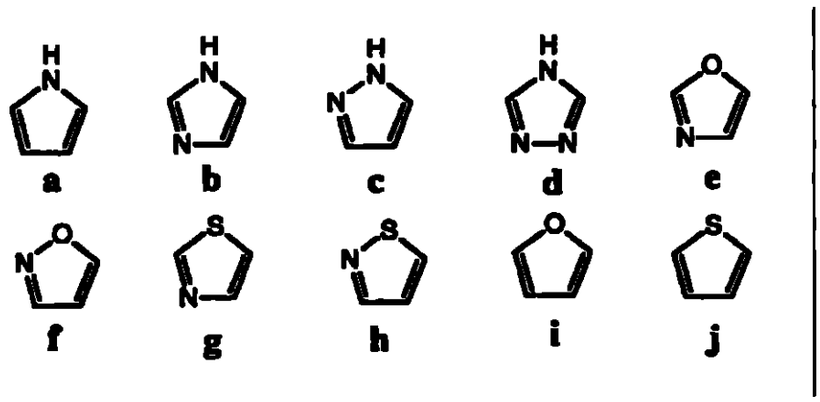
cada R^7 es seleccionado de manera independiente a partir de hidrógeno o un grupo alifático C_{1-6} substituido de manera opcional, o dos R^7 en el mismo nitrógeno son tomados junto con el nitrógeno para formar un anillo heterociclilo o heteroarilo de 5 - 8 miembros;

R^8 es seleccionado a partir de R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, o $(CH_2)_wSR^7$,

y

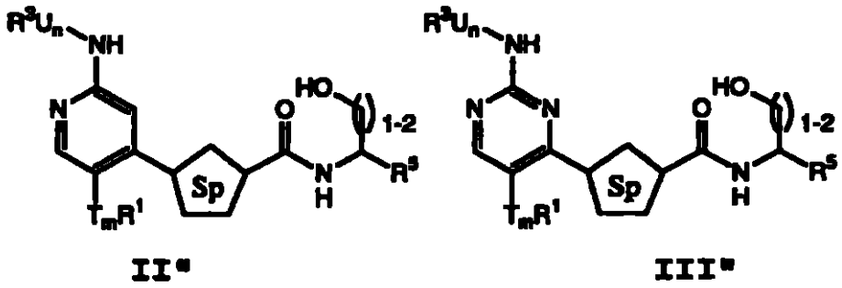
cada w es seleccionado de manera independiente a partir de 0 - 4.

Los ejemplos de grupos Sp adecuados de la fórmula I" incluyen pirrol (a), imidazol (b), pirazol (c), triazol (d), oxazol (e), isoxazol (f), 1,3-tiazol (g), 1,2-tiazol (h), furano (i), y tiofeno (j), como se muestra a continuación



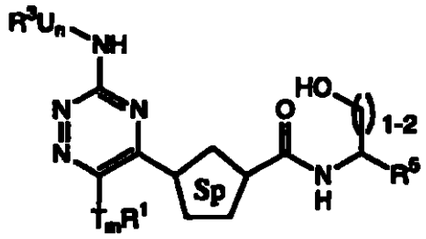
en donde cada uno de a a j es substituido de manera opcional con R^6

Por consiguiente, la presente invención se relaciona con los compuestos de la fórmula I" en donde el Anillo A es un anillo piridina (II"), pirimidina (III"), o triazina (IV") como se muestra a continuación:



II"

III"



IV"

o un derivado farmacéuticamente aceptable de los mismos, en donde Sp, T_mR^1, U_nR^3, y R^5 son como se describieron anteriormente

Los grupos T_mR^1 preferidos de la fórmula I" son hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros. Cuando R^1 es un grupo fenilo o alifático substituidos de manera opcional, los substituyentes preferidos en el grupo fenilo o alifático son R^7, halógeno, nitro, alcoxi, y amino. Los ejemplos de grupos T_mR^1 preferidos incluyen metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, y CH_2NHCH_3 Los grupos T_mR^1 más preferidos de la fórmula I" son aquellos listados más adelante en la Tabla 1

Los grupos R^3 preferidos de la fórmula I" son hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros. Los ejemplos de tales grupos incluyen metilo, etilo, propilo, ciclopropilo, ciclohexilo, bencilo, isoxazolilo, tetrahidrofuranilo, e isopropilo. Cuando R^3 es fenilo substituido de manera opcional, los substituyentes preferidos en el anillo fenilo son halógeno, alquilo, alcoxi, haloalquilo, Obencil, Ofenil, OCF_3, OH, SO_2NH_2, y metileno dioxi. Cuando R^3 es $-CH(R^8)R$, ejemplos de tales grupos incluyen $-CH(CH_2OH)$fenil, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropil, y $-CH(CH_2OH)CH_2$ciclopropil Los grupos U_n preferidos, cuando se encuentran presentes, son $-CH_2-$, $-O-$, $-NR^7-$, $-NHCO-$, y $-NHCO_2-$ Los grupos U_nR^3 más preferidos de la fórmula I" son aquellos listados en la Tabla 1 que se encuentra más adelante

.

Los grupos R^5 preferidos de la fórmula I" son los anillos arilo, heteroarilo, y carbocíclico de 6 miembros substituidos de manera opcional, tales como fenilo, piridilo, y ciclohexilo

Los compuestos preferidos de la fórmula I" son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de:

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros; y

(c) R^5 es un anillo arilo, heteroarilo, o carbocíclico de 6 miembros substituido de manera opcional

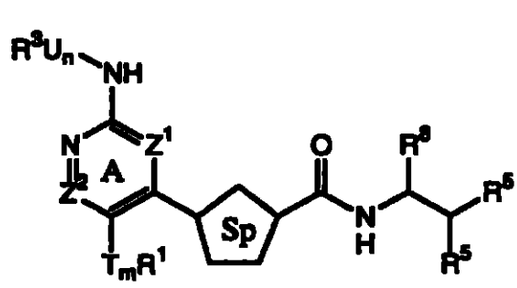
Los compuestos más preferidos de la fórmula I" son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, $-CH(CH_2OH)CH_2$ciclopropilo, o un grupo fenilo o bencilo substituido de manera opcional,

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, o CH_2NHCH_3, y

(c) R^5 es ciclohexilo o un anillo fenilo o piridilo substituido de manera opcional.

Otra realización preferida de esta invención se relaciona con los compuestos de la fórmula I°.



I°

o un derivado farmacéuticamente aceptable de los mismos, en donde

Sp es un grupo espaciador que comprende un anillo heteroaromático de 5 miembros, en donde el Anillo A y $C(O)NHCH(R^8)CH(R^5)_2$ se encuentran unidos a Sp en posiciones no adyacentes; y en donde Sp tiene hasta dos substituyentes R^6, con la condición de que dos átomos de carbono en el anillo sustituibles en Sp no se encuentran simultáneamente substituidos por R^6;

Z^1 y Z^2 son cada uno seleccionados de manera independiente a partir de N o CH,

T es un grupo ligante,

U es seleccionado a partir de $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, o $-SO_2-$;

m y n son cada uno seleccionados de manera independiente a partir de cero o uno;

R^1 es seleccionado a partir de hidrógeno, CN, halógeno, R, $N(R^7)_2$, OR, u OH,

y es 0 - 6 ;

R^3 es seleccionado a partir de R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, o $-(CH_2)_yCH(R^8)N(R^4)_2$,

cada R^4 es seleccionado de manera independiente a partir de R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, o $-(CH_2)_yCH(R^5)_2$,

cada R es seleccionado de manera independiente a partir de un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, arilo C_{6-10}, un anillo heteroarilo que tiene 5 - 10 átomos en el anillo, o un anillo heterociclilo que tiene 3 - 10 átomos en el anillo,

cada R^5 es seleccionado de manera independiente a partir de R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$;

cada R^6 es seleccionado de manera independiente a partir de R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$,

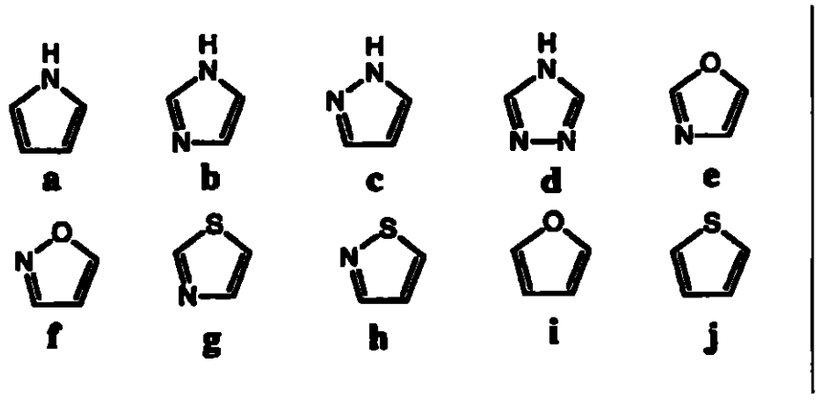
cada R^7 es seleccionado de manera independiente a partir de hidrógeno o un grupo alifático C_{1-6} substituido de manera opcional, o dos R^7 en el mismo nitrógeno son tomados junto con el nitrógeno para formar un anillo heterociclilo o heteroarilo de 5 - 8 miembros,

R^8 es seleccionado a partir de R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, o $(CH_2)_wSR^7$;

y

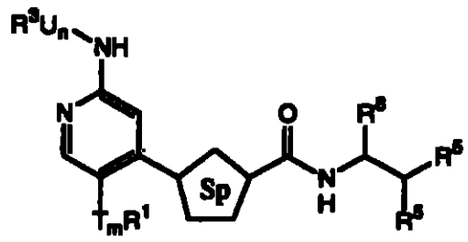
cada w es seleccionado de manera independiente a partir de 0 - 4.

Los ejemplos de grupos Sp adecuados de la fórmula I° incluyen pirrol (a), imidazol (b), pirazol (c), triazol (d), oxazol (e), isoxazol (f), 1,3-tiazol (g), 1,2-tiazol (h), furano (i), y tiofeno (j), como se muestra a continuación:

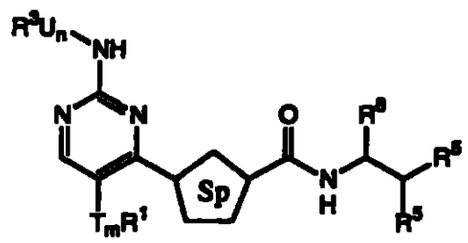


en donde cada uno de a a j es substituido de manera opcional con R^6

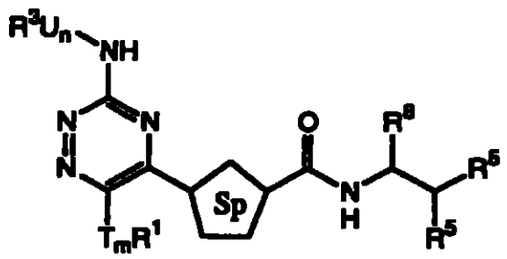
Por consiguiente, la presente invención se relaciona con los compuestos de la fórmula I° en donde el Anillo A es un anillo piridina (II°), pirimidina (III°), o triazina (IV°) como se muestra a continuación



II°



III°



IV°

o un derivado farmacéuticamente aceptable de los mismos, en donde Sp, T_mR^1, R^5, U_nR^3, y R^8 son como se describieron anteriormente.

Los grupos R^5 preferidos de la fórmula I° son R u OR^7. Los ejemplos de tales grupos incluyen OH, CH_2OH, carbocíclico, o anillos arilo o heteroarilo de 5 o 6 miembros substituidos de manera opcional, tal como fenilo, piridilo, y ciclohexilo

Los grupos R^8 preferidos de la fórmula I° son R y OR^7, en donde R es un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros. Los ejemplos de tales grupos incluyen fenilo, metilo, etilo, OH, y CH_2OH Los substituyentes preferidos

en el anillo arilo o heteroarilo R^5 son halógeno, haloalquilo, OR^o, y R^o

Los grupos T_mR^1 preferidos de la fórmula I° son hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros. Cuando R^1 es un grupo fenilo o alifático substituidos de manera opcional, los substituyentes preferidos en el grupo fenilo o alifático son R^7, halógeno, nitro, alcoxi, y amino. Los grupos T_mR^1 más preferidos son metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, y CH_2NHCH_3. Los grupos T_mR^1 aún más preferidos de la fórmula I° son aquellos listados en la Tabla 1 que se encuentra más adelante.

Los grupos R^3 preferidos de la fórmula I° son hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros. Los ejemplos de tales grupos incluyen metilo, etilo, propilo, ciclopropilo, ciclohexilo, bencilo, isoxazolilo, tetrahidrofuranilo, e isopropilo. Cuando R^3 es fenilo substituido de manera opcional, los substituyentes preferidos en el anillo fenilo son halógeno, alquilo, alcoxi, haloalquilo, Obencil, Ofenil, OCF_3, OH, SO_2NH_2, y metileno dioxi Cuando R^3 es $-CH(R^8)R$, ejemplos de tales grupos incluyen -

$CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, y $-CH(CH_2OH)CH_2$ciclopropilo Los grupos U_n preferidos, cuando se encuentran presentes, son $-CH_2-$, -O-, $-NR^7-$, -NHCO-, y $-NHCO_2-$. Los grupos U_nR^3 más preferidos de la fórmula I° son aquellos listados en la Tabla 1 que se encuentra más adelante.

Los compuestos preferidos de la fórmula I° son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, amino, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros, y

(c) R^5 es R u OR^7, en donde R es carbocíclico, o un anillo arilo o heteroarilo de 5 o 6 miembros substituido de manera opcional.

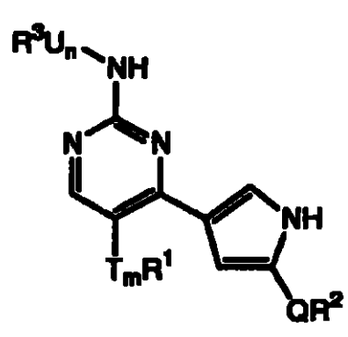
Los compuestos más preferidos de la fórmula I° son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de:

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, $-CH(CH_2OH)CH_2$ciclopropilo, o un grupo fenilo, bencilo, o isoxazolilo substituidos de manera opcional;

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, o CH_2NHCH_3, y

(c) R^5 es OH, CH_2OH, carbocíclico, o un anillo fenilo o piridilo substituido de manera opcional.

Una realización preferida se relaciona con los compuestos de la fórmula III-a



III-a

o un derivado farmacéuticamente aceptable de los mismos.

Los grupos T_mR^1 preferidos de la fórmula III-a son hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o

un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros Cuando R^1 es un grupo fenilo o alifático substituidos de manera opcional, los substituyentes preferidos en el grupo fenilo o alifático son R^7, halógeno, nitro, alcoxi, y amino. Los ejemplos de tales grupos T_mR^1 preferidos incluyen metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, y CH_2NHCH_3 Los grupos T_mR^1 más preferidos de la fórmula III-a son aquellos listados en la Tabla 1 que se encuentra más adelante

Los grupos R^3 preferidos de la fórmula III-a son hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros. Los ejemplos de tales grupos incluyen metilo, etilo, propilo, ciclopropilo, ciclohexilo, bencilo, isoxazolilo, tetrahidrofuranilo, e isopropilo Cuando R^3 es fenilo substituido de manera opcional, los substituyentes preferidos en el anillo fenilo son halógeno, alquilo, alcoxi, haloalquilo, Obencil, Ofenil, OCF_3, OH, SO_2NH_2, y metileno dioxi. Cuando R^3 es $-CH(R^8)R$, los ejemplos de tales grupos son $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, y $-CH(CH_2OH)CH_2$ciclopropilo. Los grupos U_n preferidos, cuando se encuentran presentes, son $-CH_2-$, $-O-$, $-NR^7-$, $-NHCO-$, y $-NHCO_2-$ Los grupos U_nR^3 más

preferidos de la fórmula III-a son aquellos listados en la Tabla 1 que se encuentra más adelante.

Cuando R^2 es R^5, los grupos R^5 preferidos son pirrolidin-1-il, morfolin-4-il, piperidin-1-il, y piperazin-1-il, 4-metil[1,4]diazepan-1-il, 4-fenil-piperazin-1-il, en donde cada grupo se encuentra substituido de manera opcional. Cuando R^2 es $(CH_2)_yR^5$, $(CH_2)_yCH(R^5)_2$, o $-N(R^4)_2$, los grupos R^5 preferidos son piridin-3-il, piridin-4-il, imidazolilo, furan-2-il, 1,2,3,4-tetrahidroisoquinolina, tetrahidrofuran-2-il, ciclohexilo, fenilo, bencilo, $-CH_2OH$, $-(CH_2)_2OH$, e isopropilo, en donde cada grupo es substituido de manera opcional. Los substituyentes preferidos en R^5 son -OH, piridilo, piperidinilo, y fenilo substituido de manera opcional. Cuando R^2 es $-(CH_2)_yCH(R^8)CH(R^5)_2$, los grupos R^8 preferidos son R^7 y OR^7 tal como OH y CH_2OH. Los grupos $-QR^2$ más preferidos son aquellos listados en la Tabla 1 que se encuentra más adelante.

Los compuestos preferidos de la fórmula III-a son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir

de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros,

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros,

(c) Q es -CO-, $-CO_2-$, -CONH-, $-SO_2-$, $-SO_2NH-$, -OC(O)NH-, -C(O)ONH-, o -CONHNH-,

(d) R^2 es $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, o $-(CH_2)_yCH(R^8)CH(R^5)_2$,

(f) R^4 es R, R^7 o $-(CH_2)_yCH(R^5)_2$; y

(g) R^5 es un grupo substituido de manera opcional seleccionado a partir de fenilo, heteroarilo de 5 - 6 miembros, o heterociclilo de 5 - 6 miembros

Los compuestos más preferidos de la fórmula III-a son aquellos que tienen una o más, más preferiblemente más de una, o aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de:

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, $-CH(CH_2OH)CH_2$ciclopropilo, o un grupo fenilo o bencilo substituidos de manera opcional,

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo,

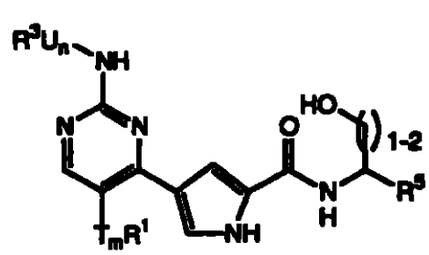
ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, o CH_2NHCH_3;

(c) Q es -CO-, -CONH-, $-SO_2-$, o $-SO_2NH-$,

(d) R^2 es $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, o $-(CH_2)_yCH(R^8)CH(R^5)_2$, en donde R^8 es OH o CH_2OH; y

(e) R^5 es $-CH_2OH$, $-(CH_2)_2OH$, isopropilo, o un grupo substituido de manera opcional seleccionado a partir de pirrolidin-1-il, morfolin-4-il, piperidin-1-il, piperazin-1-il, 4-metil[1,4]diazepan-1-il, 4-fenil-piperazin-1-il, piridin-3-il, piridin-4-il, imidazolilo, furan-2-il, 1,2,3,4-tetrahidroisoquinolina, tetrahidrofuran-2-il, ciclohexilo, fenilo, o bencilo.

Los compuestos preferidos de la fórmula III-a incluyen aquellos de la fórmula III-a':



III-a'

o un derivado farmacéuticamente aceptable de los mismos.

Los grupos R^5 preferidos de la fórmula III-a' son los anillos arilo, heteroarilo, y carbocíclico de 6 miembros

substituidos de manera opcional, tales como fenilo, piridilo, y ciclohexilo.

Los grupos T_mR^1 preferidos de la fórmula III-a' son hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros Cuando R^1 es un grupo fenilo o alifático substituidos de manera opcional, los substituyentes preferidos en el grupo fenilo o alifático son R^7, halógeno, nitro, alcoxi, y amino. Los grupos T_mR^1 preferidos son metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, y CH_2NHCH_3, y aquellos listados en la Tabla 1 que se encuentra más adelante.

Los grupos R^3 preferidos de la fórmula III-a' son hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros Los ejemplos de tales grupos incluyen metilo, etilo, propilo, ciclopropilo, ciclohexilo, bencilo, isoxazolilo, tetrahidrofuranilo, e isopropilo. Cuando R^3 es fenilo substituido de manera opcional, los substituyentes preferidos en el anillo fenilo son halógeno, alquilo, alcoxi, haloalquilo, Obencil, Ofenil, OCF_3, OH, SO_2NH_2, y metileno dioxi. Cuando R^3 es $-CH(R^8)R$, los ejemplos de tales grupos incluyen $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, -

$CH(CH_2OH)$ isopropilo, y $-CH(CH_2OH)CH_2$ ciclopropilo Los grupos U_n preferidos, cuando se encuentran presentes, son $-CH_2-$, $-O-$, $-NR^7-$, $-NHCO-$, y $-NHCO_2-$. Los U_nR^3 más preferidos de la fórmula III-a' son aquellos listados en la Tabla 1 que se encuentra más adelante

Los compuestos preferidos de la fórmula III-a' son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^6)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_nR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros; y

(c) R^5 es un anillo arilo, heteroarilo, o carbocíclico de 6 miembros substituido de manera opcional.

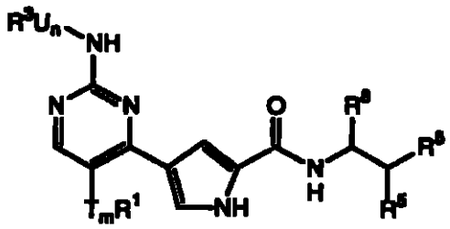
Los compuestos más preferidos de la fórmula III-a' son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de·

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, -CH(CH_2OH)fenilo, -CH(CH_2OH)etilo, -$CH(CH_2OH)_2$, -CH(CH_2OH)isopropilo, -CH(CH_2OH)CH_2ciclopropilo, o un grupo fenilo o bencilo substituidos de manera opcional;

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, NHC(O)$NHCH_3$, o CH_2NHCH_3; y

(c) R^5 es ciclohexilo o un anillo fenilo o piridilo substituido de manera opcional

Los compuestos preferidos de la fórmula III-a son además seleccionados a partir de aquellos de la fórmula III-a'.



III-a'

o un derivado farmacéuticamente aceptable de los mismos

Los grupos R^5 preferidos de la fórmula III-a' son R u OR^7. Los ejemplos de tales grupos incluyen OH, CH_2OH, o los anillos arilo, heteroarilo, y carbocíclico de 6 miembros substituidos de manera opcional, tales como fenilo,

piridilo, y ciclohexilo. Los grupos R^8 preferidos de la fórmula III-a° son R y OR^7, en donde R es un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros. Los ejemplos de tales grupos incluyen fenilo, metilo, etilo, OH, y CH_2OH.

Los grupos T_mR^1 preferidos de la fórmula III-a° son hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros. Cuando R^1 es un grupo fenilo o alifático substituidos de manera opcional, los substituyentes preferidos en el grupo fenilo o alifático son R^7, halógeno, nitro, alcoxi, y amino Los grupos T_mR^1 preferidos incluyen metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, y CH_2NHCH_3. Los grupos T_mR^1 más preferidos de la fórmula III-a° son aquellos listados en la Tabla 1 que se encuentra más adelante

Los grupos R^3 preferidos de la fórmula III-a° son hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros Los ejemplos de tales grupos incluyen metilo, etilo, propilo, ciclopropilo, ciclohexilo, bencilo, isoxazolilo, tetrahidrofuranilo, e

isopropilo Cuando R^3 es fenilo substituido de manera opcional, los substituyentes preferidos en el anillo fenilo son halógeno, alquilo, alcoxi, haloalquilo, Obencil, Ofenil, OCF_3, OH, SO_2NH_2, y metileno dioxi Cuando R^3 es $-CH(R^8)R$, los ejemplos de tales grupos son $-CH(CH_2OH)$fenil, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropil, y $-CH(CH_2OH)CH_2$ciclopropil. Los grupos U_n preferidos, cuando se encuentran presentes, son $-CH_2-$, $-O-$, $-NR^7-$, $-NHCO-$, y $-NHCO_2-$ Los grupos U_nR^3 más preferidos de la fórmula III-a° son aquellos listados en la Tabla 1 que se encuentra más adelante

Los compuestos preferidos de la fórmula III-a° son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de:

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros, y

(c) R^5 es R u OR^7, y R^8 es R^7 u OR^7.

Los compuestos más preferidos de la fórmula III-a* son aquellos que tienen una o más, más preferiblemente más de una, y aún más preferiblemente todas, de las características seleccionadas a partir del grupo que consiste de:

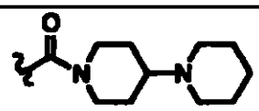
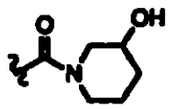
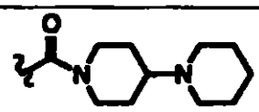
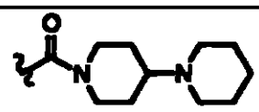
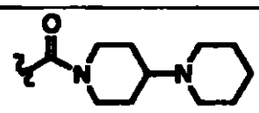
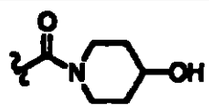
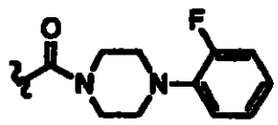
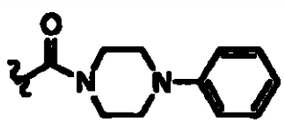
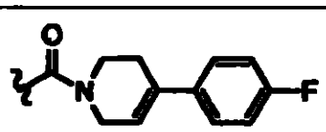
(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, -CH(CH_2OH)fenilo, -CH(CH_2OH)etilo, -CH(CH_2OH)$_2$, -CH(CH_2OH)isopropilo, -CH(CH_2OH)CH_2ciclopropilo, o un grupo fenilo o bencilo substituidos de manera opcional,

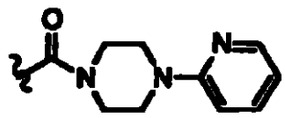
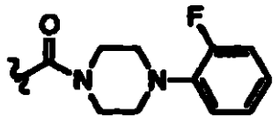
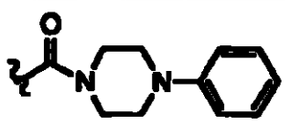
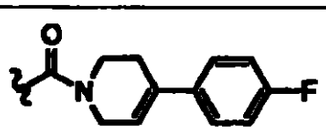
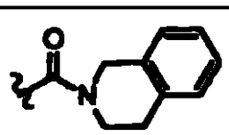
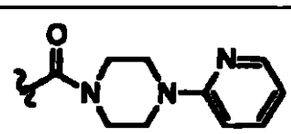
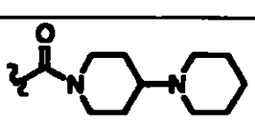
(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, NHC(O)$NHCH_3$, o CH_2NHCH_3; y

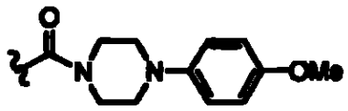
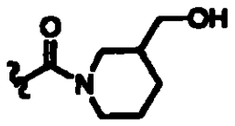
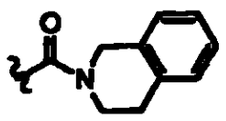
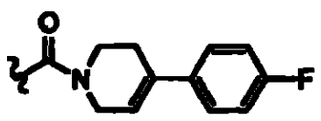
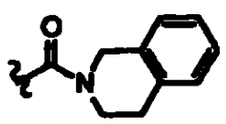
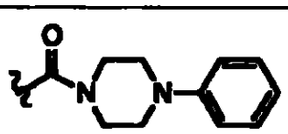
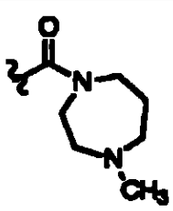
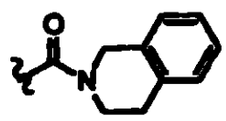
(c) R^5 es OH, CH_2OH, fenilo, piridilo, o ciclohexilo, y R^8 es metilo, etilo, OH, o CH_2OH

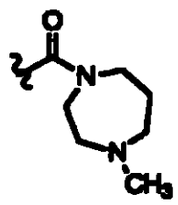
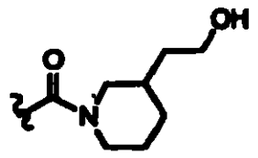
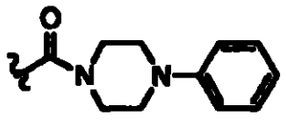
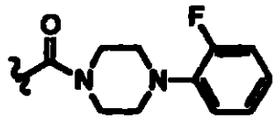
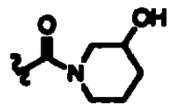
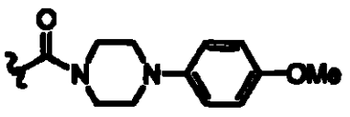
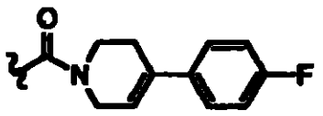
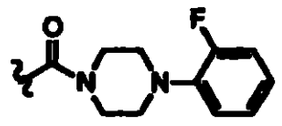
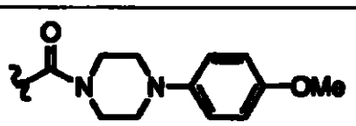
Los compuestos preferidos de la fórmula III-a son establecidos adelante en la Tabla 1 que se encuentra a continuación Los compuestos más preferidos en la Tabla 1 son aquellos de las fórmulas III-a' o III-a*.

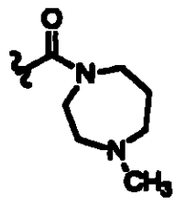
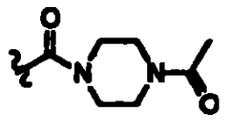
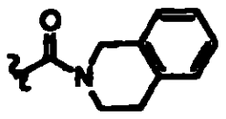
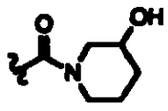
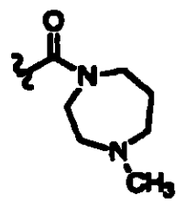
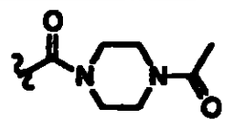
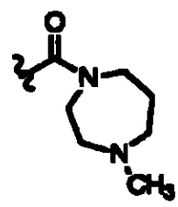
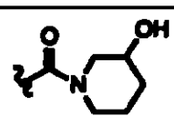
Tabla 1[A]. Compuestos de la fórmula III-a

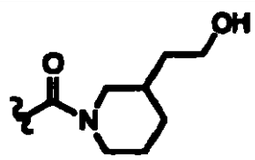
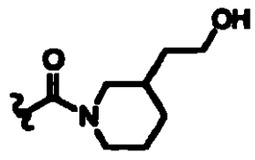
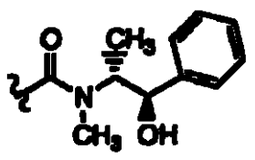
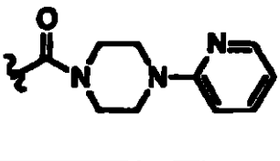
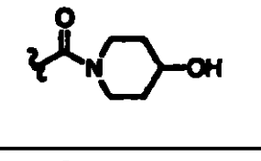
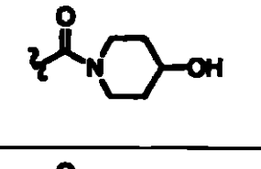
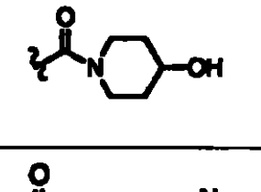
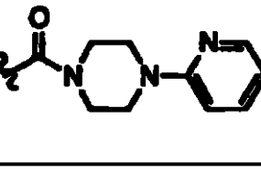
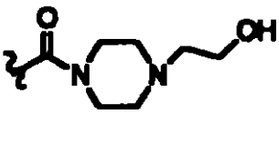
No. III-a-	R^3U_n	T_mR^1	Q-R^2
1	H	Fenil	$CON(Me)_2$
2	H	3- Cl -fenil	CO (pirrolidin -1-il)
3	H	2-F-3-Cl -fenil	CO (pirrolidin -1-il)
4	H	Fenil	$CONH(CH_2)_2$ piridin -3-il
5	H	Fenil	CO (morfolin -4- il)
6	H	Fenil	
7	H	3,4- $(CH_3O)_2$- fenil	
8	H	3,4- $(CH_3O)_2$- fenil	
9	H	3-Me- fenil	
10	H	2-F-3-Cl- fenil	
11	H	3-Me- fenil	
12	H	Fenil	
13	H	Fenil	
14	H	Fenil	

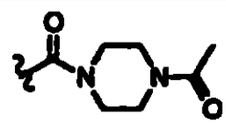
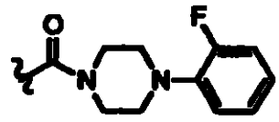
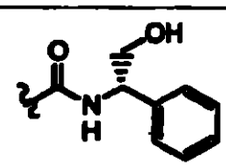
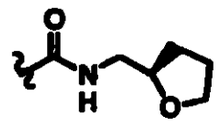
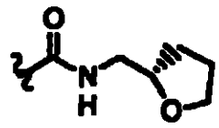
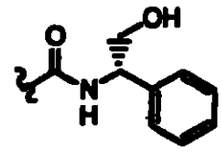
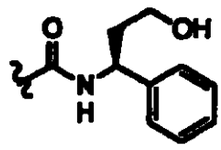
No. III-a-	R^3U_n	T_mR^1	Q-R^2
15	H	Fenil	
16	H	3,4- $(CH_3O)_2$- fenıl	CO (morfolin -4-il)
17	H	3,4- $(CH_3O)_2$- fenıl	$CONH(CH_2)_2$ piridin -3-il
18	H	3-Me- fenil	CO (morfolin -4-ıl)
19	H	3-Me- fenil	$CONH(CH_2)_2$ pırıdın -3-ıl
20	H	3-Cl- fenil	$CONH(CH_2)_2$ pırıdın -3-ıl
21	H	3-Cl- fenil	
22	H	3-Cl- fenil	
23	H	3-Cl- fenil	
24	H	3-Cl- fenil	
25	H	3-Cl- fenıl	
26	H	2-F-3-Cl- fenil	CO (morfolin -4-il)
27	H	3-Cl- fenil	CO (4-OH-piperidin -1-il)
28	H	3-Cl- fenil	
29	H	Fenil	CON(Me)CH_2Ph

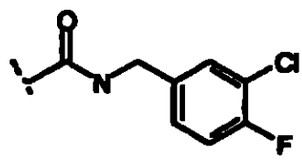
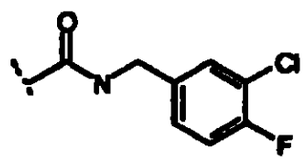
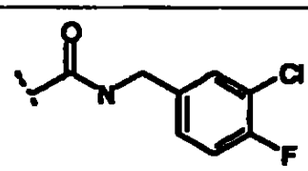
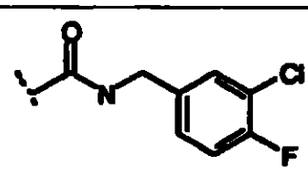
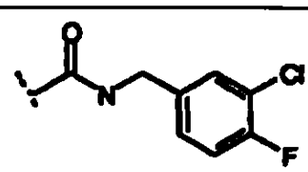
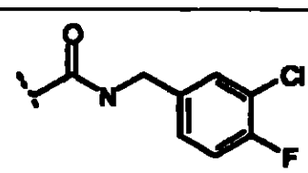
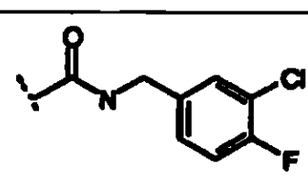
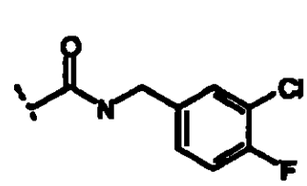
No. III-a-	R^3U_n	T_mR^1	Q-R^2
30	H	Fenil	
31	H	Fenil	
32	H	Fenil	
33	H	3,4- $(CH_3O)_2$- fenil	CON(Me)CH_2Ph
34	H	3,4- $(CH_3O)_2$- fenil	
35	H	3,4- $(CH_3O)_2$- fenil	
36	H	3-Me- fenil	CON(Me)CH_2Ph
37	H	3-Me- fenil	
38	H	3-Me- fenil	
39	H	3-Me- fenil	
40	H	3-Cl- fenil	CON(Me)CH_2Ph

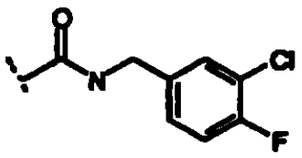
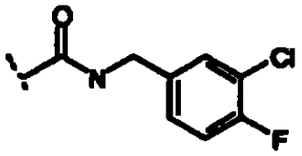
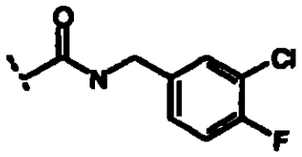
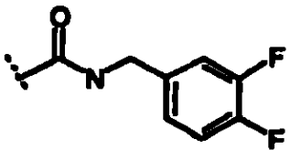
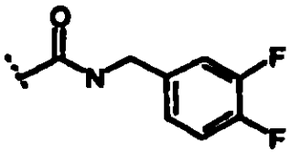
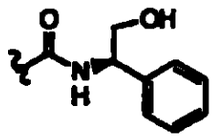
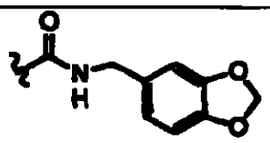
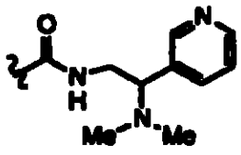
No. III-a-	R^3U_n	T_mR^1	Q-R^2
41	H	3-Cl- fenil	
42	H	2-F-3-Cl- fenil	CON(Me)CH_2Ph
43	H	3-Cl- fenil	
44	H	2-F-3-Cl- fenil	
45	H	3-Me- fenil	
46	H	3-Me- fenil	
47	H	3-Me- fenil	
48	H	3-Me- fenil	
49	H	2-F-3-Cl- fenil	
50	H	2-F-3-Cl- fenil	

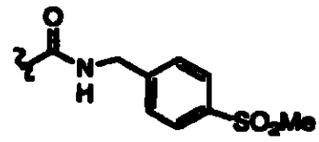
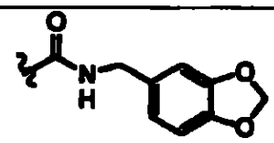
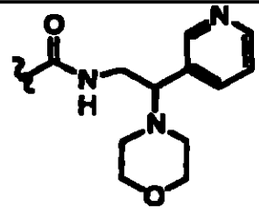
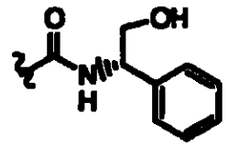
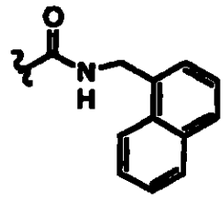
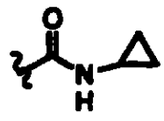
No. III-a-	R^3U_n	T_mR^1	Q-R^2
51	H	2-F-3-Cl- fenil	
52	H	2-F-3-Cl- fenil	
53	H	2-F-3-Cl- fenil	
54	H	3-Cl- fenil	
55	H	Fenil	
56	H	3,4- $(CH_3O)_2$- fenil	
57	H	3,4- $(CH_3O)_2$- fenil	
58	H	Fenil	
59	H	3-Cl- fenil	$CONH(CH_2)_2$ piridin -3-il

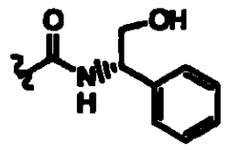
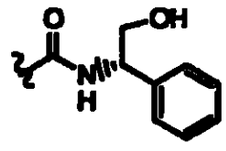
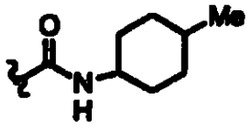
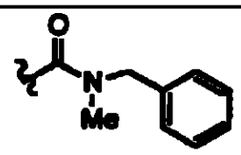
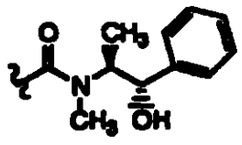
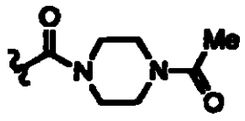
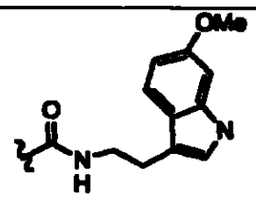
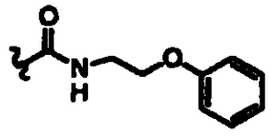
No. III-a-	R^3U_n	T_mR^1	Q-R^2
60	H	3-Me- fenil	
61	H	2-F-3-Cl- fenil	
62	H	2-F-3-Cl- fenil	
63	H	2-F-3-Cl- fenil	
64	H	Fenil	
65	H	3,4- $(CH_3O)_2$- fenil	
66	H	2-F-3-Cl- fenil	
67	H	3,4- $(CH_3O)_2$- fenil	
68	H	3-Cl- fenil	

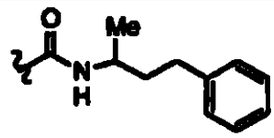
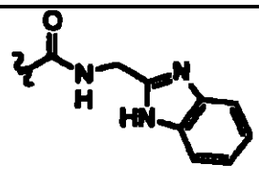
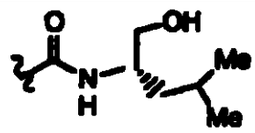
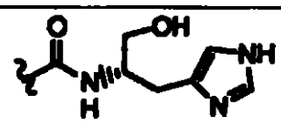
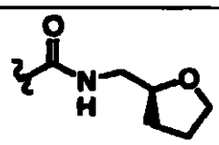
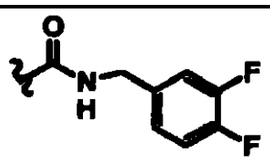
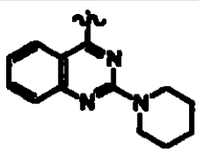
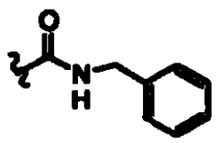
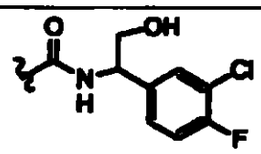
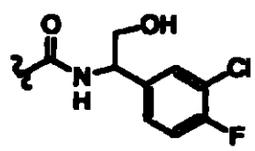
No. III-a-	R^3U_n	T_mR^1	Q-R^2
69	H	3-Me- fenıl	
70	H	3,4- $(CH_3O)_2$- fenıl	
71	H	Fenil	CO (pırrolıdın -1-il)
72	H	3-Cl- fenil	CO (morfolin -4-il)
73	H	Metıl	$CONHCH_2Ph$
74	H	Metil	$CONHCH_2$ (3,4-F_2- fenıl)
75	H	Metıl	
76	H	Metil	$CONHCH_2$ (4-F- fenil)
77	H	Metil	$CONHCH_2$ (3-Cl- fenil)
78	H	Metıl	$CONHCH_2$ (4-Ome- fenil)
79	H	Metil	$CONHCH_2$ (3-Cl, 4-F- fenıl)
80	H	Metil	
81	H	Metıl	
82	H	Metil	
83	H	Metil	

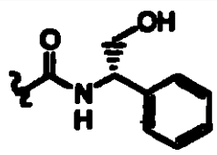
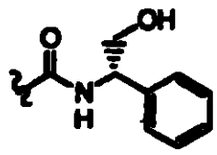
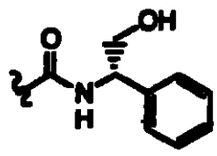
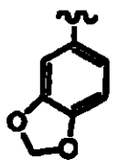
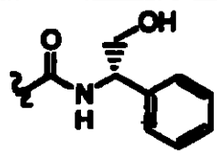
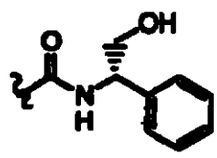
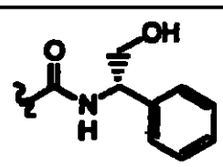
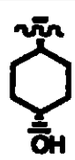
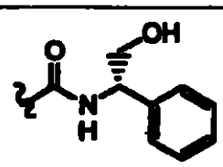
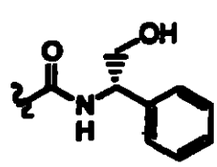
No. III-a-	R^3U_n	T_mR^1	Q-R^2
84	H	NH_2	
85	H	$NHCH_3$	
86	H	$NHC(O)CH_3$	
87	H	$NHC(O)NHCH_3$	
88	H	OH	
89	H	CH_2NHCH_3	
90	H	CH_2OH	
91	N-ciclohexilo	$NHC(O)NHCH_3$	

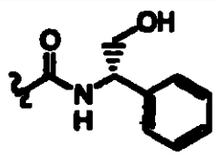
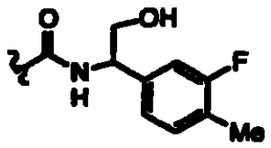
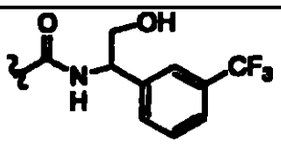
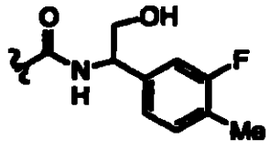
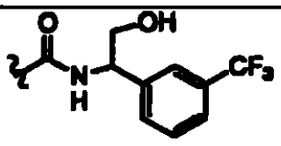
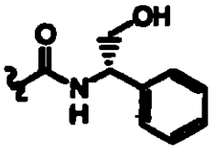
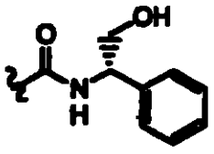
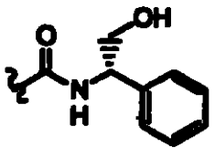
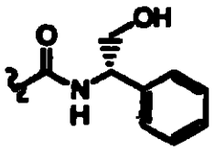
No. III-a-	R^3U_n	T_mR^1	Q-R^2
92	$C(O)CH_3$	$NHC(O)NHCH_3$	
93	SO_2CH_3	OH	
94	H	SO_2CH_3	
95	H	CH_2OH	
96	ciclohexilo	CH_3	
97	H	3,5-Cl_2- fenil	$CONHCH_2$ piridin -4-il
98	fenil	3,5-Cl_2- fenil	$CONHCH_2$ (3-CF_3- fenil)
99	H	3,5-Cl_2- fenil	
100	H	3,5-Cl_2- fenil	
101	H	3,5-Cl_2- fenil	

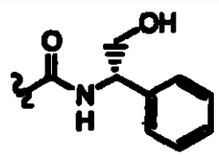
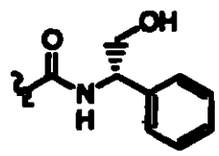
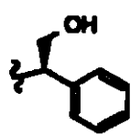
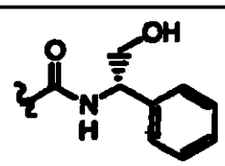
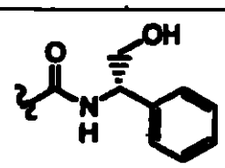
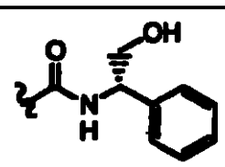
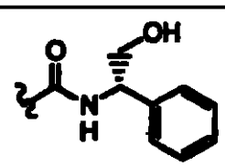
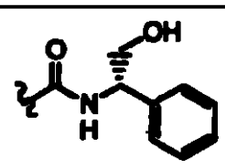
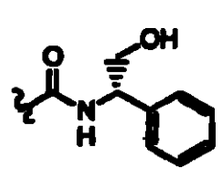
No. III-a-	R^3U_n	T_mR^1	Q-R^2
102	H	3,5-Cl_2- fenil	
103	fenil	3,5-Cl_2- fenil	
104	fenil	3,5-Cl_2- fenil	
105	H	3-F, 5-CF_3- fenil	
106	H	n-propil	CONH$(CH_2)_2$ piridin -3-il
107	H	Metil	CONH$(CH_2)_2$ piridin -3-il
108	metil	Metil	CONH$(CH_2)_2$ piridin -3-il
109	metil	H	CONH$(CH_2)_2$ piridin -3-il
110	etil	Metil	CONH$(CH_2)_2N(CH_3)_2$
111	fenil	Metil	CONH$(CH_2)_2CH_3$
112	fenil	Metil	CONH$(CH_2)_3$fenil
113	etil	Metil	
114	etil	Metil	
115	etil	H	CONHCH_2 (2-CF_3- fenil)

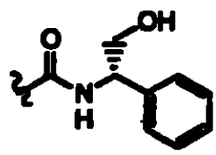
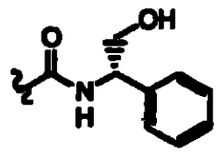
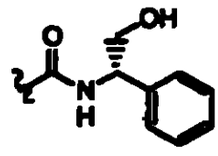
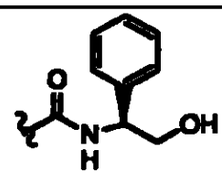
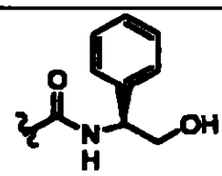
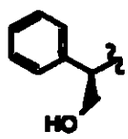
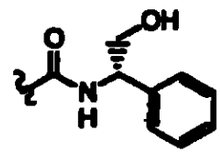
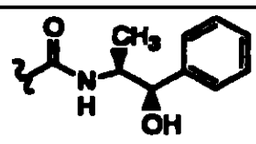
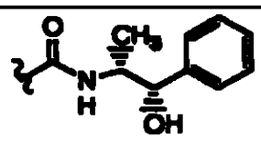
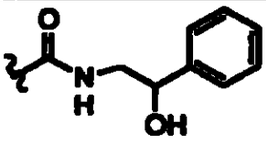
No. III-a-	R^3U_n	T_mR^1	Q-R^2
116	fenil	Metil	
117	etil	Metıl	
118	etil	H	
119	fenil	Etil	$CONHCH(CH_3)_2$
120	fenil	Metıl	$CONH(CH_2)_2NH_2$
121	H	H	
122	H	H	
123	etil	Metıl	
124	etil	Metil	$CONH(CH_2)_3$ fenil
125	H	Etil	
126	fenıl	Metil	

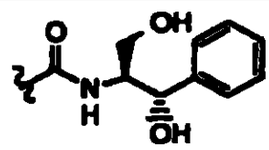
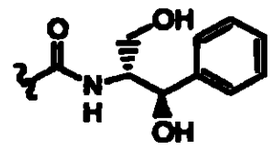
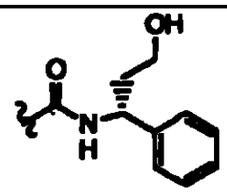
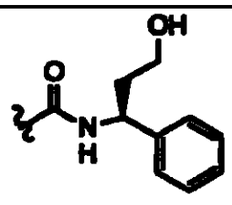
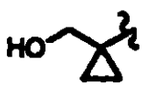
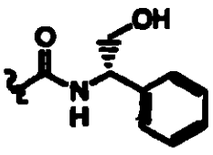
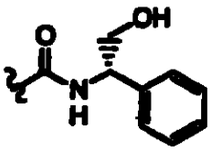
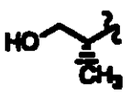
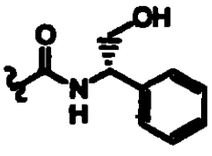
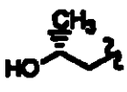
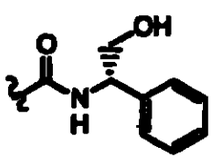
No. III-a-	R^3U_n	T_mR^1	Q-R^2
127	fenil	Metil	
128	Metil	Metil	
129	Metil	Metil	
130	Fenil	Metil	
131	H	Metil	
132	$(CH_2)_2N(Et)_2$	Metil	
133		Metil	
134	Metil	Metil	
135	Fenil	Metil	

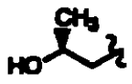
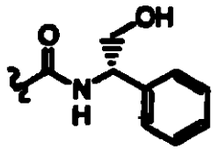
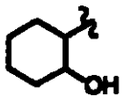
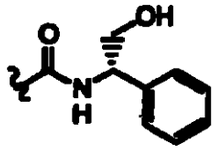
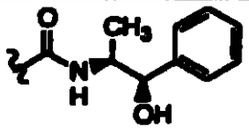
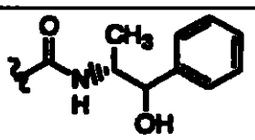
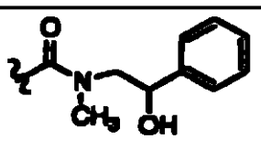
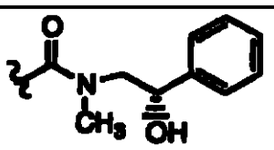
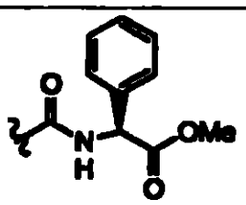
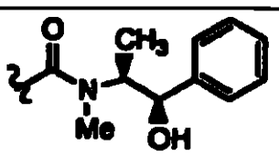
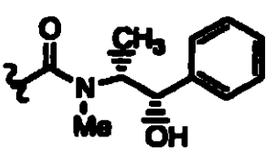
No. III-a-	R^3U_n	T_mR^1	Q-R^2
136	3-F-fenil	Metil	
137	3-OMe-fenil	Metıl	
138	3-OH-fenil	Metil	
139		Metil	
140	4- SO_2NH_2- fenil	Metil	
141	3-OBn- fenıl	Metil	
142		Metil	
143	Fenil	Ciclohexilo	

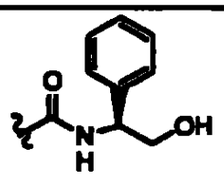
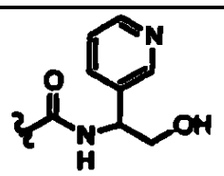
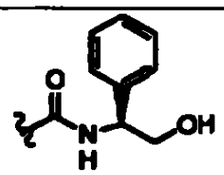
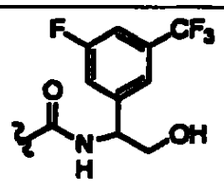
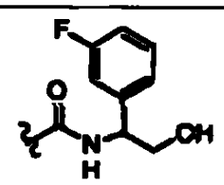
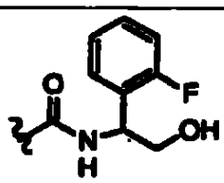
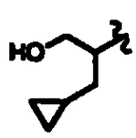
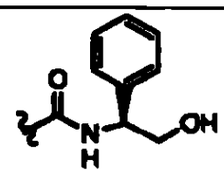
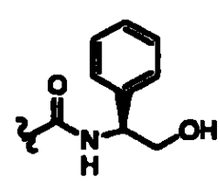
No. III-a-	R^3U_n	T_mR^1	Q-R^2
144	Fenil	Ciclopropilo	
145	Fenıl	Metıl	
146	Fenil	Metil	
147	3-F- fenil	Metil	
148	3-F- fenil	Metil	
149	3-CF_3- fenil	Metil	
150	CH_2 fenıl	Metil	
151	3,4-Me_2- fenil	Metil	
152	4-Obn- fenil	Metil	

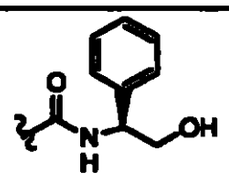
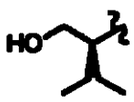
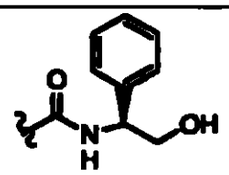
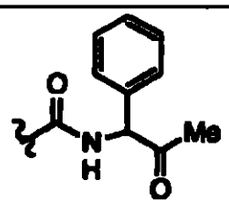
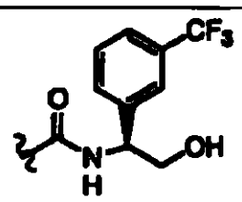
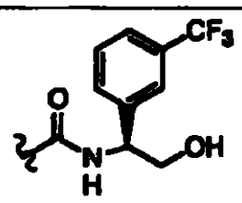
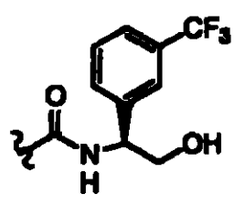
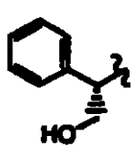
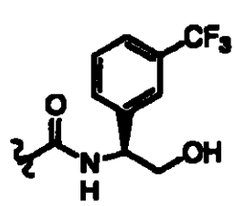
No. III-a-	R^3U_n	T_mR^1	Q-R^2
153	$CH(CH_3)_2$	Metil	
154	CH_2CF_3	Metil	
155		Metil	
156	2-Ome- fenil	Metil	
157	4-OCF_3- fenil	Metil	
158	$CH_2CH(CH_3)_2$	Metil	
159	CH_2ciclopropil	Metil	
160	fenil	CH_2OCH_3	

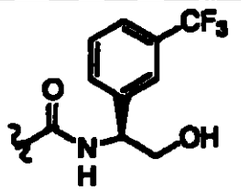
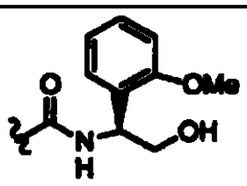
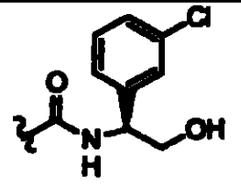
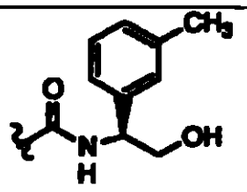
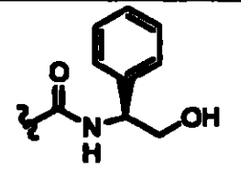
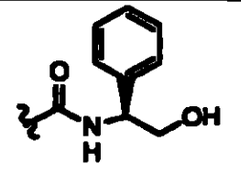
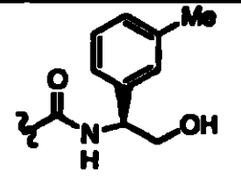
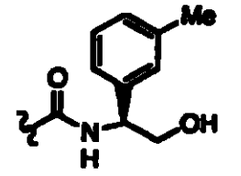
No. III-a-	R^3U_n	T_mR^1	Q-R^2
161	H	CH_2OCH_3	
162	Ciclopropilo	Metil	
163	$(CH_2)_2CH_3$	Metil	
164	Fenil	CH_2OCH_3	
165	Fenil	CH_2OH	
166		Metil	
167	Etil	Metil	
168	Etıl	Metil	
169	Etil	Metil	

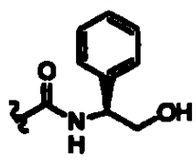
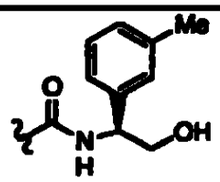
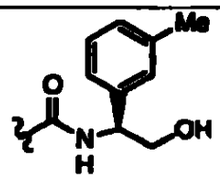
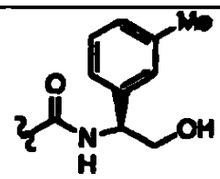
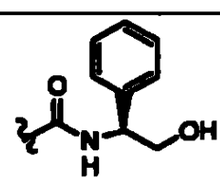
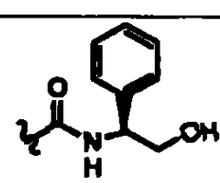
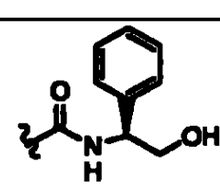
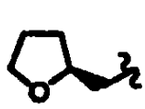
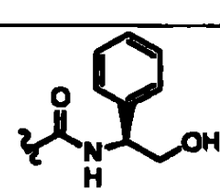
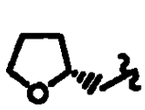
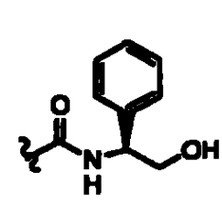
No. III-a-	R^3U_n	T_mR^1	Q-R^2
170	Etil	Metil	
171	Etil	Metil	
172	Etil	Metil	
173	Etil	Metil	
174		Metil	
175	CH_2CH_2OH	Metil	
176		Metil	
177		Metil	

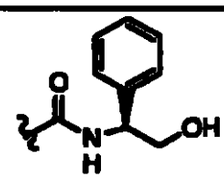
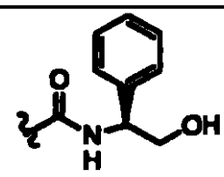
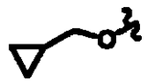
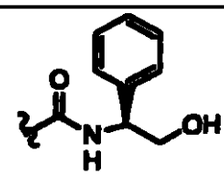
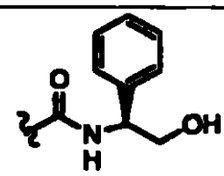
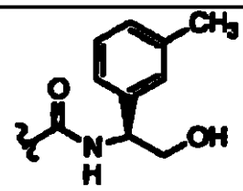
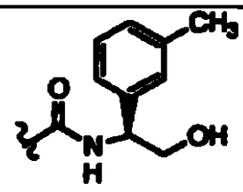
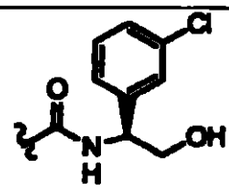
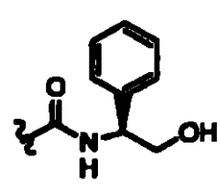
No. III-a-	R^3U_n	T_mR^1	Q-R^2
178		Metil	
179		Metil	
180	H	H	
181	H	H	
182	H	H	
183	H	H	
184	Etil	Metil	
185	H	H	
186	H	H	

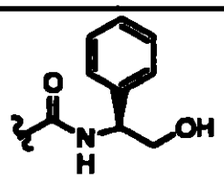
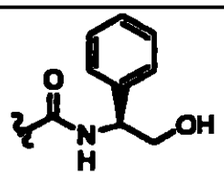
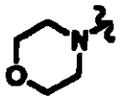
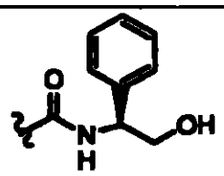
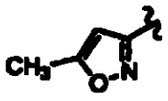
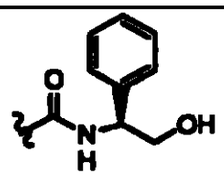
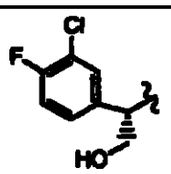
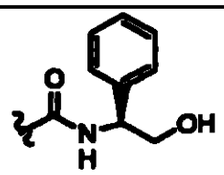
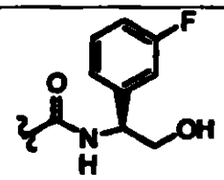
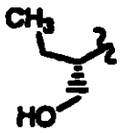
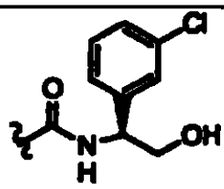
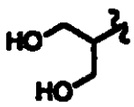
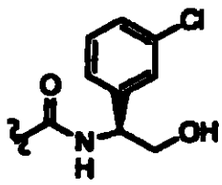
No. III-a-	R^3U_n	T_mR^1	Q-R^3
187	Etil	CH_2OCH_3	
188	Etil	Metil	
189	Etil	CH_2OH	
190	Etil	Metil	
191	Etilo	Metil	
192	Etil	Metil	
193		Metil	
194	2,3- Me_2- fenil	Metil	

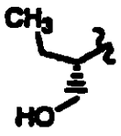
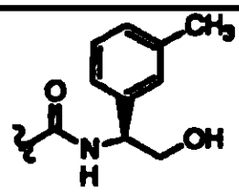
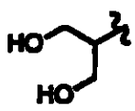
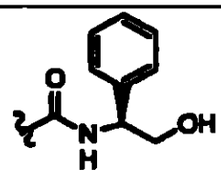
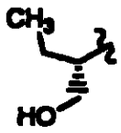
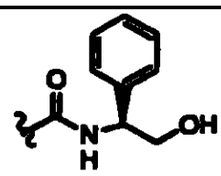
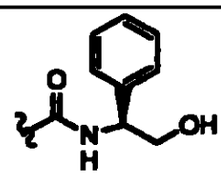
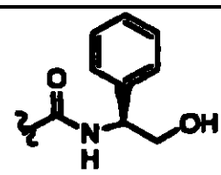
No. III-a-	R^3U_u	T_tR^1	Q-R^2
195	OCH_2CH_3	Metil	
196		Metil	
197	Etil	Metil	
198	Etil	Metil	
199	3-fluorofenil	Metil	
200	2-Cl- fenil	Metil	
201		Metil	

No. III-a-	R^3U_n	T_mR^1	Q-R^2
202	Ciclopropil	Metil	
203	Ciclopropil	Metil	
204	Cıclopropil	Metil	
205	Ciclopropil	Metil	
206	O-Me	Metıl	
207	O-isopropil	Metil	
208	3-N(Me)$_2$ fenil	Metil	
209	2-OH- fenil	Metıl	

No. III-a-	R^3U_n	T_mR^1	Q-R^2
210		Metil	
211	2,3-Me_2- fenil	Metil	
212	3-fluoro- fenil	Metil	
213	Acetil	Metil	
214	2-Me- fenil	Metil	
215	Piridin -3-il	Metil	
216		Metil	
217		Metil	

No. III-a-	R^3U_n	T_mR^1	Q-R^2
218	NC(O)OEt	Metil	
219	CH_2piridin -3-il	Metil	
220		Metil	
221	Isoxazol-3-il	Metil	
222		Metil	
223	2-Me- fenil	Metil	
224	2-Me- fenil	Metil	
225	$O(CH_2)_2OH$	Metil	

No. III-a-	R^3U_n	T_mR^1	Q-R^2
226	$N(Me)_2$	Metil	
227	2-CF_3- fenil	Metil	
228		Metil	
229		Metil	
230		Metil	
231	Fenil	Metil	
232		Metil	
233		Metil	

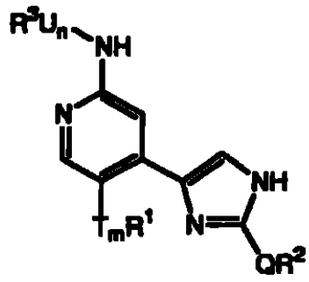
No. III-a-	R^3U_n	T_mR^1	Q-R^2
234		Metil	
235		Metil	
236		Metil	
237		Metil	
238	CN	Metil	

[A] Los nombres de los compuestos para los compuestos de la fórmula III-a mostrados anteriormente en la Tabla 1 son establecidos adelante en el Apéndice A.

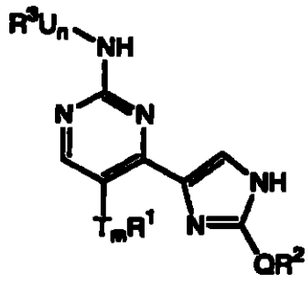
Los anteriores compuestos de la fórmula III-a son aquellos en donde el Anillo A es un anillo pirimidina y Sp es un anillo pirrol Los inhibidores de la fórmula I en donde el Anillo A es un anillo piridina, pirimidina, o triazina que tiene los otros anillos mostrados anteriormente, son de otra manera estructuralmente

similares a los compuestos de la fórmula III-a y son representados por las siguientes formulas generales II-b a II-j, III-b a III-j, y IV-b a IV-j mostrados a continuación en la Tabla 2

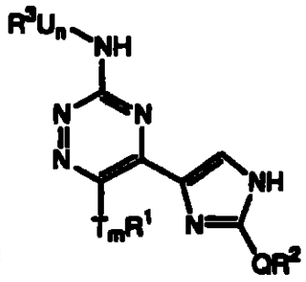
Tabla 2



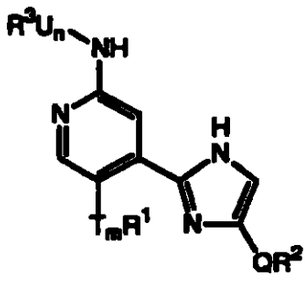
II-b



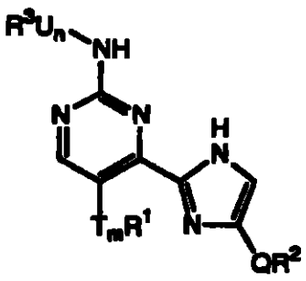
III-b



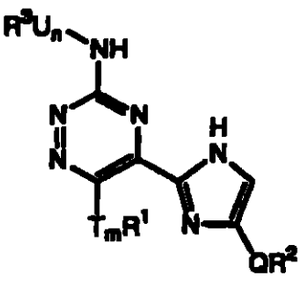
IV-b



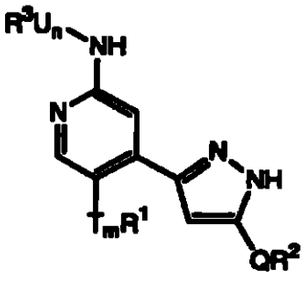
II-b'



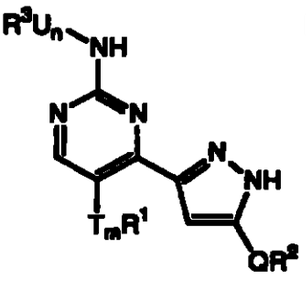
III-b'



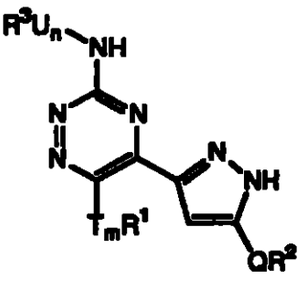
IV-b'



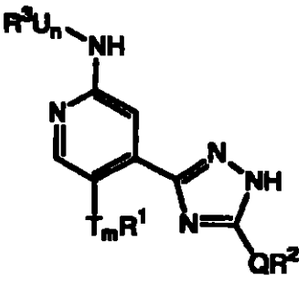
II-c



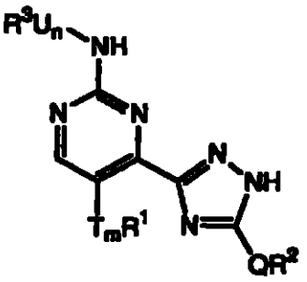
III-c



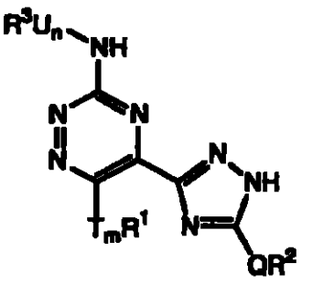
IV-c



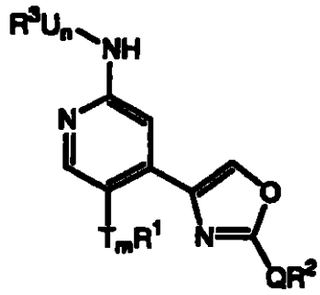
II-d



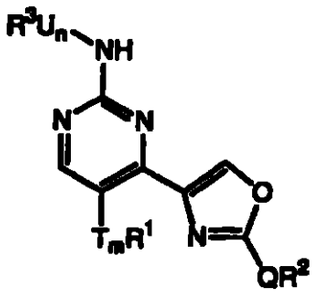
III-d



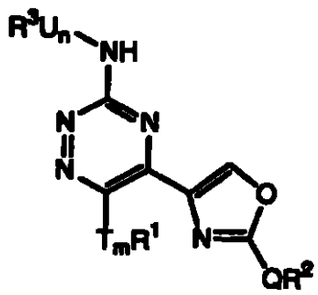
IV-d



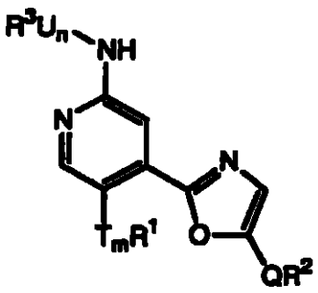
II-e



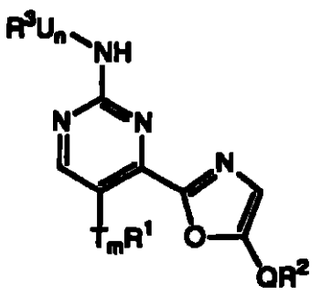
III-e



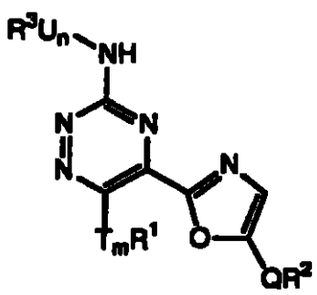
IV-e



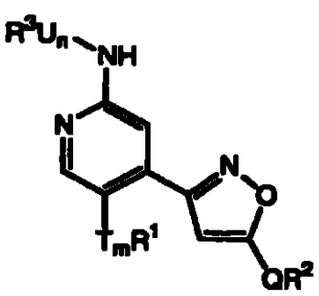
II-e'



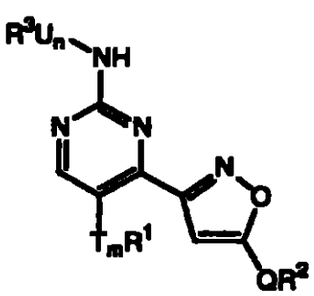
III-e'



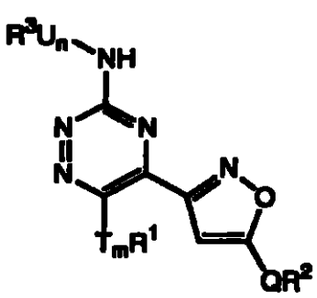
IV-e'



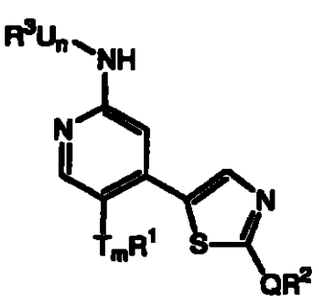
II-f



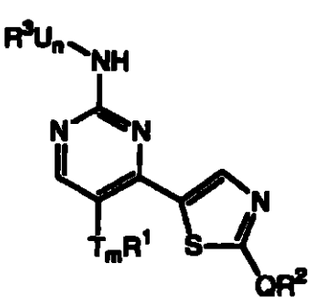
III-f



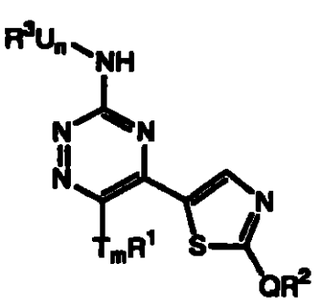
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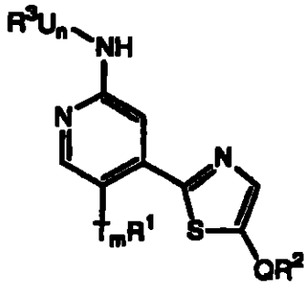
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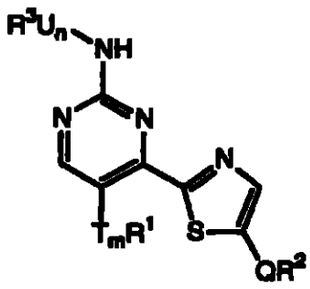
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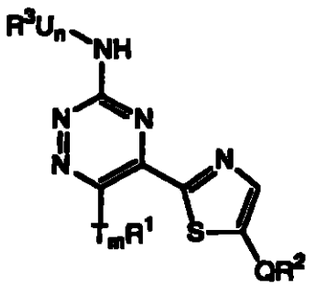
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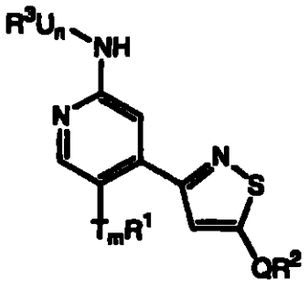
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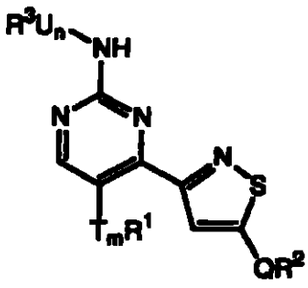
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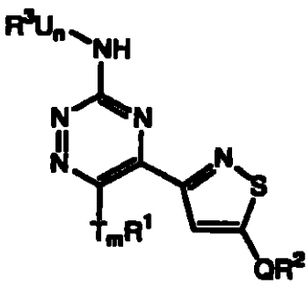
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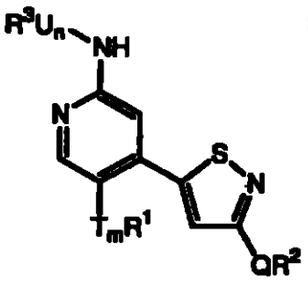
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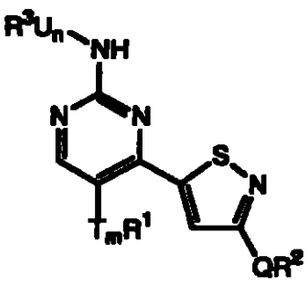
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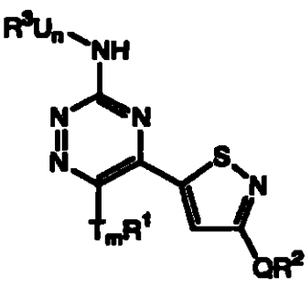
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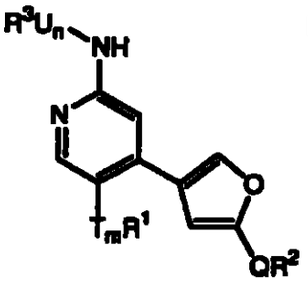
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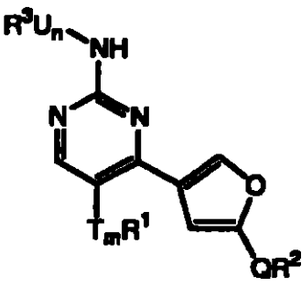
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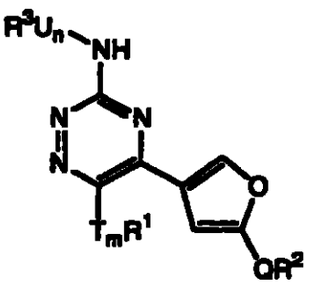
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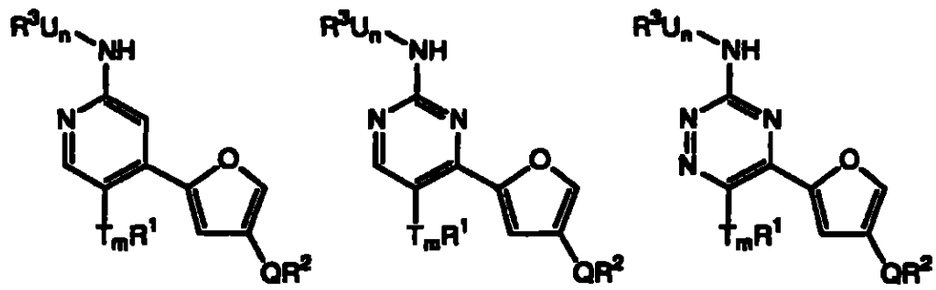
II-i



III-i



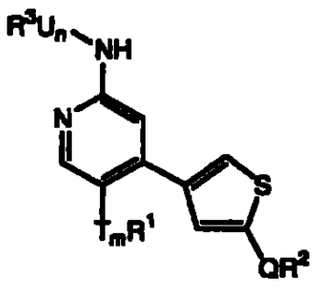
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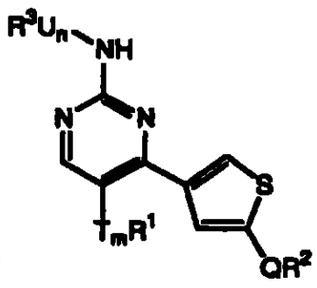
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III-i'

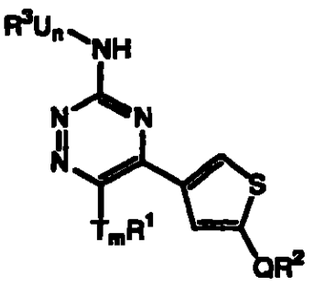
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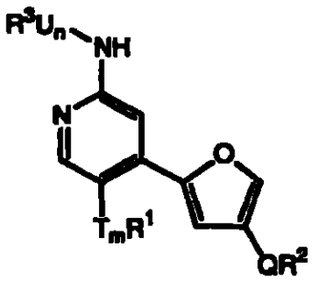
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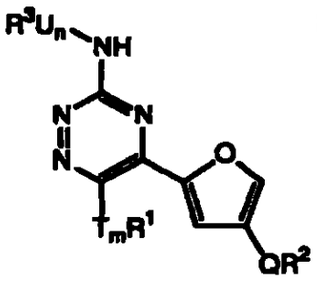
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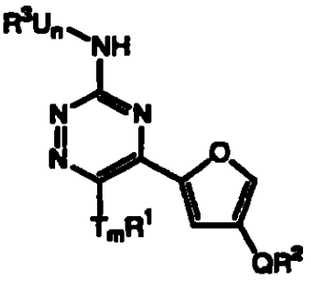
IV-j



II-j'



III-j'



IV-j'

Los compuestos mostrados anteriormente en la Tabla 2 son estructuralmente similares a los compuestos de la fórmula III-a en donde el anillo pirrol de la fórmula III-a es reemplazado por cada uno de los siguientes anillos Sp imidazol (b), pirazol (c), triazol (d), oxazol (e), isoxazol (f), 1,3-tiazol (g), 1,2-tiazol (h), furano (i), y tiofeno (j)

Por consiguiente, Los grupos QR^2, T_mR^1, y U_nR^3 preferidos de los compuestos mostrados anteriormente en la Tabla 2 son como se describieron anteriormente para los compuestos de la fórmula **III-a**

En otra realización, esta invención proporciona una composición farmacéuticamente aceptable que comprende un compuesto mostrado anteriormente en la Tabla 2 y un portador farmacéuticamente aceptable

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la ERK2, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto mostrado anteriormente en la Tabla 2 o de una composición farmacéuticamente aceptable que comprende dicho compuesto.

Otro aspecto de esta invención se relaciona con un método para inhibir la actividad de ERK2 en un paciente, método que comprende la administración al paciente de un compuesto mostrado anteriormente en la Tabla 2 o de una composición farmacéuticamente aceptable que comprende dicho compuesto

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la Aurora-2, método que comprende la administración a un

paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto mostrado anteriormente en la Tabla 2 o de una farmacéuticamente aceptable que comprende dicho compuesto.

Otro aspecto de esta invención se relaciona con un método para inhibir la actividad de la Aurora-2 en un paciente, método que comprende la administración al paciente de un compuesto mostrado anteriormente en la Tabla 2 o de una composición farmacéuticamente aceptable que comprende dicho compuesto

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la GSK-3, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto mostrado anteriormente en la Tabla 2 o de una farmacéuticamente aceptable que comprende dicho compuesto.

Un aspecto de esta invención se relaciona con un método para incrementar la síntesis de glicógeno y/o disminuir los niveles sanguíneos de glucosa en un paciente con necesidad del mismo, método que comprende la administración al paciente de una cantidad terapéuticamente efectiva de un compuesto mostrado anteriormente en la Tabla 2 o de una composición farmacéuticamente aceptable que comprende dicho

compuesto. Este método es especialmente útil para pacientes diabéticos. Otro método se relaciona con la inhibición de la producción de la proteína Tau hiperfosforilada, el cual es útil en detener o hacer más lento el progreso de la enfermedad de Alzheimer. Otro método se relaciona con la inhibición de la fosforilación de la β-catenina, el cual es útil para el tratamiento de la esquizofrenia

Otro aspecto de esta invención se relaciona con un método para inhibir la actividad de la GSK-3 en un paciente, método que comprende la administración al paciente de un compuesto mostrado anteriormente en la Tabla 2 o una composición farmacéuticamente aceptable que comprende dicho compuesto.

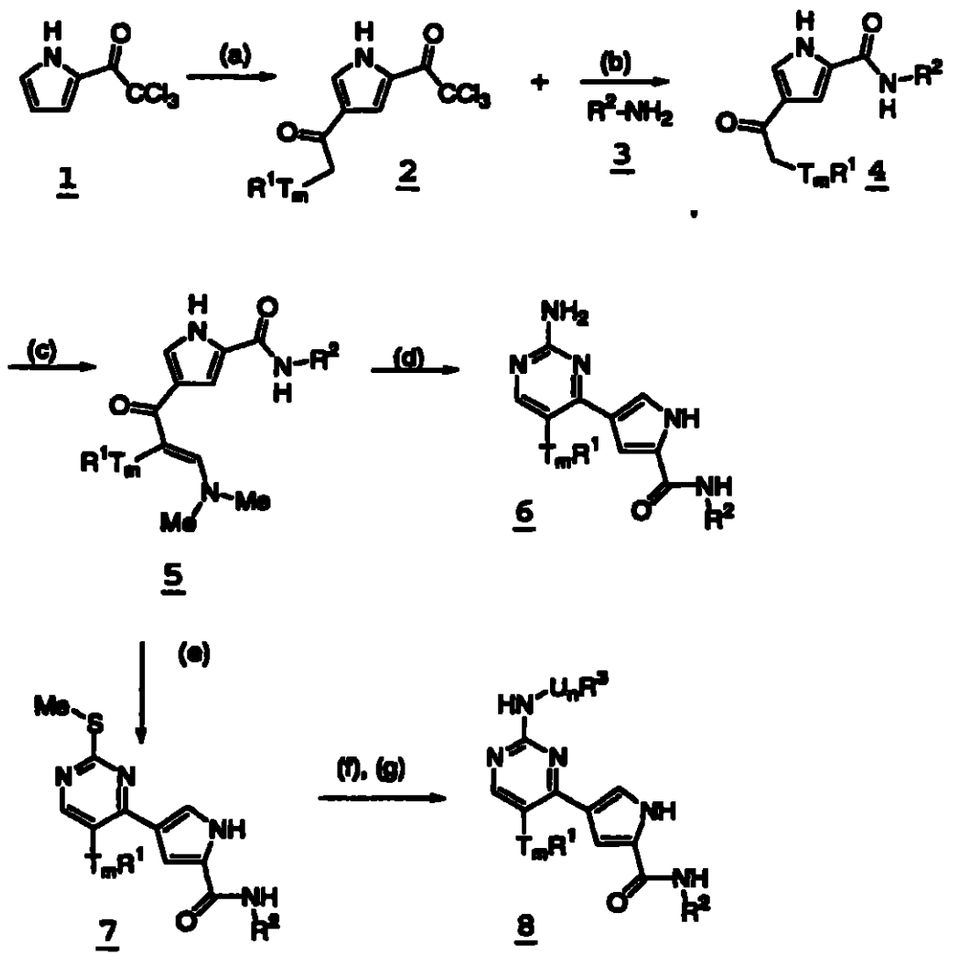
Otro método se relaciona con la inhibición de la actividad de la ERK2, la Aurora-2, o la GSK-3 en una muestra biológica, método que comprende contactar la muestra biológica con un compuesto mostrado anteriormente en la Tabla 2, o con una composición farmacéuticamente aceptable del mismo, en una cantidad efectiva para inhibir la ERK2, la Aurora-2, o la GSK-3.

Cada uno de los métodos anteriormente mencionados dirigidos a la inhibición de la ERK2, la Aurora-2 o la GSK-3, o al tratamiento de una enfermedad aliviada de ese modo, es preferiblemente llevado a cabo con un compuesto

preferido mostrado anteriormente en la Tabla 2, como se describió anteriormente.

Los compuestos de la presente invención pueden ser preparados en general por medio de métodos conocidos por aquellas personas versadas en la materia para compuestos análogos, como se ilustra en los Esquemas generales I a XII y en los ejemplos sintéticos mostrados más adelante

Esquema I



Reactivos y condiciones: (a) $T_nR^1CH_2COCl$, $AlCl_3$, CH_2Cl_2, 2 horas, RT, (b) DMF, 24 horas, temperatura ambiente, (c) $(Me_2N)_2CHOt$-Bu, THF, 24 horas, temperatura ambiente; (d) guanidina, EtOH, 12 horas, reflujo, (e) tiourea, EtOH, K_2CO_3, 12 horas reflujo; (f) *m*-CPBA, EtOH ; (g) U_nR^3-NH_2, DMSO, 130 °C.

El anterior esquema I muestra una ruta sintética general que es empleada para preparar los compuestos pirrol-3-il de la fórmula **III-a** de esta invención cuando R^2 es un grupo fenilo substituido de manera opcional o un grupo alifático. En la etapa (a), un cloruro ácido substituido de manera opcional es combinado con el compuesto 1, diclorometano, y tricloruro de aluminio para formar el compuesto 2. En los casos en donde se emplean cloruros de ácidos de benzoilo, una amplia variedad de substituyentes en el anillo fenilo son sensibles a esta reacción. Los cloruros de ácidos alifáticos son también empleados en muchos casos

Los ejemplos de los grupos R^2 adecuados incluyen, pero no se limitan a, aquellos establecidos en la anterior Tabla 1.

La formación de la amida 4 es llevada a cabo por medio del tratamiento del compuesto 2 con una amina 3 en DMF Cuando la amina 3 es una amina primaria, la reacción procede a temperatura ambiente. Cuando la amina 3 es una amina secundaria, la reacción es calentada a 50 °C para

conseguir una reacción completa y proporcionar la amida 4

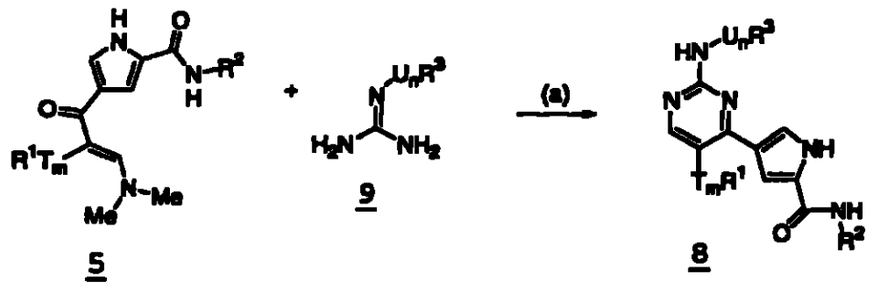
La formación de la enamina 5 en la etapa (c) es llevada a cabo por medio del tratamiento de la amida 4 con $(Me_2N)_2$-CHOt-Bu a temperatura ambiente De manera alternativa, la reacción para formar la enamina 5 en la etapa (c) es también llevada a cabo por medio del empleo de dimetilformamida-dimetilacetal (DMF-DMA) La reacción que emplea DMF-DMA típicamente requiere temperatura elevada para proporcionar la enamina 5 mientras que el empleo de $(Me_2N)_2$-OtBu tiene la ventaja de proceder a temperatura ambiente para proporcionar la enamina 5 con una pureza más alta

La formación del compuesto pirimidina 6 en la etapa (d) es llevado a cabo por medio del tratamiento de la enamina 5 con guanidina a temperatura elevada. De manera alternativa, el empleo de una guanidina substituida resulta en un substituyente amino como se ilustra por medio de 8.

Como un método alternativo, en la etapa (e), el intermediario 5 puede ser ciclizado con S-metil tiourea para formar la 2-tiometilpirimidina 7 que puede a su vez ser oxidada con m-CPBA a la sulfona El grupo sulfonilo puede ser subsecuentemente desplazado por una amina para generar la aminopirimidina substituida 8.

Los compuestos de la fórmula III-a sintetizados por medio de este método, como se ejemplifican en la Tabla 1, fueron aislados por medio de HPLC preparativa (fase reversa, 10 → 90% MeCN en agua durante 15 minutos) Los detalles de las condiciones empleadas para producir estos compuestos son establecidos más adelante en los ejemplos.

Esquema II

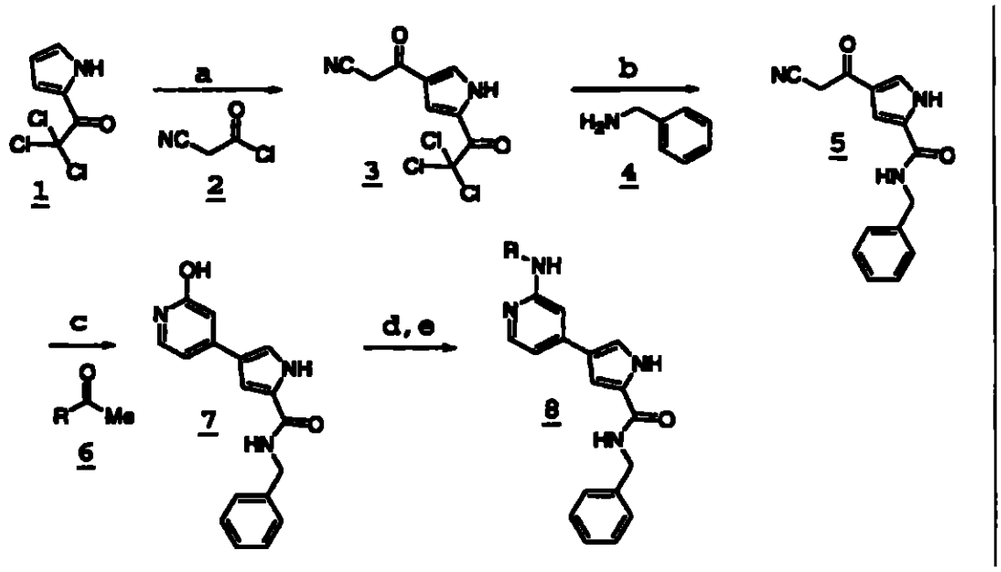


Reactivos y condiciones· (a) K_2CO_3, DMA, 100 °C.

El anterior esquema II muestra un método general para la preparación de los compuestos 8 a partir del intermediario 5 y una guanidina *N*-substituida (9). El intermediario 5 puede ser preparado de acuerdo con las etapas (a), (b), y (c) del Esquema I mostrado anteriormente El compuesto 5 es tratado con guanidina *N*-substituida (9) y carbonato de potasio en dimetilacetamida para formar el compuesto 8 Esta reacción es sensible a una variedad de guanidinas *N*-substituidas para formar los compuestos de la fórmula III-a Los detalles de las condiciones empleadas para

producir estos compuestos son establecidos adelante en los Ejemplos.

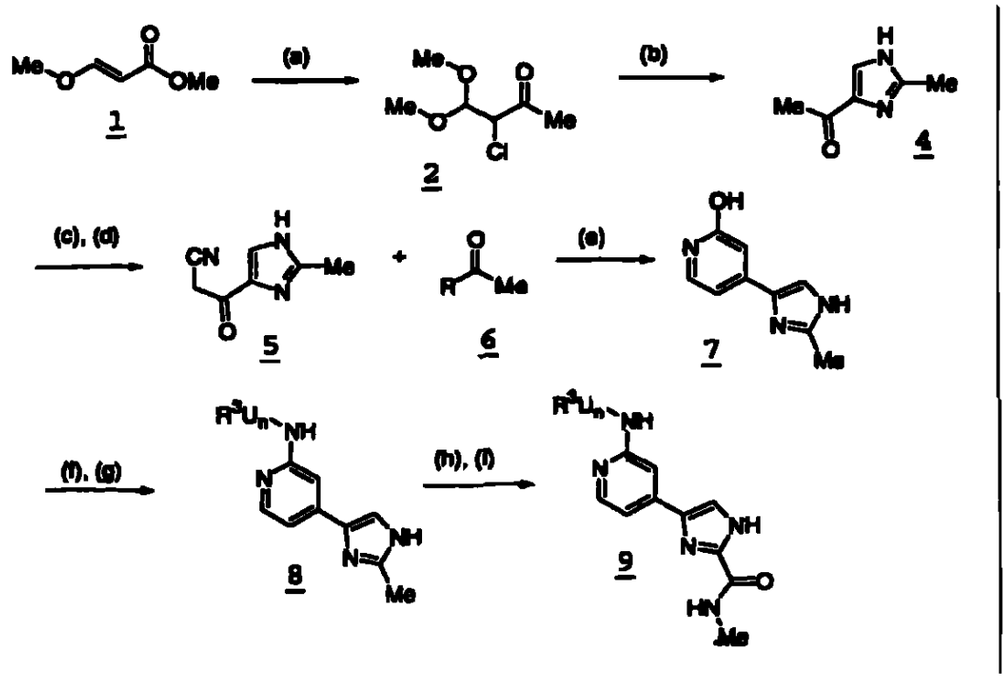
Esquema III



Reactivos y condiciones· (a) $AlCl_3$ solo, RT, (b) DMF, 24 horas, temperatura ambiente, (c) ácido polifosfórico, 1 hora, 25 - 140 °C, (d) $POCl_3$, DMF, reflujo, (e) NH_2-U_nR^3, iPrOH, reflujo.

El anterior Esquema III muestra una ruta sintética general que puede ser empleada para la preparación de los compuestos pirrol-3-il de la fórmula II-a de esta invención. La conversión del intermediario 5 para producir 8 puede ser llevada a cabo a través de las etapas (c), (d), y (e) de acuerdo con el método descrito en JACS, 1957, pp 79

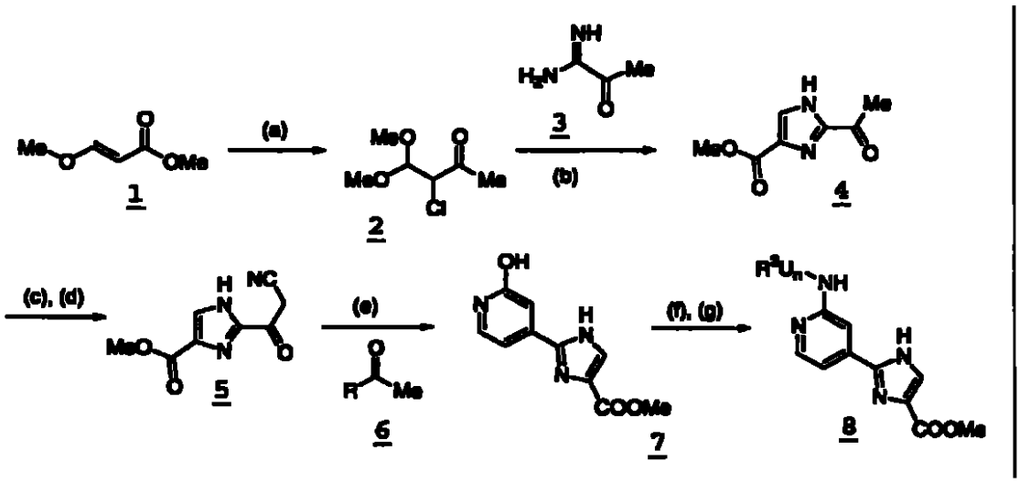
Esquema IV



Reactivos y condiciones: (a) MeOH, piridina, Cl_2; (b) guanidina, (c) bromo, ácido acético, (d) NaCN, DMF, (e) 6, ácido polifosfórico, 1 hora, 25 - 140 °C; (f) $POCl_3$, DMF, reflujo; (g) NH_2-U_nR^3, iPrOH, reflujo, (h) SeO_2; (i) MeNH.

El anterior Esquema IV muestra una ruta sintética general que puede ser empleada para la preparación de los compuestos imidazol-4-il de la fórmula II-b de esta invención. La conversión del intermediario 5 para producir 8 puede ser llevada a cabo a través de las etapas (e), (f), y (g) de acuerdo con el método descrito en JACS, 1957, pp 79

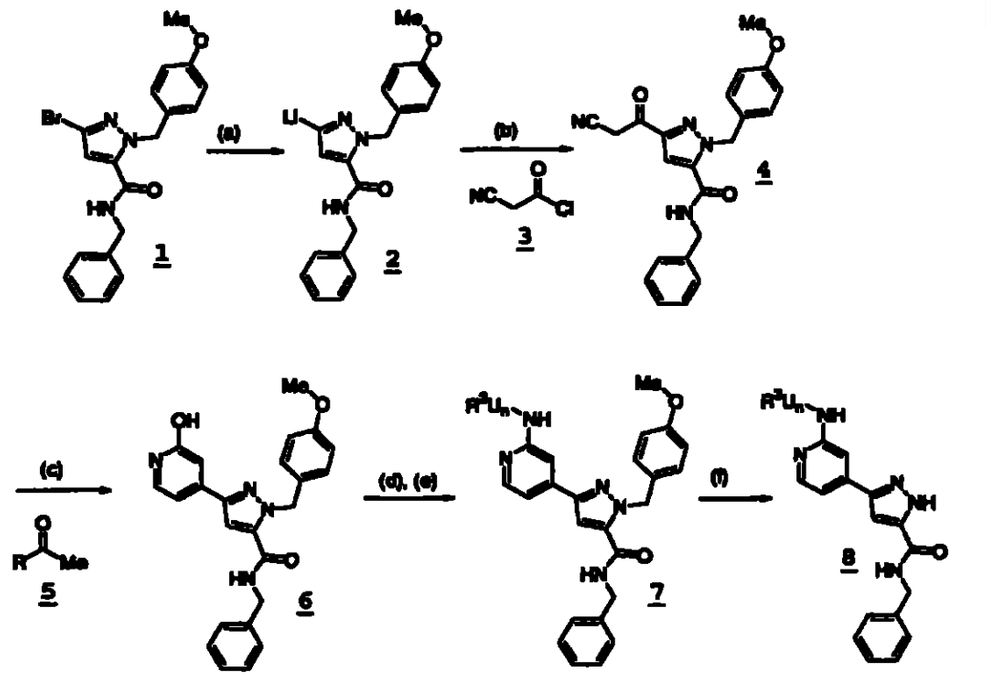
Esquema V



Reactivos y condiciones: (a) MeOH, piridina, Cl_2, (b) 3; (c) bromo, ácido acético, (d) NaCN, DMF, (e) 6, ácido polifosfórico, 1 hora, 25 - 140 °C, (f) $POCl_3$, DMF, reflujo, (g) NH_2-U_nR^3, iPrOH, reflujo.

El anterior Esquema V muestra una ruta sintética general que puede ser empleada para la preparación de los compuestos imidazol-2-il de la fórmula II-b' de esta invención. La conversión del intermediario 5 para producir 8 puede ser llevada a cabo a través de las etapas (e), (f), y (g) de acuerdo con el método descrito en JACS, 1957, pp 79.

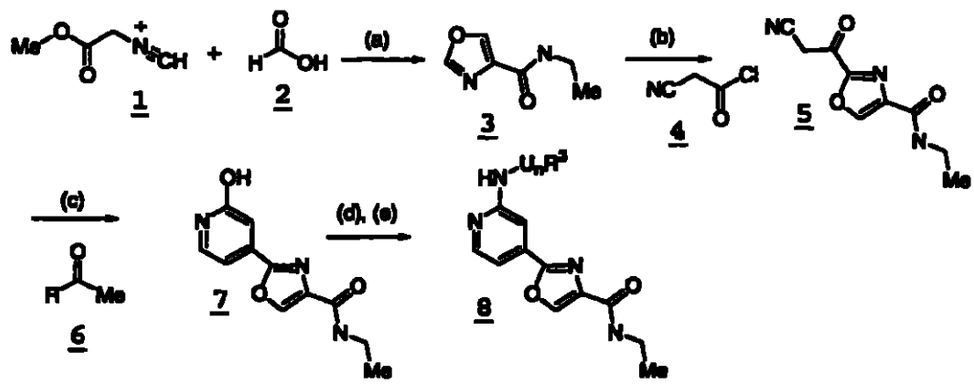
Esquema VI



Reactivos y condiciones (a) (b) 3; (c) 5, ácido polifosfórico, 1 hora, 25 - 140 °C, (d) $POCl_3$, DMF, reflujo, (e) $NH_2U_nR^3$, iPrOH, reflujo, (f) nitrato de amonio cérico.

El anterior Esquema VI muestra una ruta sintética general que puede ser empleada para la preparación de los compuestos pirazol-3-il de la fórmula II-c de esta invención La conversión del intermediario 4 para producir 7 puede ser llevada a cabo a través de las etapas (c), (d), y (e) de acuerdo con el método descrito en JACS, 1957, pp 79

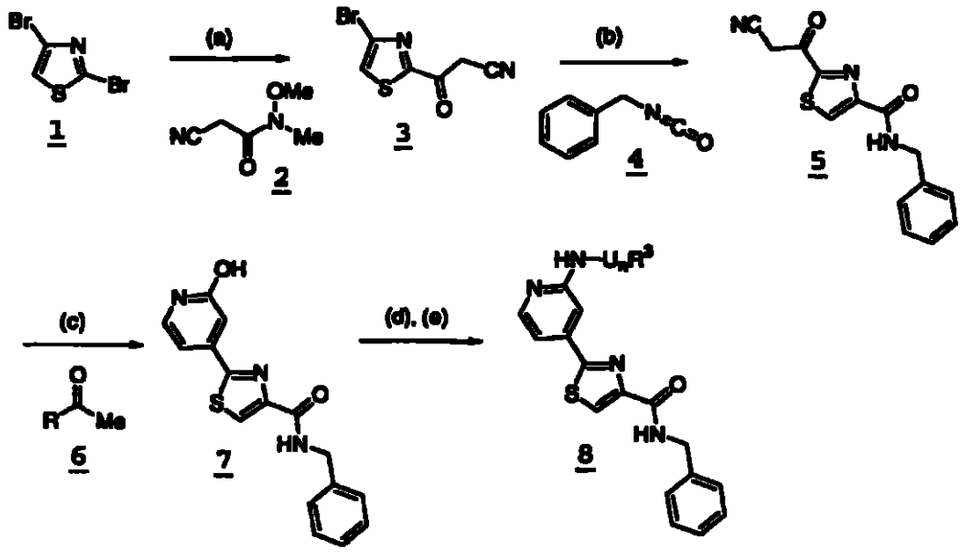
Esquema VII



Reactivos y condiciones· (a) 1,1'-carbonildiimidazol (CDI), trietilamina, THF, (b) N-butillitio, THF, -78 °C, (c) 6, ácido polifosfórico, 1 hora, 25 - 140 °C; (d) $POCl_3$, DMF, reflujo, (e) NH_2-U_nR^3, iPrOH, reflujo.

El anterior Esquema VII muestra una ruta sintética general que puede ser empleada para la preparación de los compuestos oxazol-2-il de la fórmula II-e' de esta invención La conversión del intermediario 5 para producir 8 puede ser llevada a cabo a través de las etapas (c), (d), y (e) de acuerdo con el método descrito en JACS, 1957, pp 79

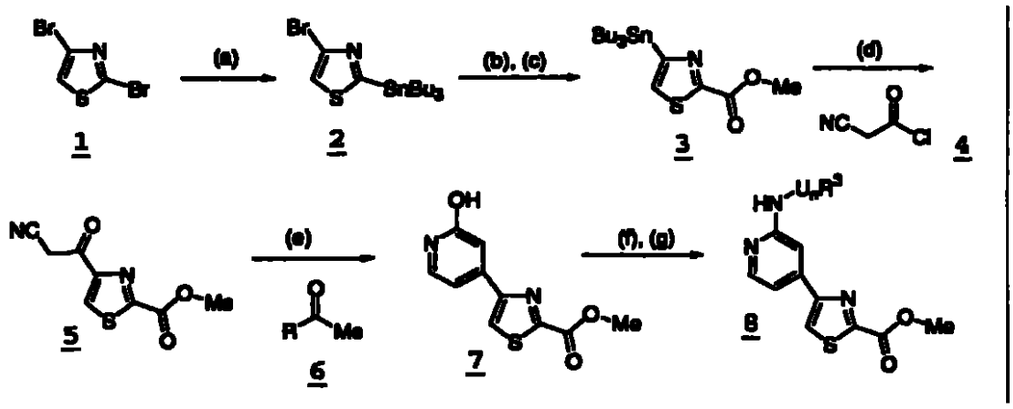
Esquema VIII



Reactivos y condiciones: (a) N-butillitio, TMEDA, -78 °C (b) t-butillitio, THF, -78 °C (c) 6, ácido polifosfórico, 1 hora, 25 - 140 °C (d) $POCl_3$, DMF, reflujo (e) NH_2-R, iPrOH, reflujo.

El anterior Esquema VIII muestra una ruta sintética general que puede ser empleada para la preparación de los compuestos tiazol-2-il de la fórmula II-g' de esta invención. La conversión del intermediario 5 para producir 8 puede ser llevada a cabo a través de las etapas (c), (d), y (e) de acuerdo con el método descrito en JACS, 1957, pp 79

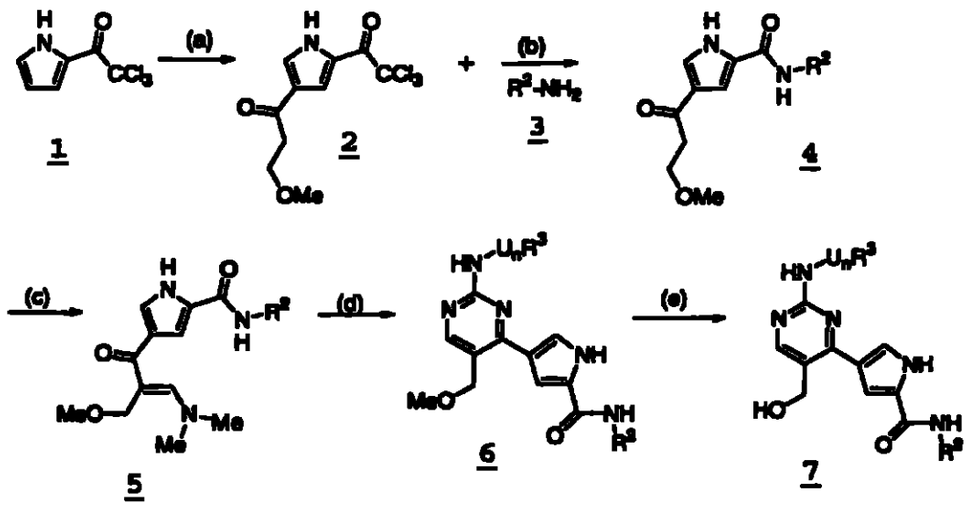
Esquema IX



Reactivos y condiciones (a) N-butillitio, Bu_3SnCl, (b) t-butillitio, THF, -78 °C, (c) $MeOCO_2Me$, (d) 4, Pd(0); (e) 6, ácido polifosfórico, 1 hora, 25 - 140 °C, (f) $POCl_3$, DMF, reflujo; (g) NH_2-UnR^3, iPrOH, reflujo

El anterior Esquema IX muestra una ruta sintética general que puede ser empleada para la preparación de los compuestos tiazol-4-il de la fórmula II-g de esta invención. La conversión del intermediario 5 para producir 8 puede ser llevada a cabo a través de las etapas (e), (f), y (g) de acuerdo con el método descrito en JACS, 1957, pp 79.

Esquema X



Reactivos y condiciones· (a) $CH_3OCH_2CH_2COCl$, $AlCl_3$, CH_2Cl_2, 2.5 horas, RT; (b) DMF, 24 horas, temperatura ambiente, (c) $(Me_2N)_2$-CHO*t*-Bu, THF, 24 horas, temperatura ambiente, (d) guanidina *N*-substituida, EtOH, 12 horas, reflujo, (e) BBr_3, CH_2Cl_2, Na_2CO_3

El anterior Esquema X muestra una ruta sintética general que es empleada para la preparación de los compuestos de la fórmula III-a en donde T_mR^1 es metoximetil o hidroximetil En la etapa (a), el cloruro de 3-metoxipropionilo es combinado con el compuesto 1, diclorometano, y tricloruro de aluminio para formar el compuesto 2

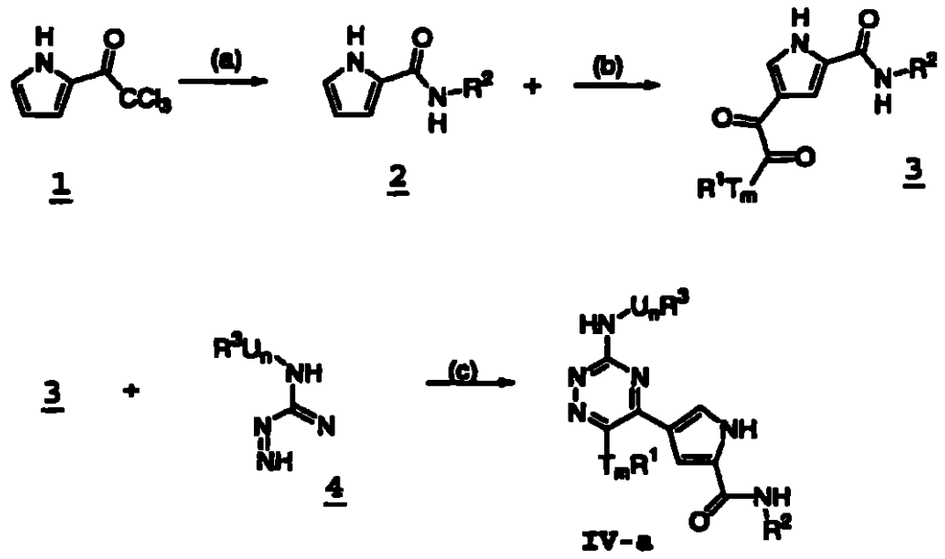
La formación de la amida 4 es llevada a cabo por medio del tratamiento del compuesto 2 con una amina 3 en DMF Cuando la amina 3 es una amina primaria, la reacción procede a temperatura ambiente Cuando la amina 3 era una amina secundaria, la reacción es calentada a 50 °C para conseguir una reacción completa y proporcionar la amida

4. La formación de la enamina 5 en la etapa (c) es llevada a cabo por medio del tratamiento de la amida 4 con $(Me_2N)_2$-CHOt-Bu a temperatura ambiente

La formación del compuesto pirimidina 6 en la etapa (d) es llevada a cabo por medio del tratamiento de la enamina 5 con una guanidina a temperatura elevada De manera alternativa, el empleo de una guanidina substituida resulta en un substituyente amino

Para formar los compuestos en donde T_mR^1 es hidroximetil, el intermediario 6 puede ser tratado con BBr3 en diclorometano para formar los compuestos 7. Una persona versada en la materia reconocería que el grupo hidroximetil del compuesto 7 podría ser además derivatizado para formar una variedad de compuestos de la fórmula III-a Los detalles de las condiciones empleadas para producir estos compuestos son establecidos adelante en los ejemplos

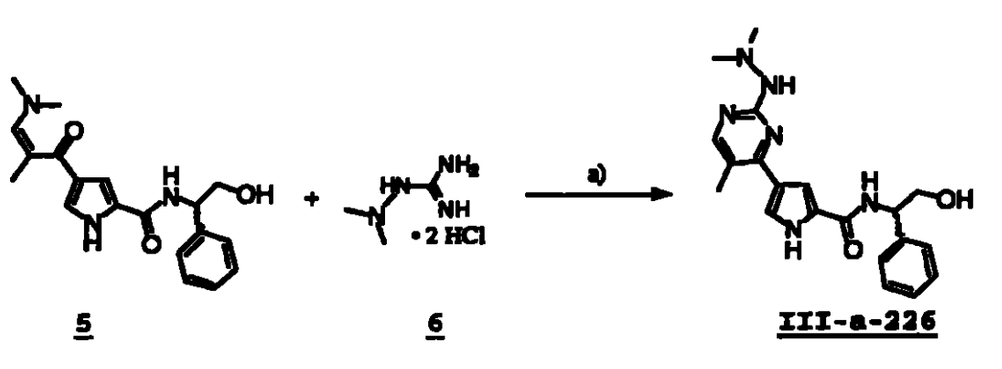
Esquema XI



Reactivos y condiciones (a) R_2NH_2, MeCN, 0 °C a 25 °C, 12 horas, (b) $AlCl_3$, CH_2Cl_2, 25 °C; (c) MeOH : H_20 (2 : 1), 37 °C.

El anterior Esquema XI muestra un método general para la preparación de los compuestos triazina de la fórmula IV-a La etapa (a) es llevada a cabo en la forma descrita en el Esquema I, la anterior etapa (b) La etapa (b) es llevada a cabo en la forma descrita en el Esquema I, la anterior etapa (a). La formación del anillo triazina en la etapa (c) puede ser llevada a cabo de acuerdo con los métodos descritos por Hirsch, J., Petrakova, E , Feather, M. S.; *J Carbohydr Chem* [JCACDM] 1995,14 (8), 1179 - 1186 De manera alternativa, la etapa (c) puede ser llevada a cabo de acuerdo con los métodos descritos por Siddiqui, A U.; Satyanarayana, Y.; Rao, U. M.; Siddiqui, A H , *J Chem Res, Synop* [JRPSDC] 1995 (2), 43

Esquema XII



5 6 III-a-226

Reactivos y condiciones (a) K_2CO_3, DMA, 100 °C, 24 horas.

Empleando la preparación del compuesto III-a-226 a modo de ilustración, el anterior Esquema XII muestra una ruta sintética general que es empleada para la preparación de los compuestos de la fórmula III-a en donde U_n es NR^7 La formación del compuesto pirimidina III-a-226 en la etapa (a) es llevada a cabo por medio del tratamiento de la enamina 5 con una guanidina 6 a temperatura elevada. De manera alternativa, el empleo de una guadinia amino substituida resulta en un substituyente hidrazino

En otra realización, esta invención proporciona una composición farmacéuticamente aceptable que comprende un compuesto de la fórmula I', I", I°, III-a, III-a', o III-a°, y un portador farmacéuticamente aceptable

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la ERK2, método que comprende la administración a un

paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I', I", I°, III-a, III-a', o III-a°, o una composición farmacéuticamente aceptable que comprende dicho compuesto.

Otro aspecto de esta invención se relaciona con un método para inhibir La actividad de la ERK2 en un paciente, método que comprende la administración al paciente de un compuesto de la fórmula I', I", I°, III-a, III-a', o III-a°, o una composición farmacéuticamente aceptable que comprende dicho compuesto.

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la Aurora-2, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I', I", I°, III-a, III-a', o III-a°, o de una composición farmacéuticamente aceptable que comprende dicho compuesto

Otro aspecto de esta invención se relaciona con un método para inhibir La actividad de la Aurora-2 en un paciente, método que comprende la administración al paciente de un compuesto de la fórmula I', I", I°, III-a, III-a', o III-a°, o de una composición farmacéuticamente aceptable que comprende dicho compuesto

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la GSK-3, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I', I", I°, III-a, III-a', o III-a°, o de una composición farmacéuticamente aceptable que comprende dicho compuesto

Un aspecto de esta invención se relaciona con un método para incrementar la síntesis de glicógeno y/o disminuir los niveles sanguíneos de glucosa en un paciente con necesidad del mismo, método que comprende la administración al paciente de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I', I", I°, III-a, III-a', o III-a°, o de una composición farmacéuticamente aceptable que comprende dicho compuesto Este método es especialmente útil para pacientes diabéticos. Otro método se relaciona con la inhibición de la producción de la proteína Tau hiperfosforilada, el cual es útil en detener o hacer más lento el progreso de la enfermedad de Alzheimer. Otro método se relaciona con la inhibición de la fosforilación de la β-catenina, el cual es útil para el tratamiento de la esquizofrenia.

Otro aspecto de esta invención se relaciona con un método para inhibir la actividad de la GSK-3 en un paciente, método que comprende la administración al paciente de un

compuesto de la fórmula I', I", I°, III-a, III-a', o III-a°, o una composición farmacéuticamente aceptable que comprende dicho compuesto.

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la CDK-2, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I', I", I°, III-a, III-a', o III-a°, o una composición farmacéuticamente aceptable que comprende dicho compuesto.

Los términos "enfermedad mediada por la CDK-2" o "condición mediada por la CDK-2", tal como se usan aquí, significan cualquier enfermedad u otra condición nociva en la cual se sabe que la CDK-2 juega un papel Los términos "enfermedad mediada por la CDK-2" o "condición mediada por la CDK-2" también significan aquellas enfermedades o condiciones que son aliviadas por el tratamiento con un inhibidor de la CDK-2. Tales condiciones incluyen, sin limitación, el cáncer, la enfermedad de Alzheimer, la restenosis, la angiogenesis, la glomerulonefritis, el citomegalovirus, el VIH, el herpes, la psoriasis, la aterosclerosis, la alopecia, y las enfermedades autoinmunes tales como la artritis reumatoide Ver Fischer, P M y Lane, D.P., *Current Medicinal Chemistry*, 7, 1213 - 1245 (2000); Mani, S , Wang, C., Wu, K , Francis, R. y Pestell, R., *Exp Opin.*

Invest. Drugs, 9, 1849 (2000); Fry, D.W. y Garrett, M D , *Current Opinion in Oncologic, Endocrine & Metabolic Investigational Drugs*, 2, 40-59 (2000)

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la Lck, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I', I", I°, III-a, III-a', o III-a°, o una composición farmacéuticamente aceptable que comprende dicho compuesto

Los términos "enfermedad mediada por la Lck" o "condición mediada por la Lck", tal como se usan aquí, significan cualquier enfermedad u otra condición nociva en la cual se sabe que la Lck juega un papel Los términos "enfermedad mediada por la Lck" o "condición mediada por la Lck" también significan aquellas enfermedades o condiciones que son aliviadas por el tratamiento con un inhibidor de la Lck. Tales enfermedades o condiciones mediadas por la Lck incluyen, pero no se limitan a, las enfermedades autoinmunes tales como el rechazo de transplantes, las alergias, la artritis reumatoide, y la leucemia Se ha descrito la asociación de la Lck con varias enfermedades [Molina y otros, *Nature*, 357, 161 (1992)].

Otro aspecto de esta invención se relaciona con un método para tratar o prevenir una enfermedad mediada por la AKT3, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I', I", I°, III-a, III-a', o III-a°, o una composición farmacéuticamente aceptable que comprende dicho compuesto.

Los términos "enfermedad mediada por la AKT3" o "condición mediada por la AKT3", tal como se usan aquí, significan cualquier enfermedad u otra condición nociva en la cual se sabe que la AKT3 juega un papel Los términos "enfermedad mediada por la AKT3" o "condición mediada por la AKT3" también significan aquellas enfermedades o condiciones que son aliviadas por el tratamiento con un inhibidor de la AKT Tales enfermedades o condiciones mediadas por la AKT3 incluyen, pero no se limitan a, trastornos proliferativos, cáncer, y trastornos neurodegenerativos. Se ha descrito la asociación de AKT3 con varias enfermedades [Zang, Q. Y , y otros, *Oncogene*, 19 (2000)] y [Kazuhiko, N., y otros, *The Journal de Neuroscience*, 20 (2000)]

Otro método se relaciona con la inhibición de la actividad de la ERK2, de la Aurora-2, de la CDK-2, de la Lck, de la AKT3, o de la GSK-3 en una muestra biológica, método que comprende contactar la muestra biológica con un compuesto de la fórmula I', I", I°, III-a, III-a', o

III-a°, o una composición farmacéuticamente aceptable que comprende dicho compuesto, en una cantidad efectiva para inhibir la ERK2, la Aurora-2, la CDK-2, la Lck, la AKT3, o la GSK-3.

Cada uno de los métodos anteriormente mencionados dirigidos a la inhibición de la ERK2, la Aurora-2, la CDK-2, la Lck, la AKT3, o la GSK-3, o al tratamiento de una enfermedad aliviada de ese modo, es preferiblemente llevado a cabao con un compuesto preferido de la fórmula I', I", I°, III-a, III-a', o III-a°, como se describió anteriormente Más preferiblemente, cada uno de los métodos anteriormente mencionados es llevado a cabo con un compuesto preferido de la fórmula I', I", I°, III-a', o III-a°, y aún más preferiblemente con un compuesto de la fórmula I", I°, III-a', o III-a°

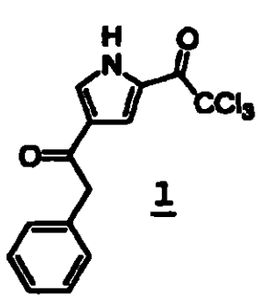
Para que la invención aquí descrita pueda ser más completamente entendida, los siguientes ejemplos son indicados Debe entenderse que estos ejemplos son solo para propósitos ilustrativos y no son para ser interpretados como limitantes de esta invención en cualquier manera.

EJEMPLOS SINTETICOS

Para compuestos en donde el método de HPLC es designado como "A", el siguiente método fue utilizado: un gradiente

de agua · MeCN, 0.1% TFA (95 5 → 0 100) fue corrido durante 22 minutos a 1 mL/min y 214 nm. Para compuestos en donde el método de HPLC es designado como "B", el siguiente método fue utilizado· un gradiente de agua MeCN, 0 1% TFA (90 10 → 0 : 100) fue corrido durante 8 minutos a 1 mL/min y 214 nm. Cada uno de los métodos A y B utilizan la columnaa YMC ODS-AQ 55 120A con unas dimensiones de 3 0 x 150 mm. Tal como se emplea aquí, el término "R_t" hace referencia al tiempo de retención, en minutos, associado con el compuesto que emplea el método de HPLC designado.

Ejemplo 1

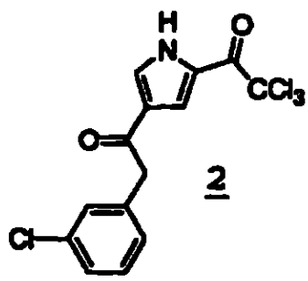


1

2,2,2- Tricloro -1- (4- fenil acetil -1H- pirrol -2- il) etanona (1) : En un frasco seco, el cloruro de fenilacetilo (1 equivalente) fue combinado con 2-tricloroacetil pirrol (1 equivalente) en una cantidad mínima de diclorometano (DCM) para disolver los reactantes A la solución resultante, a temperatura ambiente, se adicionó el tricloruro de aluminio (1 equivalente). Después de 2 horas, la mezcla de reacción

fue aplicada directamente en una columnaa de sílica gel El gradiente de elución con acetato de etilo al 10% hasta acetato de etilo al 50% en hexanos proporcionó el compuesto 1 con un rendimiento del 60% ^{1}H RMN ($CDCl_3$) δ 4 0 (s, 2H), 7 1 - 7 35 (m, 7H), 9.7 (br s, NH) El HPLC usando el método B proporcionó un R_t de 4.9 minutos. LC/EM (M+1) 330.2, (M-1) 328.1.

Ejemplo 2

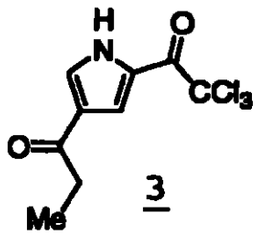


2

2,2,2- Tricloro -1- (4- (3- Clorofenil) acetil -1H-pirrol -2- yl) - etanona (2): En un frasco seco, el cloruro de 3-clorofenilacetilo (1 equivalente) fue combinado con 2-tricloroacetil pirrol (1 equivalente) en una cantidad mínima de diclorometano (DCM). A la solución resultante, a temperatura ambiente, se adicionó tricloruro de aluminio (1 equivalente) Después de 2 horas, la mezcla de reacción fue aplicada directamente en una columnaa de sílica gel El gradiente de elución con acetato de etilo al 10% hasta acetato de etilo al 50% en

hexanos proporcionó el compuesto 2 El HPLC usando el método A proporcionó un R_t de 15 minutos

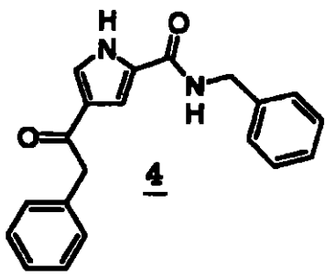
Ejemplo 3



3

1- [5- (2,2,2- Tricloro - acetil) -1H- pirrol -3- il) - propan-1-ona (3): En un frasco seco, el cloruro de 3-propionilo (1 equivalente) fue combinado con 2-tricloroacetil pirrol (1 equivalente) en una cantidad mínima de diclorometano (DCM) A la solución resultante, a temperatura ambiente, se adicionó tricloruro de aluminio (1 equivalente). Después de 2 horas, la mezcla de reacción fue aplicada directamente en una columnaa de sílica gel El gradiente de elución con acetato de etilo al 10% hasta acetato de etilo al 50% en hexanos proporcionó el compuesto 3.

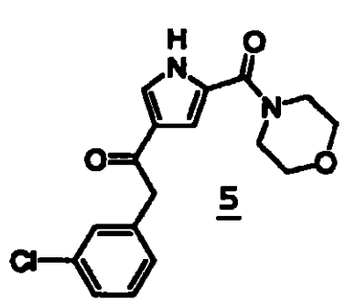
Ejemplo 4



4

Bencilamida del ácido 4- fenilacetil -1H- pirrol -2- carboxílico (4) A una solución del compuesto 1 (1 equivalente) en DMF, a temperatura ambiente, se adicionó bencilamina (1.2 equivalentes). Después de 24 horas, el solvente fue evaporado y el producto crudo 4 fue empleado sin purificación El HPLC usando el método B proporcionó un R_t de 3.8 minutos FIA/EM (M+1) 319.3, (M-1) 317.2.

Ejemplo 5

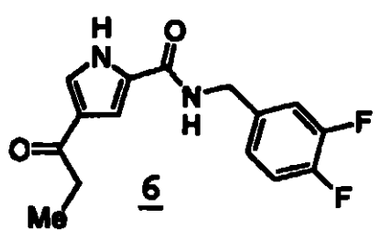


5

2- (3- Clorofenil) 1- [5- (morfolina -4- carbonilo) -1H- pirrol -3- il] - etanona (5)· A una solución del compuesto 2 (1 equivalente) en DMF, a temperatura ambiente, se adicionó morfolina (1.2 equivalentes) Después de 24 horas, el solvente fue evaporado y el

producto crudo 5 fue empleado sin purificación FIA/EM (M+1) 333 3, (M-1) 331.2. La ^{1}H RMN fue consistente con la estructura esperada

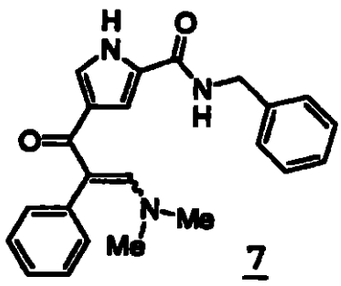
Ejemplo 6



6

3,4- difluoro - bencilamida del ácido 4- Propionil -1H- pirrol -2- carboxílico (6)· A una solución del compuesto 3 (1 equivalente) en DMF, a temperatura ambiente, se adicionó 3,4- difluorobencil amina (1.2 equivalentes) Después de 24 horas, el solvente fue evaporado y el producto crudo 6 fue empleado sin purificación.

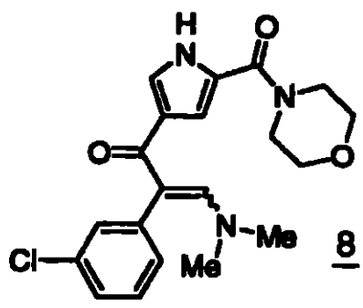
Ejemplo 7



7

Bencilamida del ácido 4- (3- Dimetilamino -2- fenil - acriloil) -1H- pirrol -2- carboxílico (7): A una solución del compuesto 4 (1 equivalente) en THF, a temperatura ambiente, se adicionó $(Me_2N)_2CHOt\text{-}Bu$ (3 equivalentes) Después de 24 horas, el solvente fue evaporado y el producto crudo 7 fue empleado sin purificación ^1H RMN ($CDCl_3$) δ 4.4 (s, 2H), 4 8 (s, NH), 6.8 - 7.4 (m, 13H).

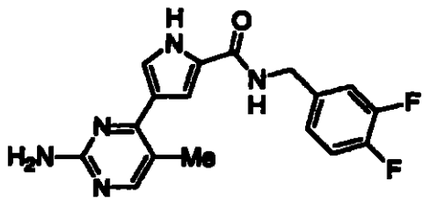
Ejemplo 8



8

2- (3- Cloro - fenil) -3- dimetilamino -1- [5- (morfolina -4- carbonil) -1H- pirrol -3- il]- propenona (8) : A una solución del compuesto 5 (1 equivalente) en THF, a temperatura ambiente, se adicionó $(Me_2N)_2CHOt\text{-}Bu$ (3 equivalentes). Después de 24 horas, el solvente fue evaporado y el producto crudo 8 fue empleado sin purificación El HPLC usando el método B proporcionó un R_t de 11.2 minutos

Ejemplo 9



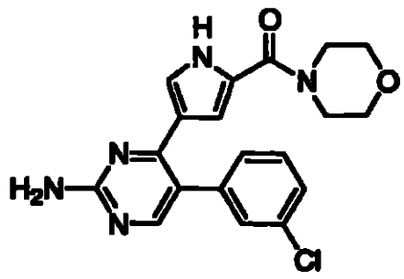
III-a-74

3,4- difluoro - bencilamida del ácido 4- (2- Amino -5- metil - pirimidin -4- il) -1H- pirrol -2- carboxílico (III-a-74)

Etapa 1 A una solución del compuesto 6 (1 equivalente) en THF, a temperatura ambiente, se adicionó $(Me_2N)_2CHOt\text{-}Bu$ (3 equivalentes) Después de 24 horas, el solvente fue evaporado y el producto crudo fue utilizado sin purificación.

Etapa 2: A una solución del compuesto formado anteriormente en la etapa 1 (1 equivalente) en etanol, a temperatura ambiente, se adicionó guanidina (3 equivalentes) y la mezcla resultante se calentó bajo reflujo. Después de 12 horas, el solvente fue evaporado y el producto crudo fue purificado por medio de HPLC preparativa (fase reversa; 10 → 90% MeCN en agua, 15 minutos) para proporcionar el compuesto deseado III-a-74. El HPLC usando el método B proporcionó un R_t de 7.9 minutos. La ^1H RMN fue consistente con la estructura esperada. FIA/EM Obs M+1/M1

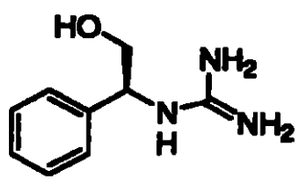
Ejemplo 10



III-a-72

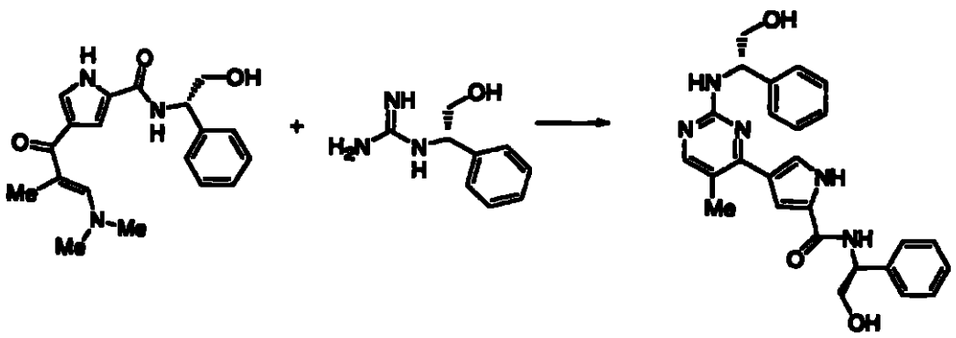
{4- [2- Amino -5- (3- clorofenil) - pirimidina -4- il]- 1*H*- pirrol -2- il}- morfolin -4-il - metanona (III-a-72)· A una solución del compuesto 8 (1 equivalente) en etanol, a temperatura ambiente, se adicionó guanidina (3 equivalentes) y la mezcla resultante se calentó bajo reflujo Después de 12 horas, el solvente fue evaporado y el producto crudo fue purificado por medio de HPLC preparativa (fase reversa; 10 → 90% MeCN en agua, 15 minutos) para proporcionar el compuesto deseado **IIIa-72** El HPLC usando el método B, R_t = 7 9 minutos La ^1H RMN fue consistente con la estructura esperada FIA/EM Obs (M+1) 384.4 amu

Ejemplo 11



N- (2- Hidroxi -1- (*S*)- fenil - etil)- guanidina • HCl: (*S*)- Fenilglicinol (0 38 g, 2.7 mmol) y bis-Boc guanidina -(*N*)- triflato (0 9 g, 2.3 mmol) fueron combinados en cloruro de metileno (anhidro, 5 mL) y fueron agitados a temperatura ambiente durante la noche. El fin de la reacción fue verificado por medio de HPLC La mezcla fue diluida con acetato de etilo, lavada con bisulfito de sodio 2M, salmuera, luego secada sobre $MgSO_4$, filtrada y concentrada al vacío El intermediario bis-Boc guanidina fue tratado con HCl 4N / dioxano (5 mL) y agitado a temperatura ambiente hasta completar la desprotección (48 h) para proporcionar el compuesto del título.

Ejemplo 12

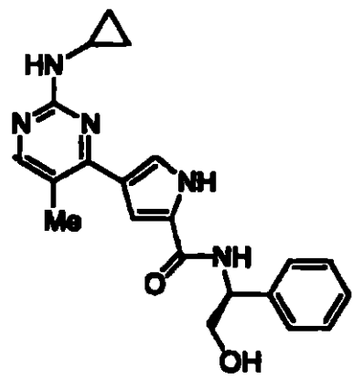


III-a-155

(2- hidroxi -1- (*S*)- fenil - etil)- amida del ácido 4- [2- (2- Hidroxi -1- (*S*)- fenil - etilamino) -5- metil - pirimidin -4- il] -1*H*- pirrol -2- carboxílico (III-a-155) la (2- hidroxi -1- fenil - etil)- amida del ácido

4-(3- Dimetilamino -2- metil - acriloil) -1*H*- pirrol -2-carboxílico (100 mg, 0 29 mmol) fue combinada con N- (*S*)-fenilglicinol guanidina • HCl (126 mg) y carbonato de potasio (121 mg) en N,N-dimetilacetamida (2 mL) La suspensión resultante fue calentada y agitada a 100 °C por 24 horas. El material crudo fue diluido con acetato de etilo, lavado con $NaHCO_3$ saturado, salmuera, secado sobre MgSO4 y concentrado al vacío. Purificación por medio de HPLC preparativa (Gilson· Columna = CombiHT SB-C189 5 µM 21 2 mm x 100 mm, eluente = 0 1% TFA gradiente MeCN/H_2O) seguido por TLC preparativa (silica, 5% MeOH en CH_2Cl_2) proporcionó el compuesto **III-a-155** como un sólido amarillo pálido (8 0 mg). HPLC Método B, R_t = 4.76 minutos; EM (FIA) 458.2 (M+1), 456 1 (M-1); ^1H RMN consistente con la estructura

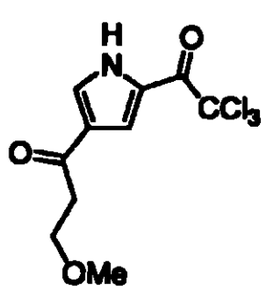
Ejemplo 13



III-a-162

(2- hidroxi -1- (*S*)- fenil - etil)- amida del ácido 4- (2- ciclopropilamino -5- metil - pirimidin -4-il)- 1*H*- pirrol -2- carboxílico (III-a-162)· la (2- hıdroxı -1- fenıl -etıl) amıda del ácıdo 4- (3- Dımetılamıno -2- metıl - acrıloıl)- 1*H*- pirrol -2- carboxílıco (100 mg, 0.29 mmol) fue combınada con cıclopropıl guanıdına • HCl (80 mg) y carbonato de potasıo (121 mg) en N,N- dımetılacetamıda (2 mL). La suspensıón resultante fue calentada y agıtada a 100 °C por 24 horas. El materıal crudo fue dıluıdo con acetato de etılo, lavado con $NaHCO_3$ saturado y salmuera, secado sobre MgSO4 luego concentrado al vacío La purıfıcacıón por medıo de TLC preparatıva (sılıca, 1:1 EtOAc Hexanos) proporcıonó el III-a-162 como un sólıdo amarıllo (7 8 mg). HPLC Método B, R_t = 4.29 mınutos, LC/EM (m/z) 378 2 (M+1), 376.2 (M-1); la ^1H RMN fue consıstente con la estructura.

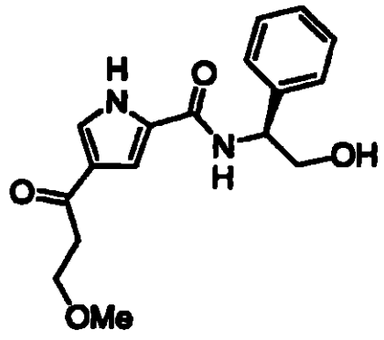
Ejemplo 14



3- Metoxi -1- [5- (2,2,2- tricloro - acetil)- 1*H*- pirrol -3-il]propan -1-ona A una solucıón de 2-trıcloroacetıl

pirrol (1.0 equivalente, 4.67 g, 22 mmol) en cloruro de metileno (5 mL) se adicionó cloruro de 3-metoxipropionilo (1.0 equivalente, 22 mmol) luego se adicionó tricloruro de aluminio (1.0 equivalente, 2 93 g, 22 mmol) en pequeñas porciones. Después de 2 5 horas, la mezcla cruda fue cromatografiada sobre sílica gel (MeOH 2% en DCM) para proporcionar 3.0 g del producto de Friedel-Craft. La ^1H RMN fue consistente con la estructura.

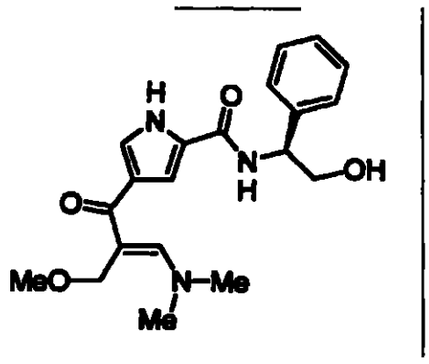
Ejemplo 15



(2- hidroxi -1- (*S*)- fenil - etil)- amida del ácido 4- (3- Metoxi - propionil)- 1*H*- pirrol -2- carboxílico A una solución de 3- metoxi -1- [5- (2,2,2- tricloro- acetil)- 1*H*- pirrol -3-il]propan -1- ona (3 0 g, 10 mmol) en acetonitrilo (50 mL), enfriada a 0 °C, se adicionó (*S*)-(+)-fenil glicinol (1.2 equivalentes, 1 65 g, 12 mmol) y la mezcla resultante fue agitada por 3 días a temperatura ambiente. El solvente fue removido bajo presión reducida y el residuo fue purificado por medio de cromatografía sobre sílica gel (MeOH 5% en DCM) para

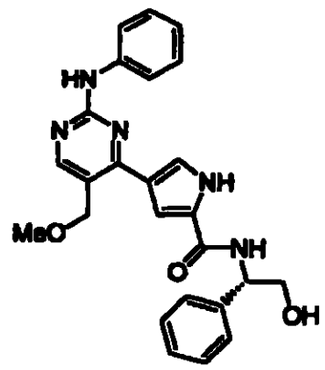
proporcionar 5.3 g del compuesto del título como un sólido blanco. HPLC Método B, R_t = 4.2 minutos; LC/EM (m/z) 317 03 (M+1), 315 00 (M-1); la ^1H RMN fue consistente con la estructura.

Ejemplo 16



(2- hidroxi -1- (*S*)- fenil- etil)- amida del ácido 4- (3- Dimetilamino -2- metoximetil - acriloil)- 1*H*- pirrol- 2- carboxílico · la (2- hidroxi -1- (*S*)- fenil- etil)- amida del ácido 4- (3- Metoxi - propionil)- 1*H*- pirrol -2- carboxílico fue tratada con un exceso del reactivo de Bredereck en THF a temperatura ambiente a 50 °C por 3 días. El solvente fue removido bajo presión reducida y el concentrado fue empleado directamente en la siguiente etapa HPLC Método B, R_t = 5.0 minutos "pico ancho".

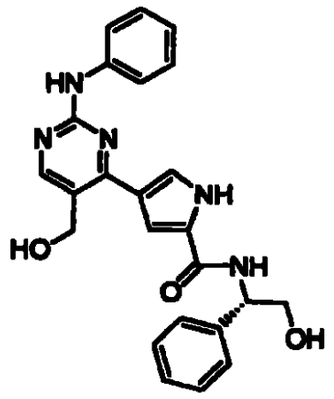
Ejemplo 17



III-a-164

(2- hidroxi -1- (*S*)- fenil -etil) amida del ácido 4- (5- Metoximetil -2- fenilamino- pirimidin- 4-il)- 1*H*- pirrol- 2- carboxílico (III-a-164) : la (2- hidroxi- 1- (*S*)- fenil- etil)- amida del ácido 4- (3- Dimetilamino- 2- metoximetil- acriloil)- 1*H*- pirrol- 2- carboxílico (0 27 mmol) fue combinada con fenil guanidina (73 mg) en N,N- dimetilacetamida (2 mL) y la suspensión resultante fue calentada a 90 °C por 35 horas La mezcla de reacción fue diluida con acetato de etilo, lavada con $NaHCO_3$ saturado y salmuera, secada sobre MgSO4 y concentrada al vacío El producto crudo fue purificado por medio de HPLC preparativa (Gilson: Columna = CombiHT SB-C189 5 µM, 21 2 mm x 100 mm, eluente = 0 1% TFA gradiente MeCN/H_2O) para proporcionar III-a-164 como un sólido amarillo (3 2 mg) LC/EM (m/z) 444.16 (M+1), 442 19 (M-1), HPLC Método B, R_t = 5 16 minutos : la ^1H RMN fue consistente con la estructura.

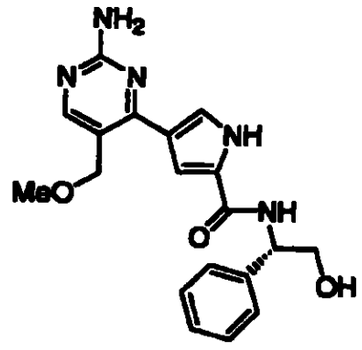
Ejemplo 18



III-a-165

(2- hidroxi- 1- (*S*)- fenil- etil)- amida del ácido 4- (5- hidroximetil- 2- fenilamino- pirimidin- 4-il)- 1*H*- pirrol- 2- carboxílico (III-a-165) A una solución de III-a-164 (15 mg, 0.03 mmol) en diclorometano (2 mL), enfriada a -78 °C, se adicionó BBr_3 (135 µL, 0 13 mmol). Después de 15 minutos, se permitió que la reacción se calentara hasta la temperatura ambiente Después de 45 minutos, la reacción fue extinguida con una solución saturada de carbonato de sodio y la mezcla resultante fue agitada por 30 minutos adicionales antes de la extracción con acetato de etilo Las capas orgánicas fueron combinadas y lavadas con salmuera, luego secadas sobre sulfato de sodio. La mezcla cruda fue purificada por medio de TLC preparativa (silica, 7% MeOH en CH_2Cl_2) para proporcionar III-a-165 como un sólido beige (1.6 mg) HPLC Método B, R_t = 4 54 minutos, LC/EM (m/z) 430 15 (M+1), 428 03 (M-1); la ^1H RMN fue consistente con la estructura

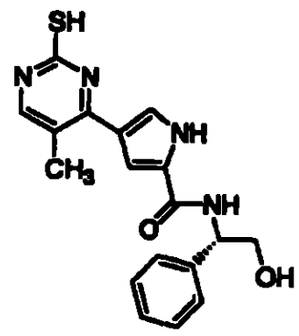
Ejemplo 19



III-a-161

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- amino- 5- metoximetil- pirimidin- 4-il)- 1H- pirrol- 2- carboxílico (III-a-161) : La enamina formada anteriormente en el Ejemplo 16 (0 27 mmol) fue combinada con guanidina • HCl (51 mg), y K_2CO_3 (100 mg) en N,N-dimetilacetamida (4 mL) La mezcla heterogenea fue calentada y agitada a 90 °C por 35 h El material crudo fue diluido con acetato de etilo, lavado con $NaHCO_3$ saturado y salmuera, secado ($MgSO_4$) y concentrado al vacío. La purificación por medio de HPLC preparativa (Gilson Columna = CombiHT SB-C189 5 µM, 21.2 mm x 100 mm, eluente = 0.1% TFA gradiente MeCN/H_2O) proporcionó el III-a-161 como un sólido amarillo (2.0 mg) LC/EM (m/z) 368.12 (M+1), 366 15 (M-1), R_t (HPLC) = 3.77 min, la ^1H RMN fue consistente con la estructura.

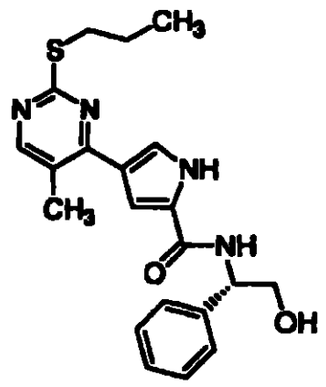
Ejemplo 20



(2- hidroxi- 1- (*S*)- fenil- etil)- amida del ácido 4- (2- mercapto- 5- metil- pirimidin- 4-il)- 1*H*- pirrol- 2- carboxílico la (2- hıdroxı- 1- (*S*)- fenıl- etıl)- amıda del ácıdo 4- (3- dımetılamıno- 2- metoxımetıl- acrıloıl)- 1*H*- pırrol- 2- carboxílıco (17 6 mmol, 6.0 g) fue combinada con tıourea (39 mmol, 3 0 g) y carbonato de potasıo (53 mmol, 7 3 g) en etanol (50 mL) y la suspensión resultante fue calentada a 90 °C por 24 horas. El solvente fue removıdo al vacío y el sólıdo negro resultante fue dıluıdo con agua y el sólıdo fue removıdo por medıo de fıltracıón El sólıdo fue lavado con acetato de etılo dos veces y la solucıón acuosa fue acidıfıcada a pH 5 - 6 con HCl (2N) El sólıdo formado fue removido por medıo de fıltracıón y la solucıón acuosa fue luego extraıda dos veces con acetato de etilo. Las fases orgánıcas combınadas fueron secadas sobre sulfato de sodıo. El solvente fue removıdo al vacío para proporcıonar el compuesto del título como un sólıdo café

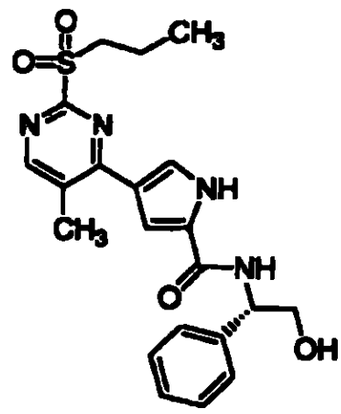
(3 0 g, rendimiento del 48%) HPLC Método B, R_t = 3 7 minutos, la ^{1}H RMN fue consistente con la estructura

Ejemplo 21



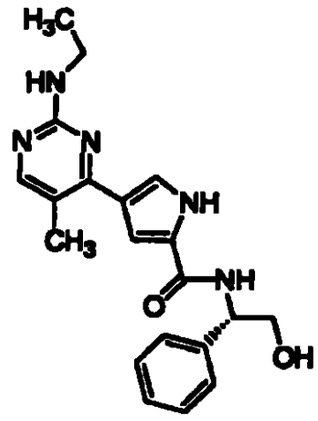
(2- hidroxi- 1- (*S*)- fenil- etil)- amida del ácido 4- (5- metil- 2- propilsulfanil- pirimidin- 4-il)- 1*H*- pirrol- 2- carboxílico A una solución de la (2- hidroxi- 1- (*S*)- fenil- etil)- amida del ácido 4- (2- mercapto- 5- metil- pirimidin- 4-il)- 1*H*- pirrol- 2- carboxílico (7.7 mmol, 2 74 mmol) en amoniaco acuoso (15%) se adicionó, a temperatura ambiente, n-propilyoduro (11 6 mmol, 1.1 mL). La solución fue agitada durante la noche a temperatura ambiente El sólido resultante fue recolectado por medio de filtración y empleado directamente en la siguiente etapa La ^{1}H RMN fue consistente con la estructura

Ejemplo 22



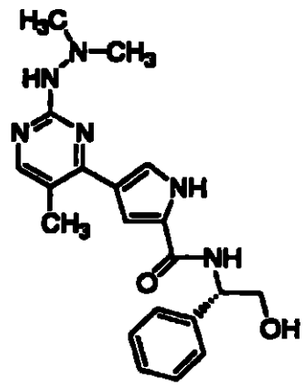
(2- hidroxi- 1- (*S*)- fenil- etil)- amida del ácido 4- [5- metil- 2- (propano- 1- sulfonil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico · El compuesto tiopropil (7.7 mmol, 3 05 g) preparado en el anterior Ejemplo 21 fue disuelto en 120 mL de etanol. A esta solución, mantenida a temperatura ambiente, se adicionó *m*-CPBA (70% p/p%, 23 1 mmol, 4.0 g) La solución fue agitada por 4 horas adicionales a temperatura ambiente. El solvente fue removido al vacío y el residuo fue disuelto en acetato de etilo, luego fue lavado 4 veces con una solución de hidróxido de sodio (1N) La fase orgánica fue secada sobre sulfato de sodio y concentrada al vacío para proporcionar el compuesto del título como un sólido blanco (1 7 g, rendimiento del 51% rendimiento para 2 etapas). HPLC Método B, R_t = 5 4 minutos. La ^1H RMN fue consistente con la estructura.

Ejemplo 23



(2- hidroxi- 1- (*S*)- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico . A una solución de (2- hidroxi- 1- (*S*)- fenil- etil)- amida del ácido 4- [5- metil- 2- (propano- 1- sulfonil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico (47 µmol, 20 mg) en DMSO (1 mL) se adicionó etilamina (0 5 mmol, 150 µL). La mezcla fue calentada a 130 °C por 24 horas para proporcionar el compuesto del título LC/EM (m/z) 366 2 (M+1); HPLC Método B, R_t = 4 2 minutos, la ^{1}H RMN fue consistente con la estructura

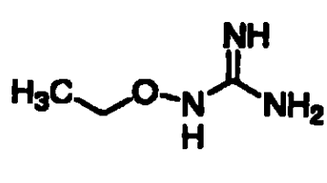
Ejemplo 24



III-a-226

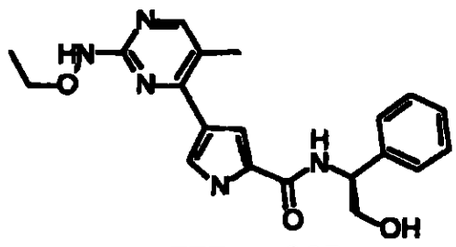
(2- hidroxi- 1- (*S*)- fenil- etil)- amida del ácido 4- [2- (*N'*,*N'*- dimetil- hidrazino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico (III-a-226) A una solución de (2- hidroxi- 1- (*S*)- fenil- etil)- amida del ácido 4- (3- dimetilamino- 2- metoximetil- acriloil)- 1*H*- pirrol- 2- carboxílico (0 15 mmol, 50 mg) en DMA (2 mL) se adicionó dimetil- N,N- aminoguanidina • 2HCl (0.17 mmol, 30 mg) y carbonato de potasio (0.36 mmol, 50 mg) La mezcla de reacción fue agitada por 48 horas a 100 °C. El solvente fue removido por medio de alto vacío "GeneVac" y el residuo fue purificado por medio de HPLC preparativa (Gilson. Columna = CombiHT SB-C189 5 µM 21.2 mm x 100 mm, eluente = 0 1% TFA gradiente MeCN/H_2O) seguido por TLC preparativa (silica, 5% MeOH en CH_2Cl_2), "eluciones dobles" proporcionaron el compuesto **III-a-226** como un sólido amarillo pálido (1 3 mg). HPLC Método B, R_t = 4 03 min., LC/EM (m/z) 381 1 (M+1), 379.1 (M-1); la ^1H RMN fue consistente con la estructura

Ejemplo 25



Etanolguanidina El clorhidrato de etanolamina (200 mg, 2 mmol) se adicionó a una mezcla de N, N'-di-boc -N''-triflilguanidina (800 mg, 2 mmol) y TEA (0.28 mL, 2 mmol) en diclorometano (10 mL). La mezcla fue agitada durante la noche luego fue diluida con EtOAc, lavada con bisulfato de sodio (2M), bicarbonato de sodio saturado, secada sobre $NaSO_4$ y concentrada al vacío El residuo crudo fue purificado por medio de cromatografía flash (instantanea) de columna eluyendo con 20% CH_2Cl_2/hexano para proporcionar un sólido blanco (0 56 g, 92%).). ^1H RMN ($CDCl_3$) : δ 4.18 (q, 2H), 1.60 (d, 18H), 1.37 (t, 3H). A esta bis-Boc guanidina se adicionó HCl 4M/dioxano (5 mL) La mezcla fue agitada por 24 h y luego concentrada para proporcionar el compuesto del título (0.26 g) ^1H RMN (MeOD) δ 3.92 (q, 2H), 1.27 (t, 3H). EM (M+1) 104

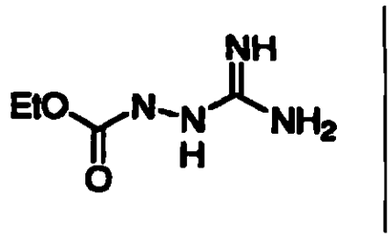
Ejemplo 26



III-a-195

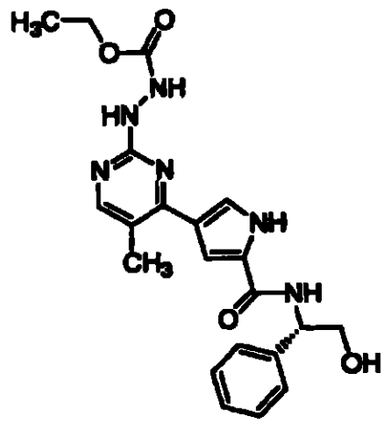
(2- hidroxi- 1- (*s*)- fenil- etil)- amida del ácido 4- (2- etanolamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico (III-a-195) . A una mezcla de (2- hidroximetil- 1- (*S*)- fenil- etil) amida del ácido 4- (3- dimetilamino- 2- metil- acriloil)- 1*H*- pirrol- 2- carboxílico (0.1 mmol) y K_2CO_3 (55 mg, 0.4 mmol) en DMF (1 mL) se adicionó cloruro de hidrógeno de etanolguanidina (0 2 mmol). La suspensión resultante fue agitada por 6 horas a 90 °C La mezcla de reacción fue filtrada y el filtrado fue concentrado al vacío El residuo crudo fue purificado por medio de HPLC preparativa (Gilson: Columna = CombiHT SB-C189 5 µM 21 2 mm x 100 mm, eluente = 0 1% TFA gradiente MeCN/$H_2$0) para proporcionar el compuesto III-a-195 como un aceite amarillo (21 mg) HPLC (método B) R_t = 4.08 min; EM (M+1) 382 1

Ejemplo 27



Etil carbamato de guanidina: El etilcarbazato (208 mg, 2 mmol) fue adicionado a una solución de N'N' -di-boc N''-trifilguanidina (800 mg, 2 mmol) en diclorometano (10 mL). La mezcla fue agitada durante la noche, luego diluida con EtOAc, lavada con bisulfato de sodio (2M), bicarbonato de sodio saturado, secado sobre $NaSO_4$ anhidro y concentrado al vacío El residuo crudo fue purificado por medio de cromatografía flash (instantanea) de columna eluyendo con 30% EtOAc/hexano para proporcionar un sólido blanco (0.55g) A esta bis-boc guanidina se adicionó HCl 4M/Dioxano (5 mL). La mezcla fue agitada por 24 horas y luego concentrada para proporcionar el compuesto del título. ^1H RMN (MeOD) : δ 3 4 18 (d, 2H), 3 26 (s, 1H), 1 28 (t, 3H) EM (M+1) 134.

Ejemplo 28



III-a-218

(2- hidroxi- 1- (*s*)- fenil- etil)- amida del ácido 4- (2- etil carbamato- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico (III-a-218) . A una mezcla de (2- hidroximetil- 1- (*S*)- fenil- etil) amida del ácido 4- (3- dimetilamino- 2- metil- acriloil)- 1*H*- pirrol- 2- carboxílico (0 1 mmol) y K_2CO_3 (55 mg, 0.4 mmol) en DMF (1 mL) se adicionó cloruro de hidrógeno de etil carbamato de guanidina (0.2 mmol) La suspensión resultante fue agitada por 6 horas a 90 °C. La mezcla de reacción fue filtrada y el filtrado fue concentrado al vacío. El residuo crudo fue purificado por medio de HPLC preparativa (Gilson: Columna = CombiHT SB-C189 5 µM 21.2 mm x 100 mm, eluente = 0 1% TFA gradiente MeCN/H_2O) para proporcionar el compuesto **III-a-218** como un aceite amarillo (10 mg). HPLC (método B) R_t = 4.03; EM (M+1) 425.1. ^1H RMN (MeOD) 8 08 (s, 1H); 7.87 (s, 1H), 7.7 (s, 1H), 7 24 - 7 5 (m, 5H); 5 15 (t, 1H), 4 2 (m, 2H), 3 85 (m, 2H); 2.5 (s, 3H).

Ejemplo 29

Nosotros hemos preparado otros compuestos de la fórmula III-a por medio de métodos substancialmente similares a aquellos descritos en los anteriores Ejemplos 1 - 28 y aquellos ilustrados en los Esquemas I - XII. Los datos de caracterización para estos compuestos se encuentran resumidos en la Tabla 3 que se encuentra a continuación e incluye datos de LC/EM, HPLC, y ^{1}H RMN.

En donde sea aplicable, los datos de ^{1}H RMN que son resumidos en la siguiente Tabla 3 y en los cuales "Y" designa dichos datos de ^{1}H RMN, se encuentran disponibles y se encontró que los mismos fueron consistentes con la estructura Los números de compuesto corresponden a los números de compuesto listados en la Tabla 1

Tabla 3 Datos de Caracterización para Compuestos Seleccionados

Compuesto No IIIa-	M+1	M-1	Método de HPLC	R_t (min)	^{1}H RMN
122	352 17	-	-	-	-
136	432 2	429.8	B	5 53	-
137	444 3	442.3	B	5 00	-
138	430.2	428.3	B	4.47	Y
139	458 3	456.3	B	4 72	-
140	493.3	491 3	B	4.45	-
141	520.2	518.2	B	5.98	-
142	436.2	-	B	4.0	-

Compuesto No IIIa-	M+1	M-1	Método de HPLC	R_t (min)	^1H RMN
144	440 17	-	A	10 1	Y
145	446 2	444.1	B	5 45	-
146	482 2	-	B	5.69	-
147	464 2	-	B	5.87	-
148	500.1	-	B	6.12	-
149	482.2	480.4	B	6.11	-
150	428 2	426 2	B	5.13	-
153	380.2	378 2	B	4.63	Y
154	420.1	418.1	B	4.74	Y
155	458 2	456.1	B	4.76	Y
156	441 13	-	B	5.14	-
157	498.2	-	B	6.00	-
159	392.2	390.1	B	4.75	Y
162	378.2	376.2	B	4.29	Y
163	380.2	378.0	B	4.65	Y
180	338.15	-	B	3 8	-
181	396 22	-	B	3.9	-
182	382 18	-	B	4.1	-
183	352.17	-	-	-	-
188	367.2	-	B	2.86	Y
190	453.1	-	B	5.86	Y
191	384 1	-	B	4.46	Y
192	384 1	-	B	4.41	Y
214	428.1	-	B	4.9	-
215	415 1	-	B	4.3	Y
216	422 1	-	B	4.43	Y
217	422.1	-	B	4.44	-
219	429 3	-	B	3.64	Y
221	405 19	-	B	4 5	-
227	482.4	-	B	5 5	-
229	419 03	-	B	429	Y
230	510 4	-	B	5 19	-
231	432 3	-	B	5 23	Y

ENSAYOS BIOLOGICOS

La actividad de los compuestos de la presente invención como inhibidores de las proteínas cinasas puede ser evaluada *in vitro*, *in vivo* o en una línea celular Los ensayos *in vitro* incluyen ensayos que determinan la inhibición ya sea de la actividad de fosforilación o de la actividad ATPasa de la proteína cinasa activada Los ensayos in vitro alternativos cuantifican la habilidad del inhibidor para unirse a la proteína cinasa La unión del inhibidor puede ser medida mediante el radioetiqueteado del inhibidor antes de la unión, aislando el complejo inhibidor/proteína cinasa y determinando la cantidad de unión radioetiqueteada. De manera alternativa, la unión del inhibidor puede ser determinada corriendo un experimento de competición en el cual los nuevos inhibidores son incubados con la proteína cinasa unida a radioligandos conocidos Los detalles de las condiciones empleadas para llevar a cabo estos ensayos se encuentran establecidos en los Ejemplos 30 a 37.

Ejemplo 30

ENSAYO DE INHIBICION DE ERK

Los compuestos fueron ensayados para la inhibición de la ERK2 mediante un ensayo espectrofotométrico de enzimas acopladas (Fox y otros (1998,) *Protein Sci* 7, 2249) En

este ensayo, una concentración fija de ERK2 activada (10 nm) fue incubada con varias concentraciones del compuesto en DMSO (2 5%) por 10 min. a 30 °C en amortiguador HEPES 0 1 M, pH 7 5, que contiene $MgCl_2$ 10 mM, fosfoenolpiruvato 2 5 mM, NADH 200 µm, 150 µg/mL de piruvato cinasa, 50 µg/mL de lactato deshidrogenasa, y péptido erktido 200 µM La reacción fue iniciada mediante la adición de ATP 65 µM. La velocidad de disminución de la absorbancia a 340 nM fue monitoreada. La IC_{50} fue evaluada a partir de los datos de velocidad como una función de la concentración del inhibidor.

La Tabla 4 muestra los resultados de la actividad de compuestos seleccionados de esta invención en el ensayo de inhibición de la ERK2 Los números de los compuestos corresponden a los números de compuesto en la Tabla 1 Los compuestos que tienen una actividad designada como "A" proporcionaron un porcentaje de inhibición menor que o igual a 33%; los compuestos que tienen una actividad designada como "B" proporcionaron un porcentaje de inhibición de entre 24% y 66%, y los compuestos que tienen una actividad designada como "C" proporcionaron un porcentaje de inhibición de entre 67% y 100%. Los compuestos que tienen una actividad designada como "D" proporcionaron un K_i de menos de 0 1 micromolar; los compuestos que tienen una actividad designada como "E" proporcionaron un K_i de entre 0 1 y 1 0 micromolar; y los

compuestos que tienen una actividad designada como "F" proporcionaron un K_i superior a 1 0 micromolar

Tabla 4. Actividad Inhibidora de la ERK2 de Compuestos Seleccionados

No. III-a-	Actividad	No. III-a-	Actividad	No. III-a-	Actividad
2	B	3	A	4	A
5	A	6	A	7	A
8	A	9	A	10	A
11	A	12	B	13	A
14	B	15	A	16	A
17	A	18	A	19	A
20	A	21	B	22	A
23	C	24	A	25	A
26	A	27	A	28	A
29	C	30	A	31	A
32	A	33	A	34	B
35	B	36	B	37	c
39	c	40	C	41	A
42	C	43	A	44	C
45	B	46	A	47	C
48	B	49	A	50	A
51	A	52	A	53	A
54	A	55	A	56	A
57	A	58	A	59	A
60	A	61	A	62	C
63	A	64	A	65	A
66	A	67	A	68	A
69	A	70	A	71	A
72	B	100	A	101	A
102	A	103	F	104	A
105	E	107	F	111	D
112	D	114	F	117	D

No. III-a-	Actividad	No. III-a-	Actividad	No. III-a-	Actividad
120	E	121	A	122	C
123	A	124	C	125	A
131	A	132	F	133	F
134	D	135	C	139	D
140	D	141	D	142	D
144	E	145	D	147	D
148	D	149	D	150	D
151	D	152	D	153	D
154	D	155	D	157	D
158	D	159	D	160	E
161	E	162	D	163	D
166	E	168	F	169	E
170	F	171	F	172	F
173	E	174	D	175	D
176	D	177	D	178	D
179	D	180	F	184	E
188	E	189	D	190	E
191	D	192	E	193	D
194	D	195	D	196	D
197	F	198	D	199	D
200	D	201	D	202	D
203	D	204	D	205	D
206	D	207	D	208	D
209	D	210	D	211	D
212	D	213	D	214	D
215	D	216	D	217	D
218	E	219	D	220	D
221	D	222	D	223	D
224	D	225	D	226	D
227	D	229	E	230	D
231	D	232	D	233	D
234	D	235	D	236	D
237	D	238	D	-	-

Ejemplo 31

INHIBICION DE LA ERK2: Ensayo de Proliferación Celular

Los compuestos pueden ser ensayados con relación a la inhibición de la ERK2 por medio de un ensayo de proliferación celular. En este ensayo, un medio completo es preparado mediante la adición de suero fetal bovino al 10% y una solución de penicilina/estreptomicina al medio RPMI 1640 (JRH Biosciences). La células de cáncer de colon (línea celular HT-29) son adicionadas a cada uno de los 84 pozos de una placa de 96 pozos con una densidad de sembrado de 10,000 células/pozo/150 µL A las células se les permite unirse a la placa mediante la incubación a 37 °C por 2 horas Una solución del compuesto de ensayo es preparada en el medio completo por dilución en serie para obtener las siguientes concentraciones · 20 µM, 6 7 µM, 2 2 µM, 0 74 µM, 0.25 µM, y 0.08 µM La solución del compuesto de ensayo (50 µL) es adicionada a cada uno de los 72 pozos que contienen células A los 12 pozos remanentes que contienen células, solo se agregó medio completo (200 µL) para formar un grupo de control para medir la proliferación máxima A los 12 pozos vacíos remanentes, se adicionó medio completo para formar un grupo de control de vehículo para medir el fondo. Las placas fueron incubadas a 37 °C por 3 días. Una solución patrón de ^{3}H-timidina (1 mCi/mL, New England Nuclear, Boston, MA) es diluida a 20 µCi/mL en medio RPMI, luego 20 µL de esta solución son adicionados a cada pozo. Las

placas son además incubadas a 37 °C por 8 horas, luego son cosechadas y analizadas con respecto a la captación de ^{3}H-timidina empleando un contador de centelleo líquido

Cada uno de los compuestos III-a-116, III-a-139, y III-a-136 mostraron tener un IC_{50} de menos de 0 1 µM

Ejemplo 32

ENSAYO DE INHIBICION DE ERK1

Los compuestos fueron ensayados con respecto a la inhibición de la ERK1 mediante un ensayo espectrofotométrico de enzimas acopladas (Fox y otros (1998,) *Protein Sci* 7, 2249) En este ensayo, una concentración fija de ERK1 activada (20 nm) fue incubada con varias concentraciones del compuesto en DMSO (2 0%) por 10 min a 30 °C en amortiguador HEPES 0 1 M, pH 7 6, que contiene $MgCl_2$ 10 mM, fosfoenolpiruvato 2.5 mM, NADH 200 µm, 30 µg/mL de piruvato cinasa, 10 µg/mL de lactato deshidrogenasa, y péptido erktido 150 µM La reacción fue iniciada mediante la adición de ATP 140 µM (20 µL) La velocidad de disminución de la absorbancia a 340 nM fue monitoreada La K_i fue evaluada a partir de los datos de velocidad como una función de la concentración del inhibidor.

Los ejemplos de los compuestos en los cuales se encontró que inhiben la ERK1 con una actividad de menos de 0.1 μM incluyen el III-a-202, el III-a-204, y el III-a-205.

Ejemplo 33

ENSAYO DE INHIBICION DE LA GSK-3

Los compuestos fueron evaluados por su habilidad al inhibir la actividad de la GSK-3β (AA 1-420) empleando un sistema de enzimas acopladas estándar (Fox y otros (1998) *Protein Sci.* 7, 2249) Se llevaron a cabo las reacciones en una solución que contenía HEPES 100 mM (pH 7.5), $MgCl_2$ 10 mM, NaCl 25 mM, NADH 300 μM, DTT 1 mM y DMSO 1 5%. Las concentraciones finales de substrato en el ensayo fueron 20 μm ATP (Sigma Chemicals, St Louis, MO) y 300 μM peptido (HSSPHQS(PO_3H_2)EDEEE, American Peptide, Sunnyvale, CA). Las reacciones fueron llevadas a cabo a 30 °C y 20 nM GSK-3β. Las concentraciones finales de los componentes del sistema de enzimas acopladas fueron de 2 5 mM fosfoenolpiruvato, 300 μM NADH, 30 μg/ml piruvato cinasa y 10 μg/ml lactato deshidrogenasa

Una solución amortiguadora patrón del ensayo fue preparada conteniendo todos los reactivos listados anteriormente con excepción del ATP y del compuesto de ensayo de interés La solución amortiguadora patrón del ensayo (175 μl) fue incubada en una placa de 96 pozos con

5 µl del compuesto de ensayo de interés en una partición de concentraciones finales de 0 002 µM a 30 µM a 30 °C por 10 min Típicamente, un punto de titulación 12 fue conducido al preparar diluciones seriadas (desde patrones del compuesto 10 mM) con DMSO de los compuestos de ensayo en placas hijas La reacción fue iniciada mediante la adición de 20 µl de ATP (concentración final 20 µM) Las velocidades de reacción fueron obtenidas empleando un lector de placas Molecular Devices Spectramax (Sunnyvale, CA) durante 10 min a 30 °C. Los valores K_i fueron determinados a partir de los datos de velocidad como una función de la concentración del inhibidor

La Tabla 5 muestra los resultados de la actividad de compuestos seleccionados de esta invención en el ensayo de inhibición de la GSK3 Los números de los compuestos corresponden a los números de compuesto en la Tabla 1. Los compuestos que tienen una actividad designada como "A" proporcionaron un K_i de menos de 0 1 micromolar; los compuestos que tienen una actividad designada como "B" proporcionaron un K_i de entre 0.1 y 1.0 micromolar, y los compuestos que tienen una actividad designada como "C" proporcionaron un K_i superior a 1.0 micromolar

Tabla 5. Actividad Inhibidora de la GSK3 de Compuestos Seleccionados

No. III-a-	Actividad	No. III-a-	Actividad	No. III-a-	Actividad
116	A	117	A	134	C
136	A	137	A	138	A
139	A	140	A	141	A
142	A	144	C	145	A
146	B	147	A	148	A
149	A	150	B	151	A
152	A	153	A	154	A
155	B	156	B	157	A
158	A	159	A	162	A
166	C	172	C	173	C
174	A	175	B	176	A
177	B	178	B	179	A
181	C	184	C	187	C
188	C	189	C	190	B
191	B	193	B	194	A
196	C	198	C	199	A
200	C	201	B	202	C
203	B	205	B	206	A
207	B	208	A	209	A
210	C	211	B	212	A
213	B	214	B	215	A
216	A	217	A	222	B
223	A	224	A	225	A
227	C	228	A	230	B
231	A	232	B	233	C

Ejemplo 34

ENSAYO DE INHIBICION DE LA AURORA-2

Los compuestos fueron evaluados de la siguiente forma por su habilidad al inhibir la Aurora-2 empleando un ensayo

de enzimas acopladas estándar (Fox y otros (1998) *Protein Sci* 7, 2249).

A una solución amortiguadora patrón de ensayo que contiene HEPES 0.1 M 7.5, $MgCl_2$ 10 mM, DTT 1 mM, NaCl 25 mM, fosfoenolpiruvato 2.5 mM, NADH 300 mM, 30 mg/ml de piruvato cinasa, 10 mg/ml de lactato deshidrogenasa, ATP 40 mM, y péptido 800 µM (LRRASLG, American Peptide, Sunnyvale, CA) fue agregada una solución de DMSO de un compuesto de la presente invención hasta una concentración final de 30 µM. La mezcla resultante fue incubada a 30 °C por 10 min La reacción fue iniciada mediante la adición de 10 µL de la solución patrón de Aurora-2 para dar una concentración final de 70 nM en el ensayo Las velocidades de reacción fueron obtenidas al monitorear la absorbancia a 340 nm durante un tiempo de lectura de 5 minutos a 30 °C empleando un lector de placas BioRad Ultramark (Hercules, CA). Los valores K_i fueron determinados a partir de los datos de velocidad como una función de la concentración del inhibidor.

Los ejemplos de compuestos en los cuales se encontró que inhiben la Aurora-2 incluyen III-a-116, III-a-117, III-a-136, III-a-138, III-a-139, III-a-140, y III-a-141.

Ejemplo 35

ENSAYO DE INHIBICION DE LA CDK-2

Los compuestos fueron evaluados de la siguiente manera por su habilidad para inhibir la CDK-2, empleando un ensayo de enzimas acopladas estándar (Fox y otros (1998) *Protein Sci* 7, 2249).

A una solución amortiguadora patrón de ensayo que contiene HEPES 0.1 M 7 5, $MgCl_2$ 10 mM, DTT 1 mM, NaCl 25 mM, fosfoenolpiruvato 2 5 mM, NADH 300 mM, 30 mg/ml de piruvato cinasa, 10 mg/ml de lactato deshidrogenasa, ATP 100 mM, y péptido 100 µM (MAHHHRSPRKRAKKK, American Peptide, Sunnyvale, CA) fue agregada una solución de DMSO de un compuesto de la presente invención hasta una concentración final de 30 µM La mezcla resultante fue incubada a 30 °C por 10 min.

La reacción fue iniciada por medio de la adición de 10 µL de solución patrón de CDK-2/Ciclina A para dar una concentración final de 25 nM en el ensayo. Las velocidades de reacción fueron obtenidas mediante el monitoreo de la absorbancia a 340 nm durante un tiempo de lectura de 5 minutos a 30 °C empleando un lector de placas BioRad Ultramark (Hercules, CA). Los valores K_i fueron determinados a partir de los datos de velocidad como una función de la concentración del inhibidor.

Los siguientes compuestos mostraron tener valores de K_i de 0.1 μM para CDK-2 III-a-116, III-a-142, III-a-149, y III-a-152

Los siguientes compuestos mostraron tener valores de K_i entre 0.1 μM y 1 μM para CDK-2· III-a-146, III-a-148, III-a-150, III-a-155, III-a-162, y III-a-174

Los siguientes compuestos mostraron tener valores de K_i entre 1.0 y 20.0 μM para CDK-2· III-a-117, III-a-156, y III-a-159

Ejemplo 36

ENSAYO DE INHIBICION DE LA LCK

Los compuestos fueron evaluados como inhibidores de la Lck cinasa humana empleando ya sea un ensayo basado en radioactividad o un ensayo espectrofotométrico

Ensayo A de inhibición de la Lck Ensayo basado en radioactividad

Los compuestos fueron ensayados como inhibidores de la Lck cinasa del timo bovino de longitud completa (proveniente de Upstate Biotechnology, cat no. 14-106) expresada y purificada a partir de células baculo virales. La actividad de la Lck cinasa fue monitoreada

mediante el seguimiento de la incorporación de ^{33}p de ATP en la tirosina de un substrato polimérico aleatorio poli Glu-Tyr de la composición, Glu Tyr = 4:1 (Sigma, cat no P-0275) Las siguientes fueron las concentraciones finales de los componentes del ensayo: HEPES 0 025 M, pH 7 6, $MgCl_2$ 10 mM, DTT 2 mM, BSA 0 25 mg/ml, ATP 10 µM (1-2 µCi ^{33}P-ATP por reacción), 5 mg/ml de poli Glu-Tyr, y 1-2 unidades de Src cinasa humana recombinante En un ensayo típico, todos los componentes de la reacción con la excepción del ATP son pre-mezclados y alicuotados en los pozos de la placa de ensayo Los inhibidores disueltos en DMSO fueron adicionados a los pozos para dar una concentración final de DMSO de 2 5%. La placa de ensayo fue incubada a 30 °C por 10 min antes de iniciar la reacción con la ^{33}P-ATP. Después de 20 minutos de reacción, las reacciones fueron extinguidas con 150 µl de ácido tricloroacético (TCA) al 10% conteniendo Na_3PO_4 20 mM Las muestras extinguidas son luego transferidas a una placa de filtro de 96 pozos (Whatman, Filtro de Fibra de Vidrio UNI-Filter GF/F, cat no 7700-3310) instalada en una placa de filtro de vacio múltiple Las placas de filtro fueron lavadas cuatro veces con TCA 10% conteniendo Na_3PO_4 20 mM y luego cuatro veces con metanol. 200 µl del fluido de centelleo fueron luego adicionados a cada pozo. Las placas fueron selladas y la cantidad de radioactividad asociada con los filtros fue cuantificada en un medidor de centelleo TopCount. La radioactividad incorporada fue graficada como una función de la

concentración del inhibidor Los datos fueron ajustados a un modelo de cinética de inhibición competitiva para obtener el K_i para el compuesto

Ensayo B de inhibición de la Lck: Ensayo Espectrofotométrico

La ADP producida a partir de la ATP por la fosforilación catalizada por la Lck cinasa recombinante humana del substrato poli Glu-Tyr fue cuantificada empleando un ensayo de enzimas acopladas (Fox y otros (1998) *Protein Sci* 7, 2249) En este ensayo, una molécula de NADH es oxidada a NAD por cada molécula de ADP producida en la reacción de la cinasa. La desaparición del NADH puede ser convenientemente seguida a 340 nm

Las siguientes fueron las concentraciones finales de los componentes del ensayo: HEPES 0.025 M, pH 7 6, $MgCl_2$ 10 mM, DTT 2 mM, 5 mg/ml de poli Glu-Tyr, y 50 nM de Lck cinasa humana recombinante Las concentraciones finales de los componentes del sistema de enzimas acopladas fueron fosfoenolpiruvato 2 5 mM, NADH 200 µM, 30 µg/ml de piruvato cinasa y 10 µg/ml de lactato deshidrogenasa.

En un ensayo típico, todos los componentes de la reacción con la excepción del ATP fueron pre-mezclados y alicuotados en pozos de una placa de ensayo. Los inhibidores disueltos en DMSO fueron adicionados a los

pozos para dar una concentración final de DMSO de 2 5% La placa de ensayo fue incubada a 30 °C por 10 minutos antes de iniciarse la reacción con ATP 150 µM El cambio de absorbancia a 340 nm con el tiempo, la velocidad de la reacción, fue monitoreada en un lector de placas Molecular Devices. Los datos de velocidad como una función de la concentración del inhibidor fueron ajustados al modelo de cinética de inhibición competitiva para obtener el K_i para el compuesto.

Los siguientes compuestos mostraron tener vlaroes de K_i de 1 µM para Lck III-a-170, III-a-171, III-a-172, III-a-173, III-a-181, y III-a-203

Los siguientes compuestos mostraron tener valores de K_i de entre 1 0 y 20 0 µM para Lck: III-a-204, III-a-205, III-a-206, y III-a-207.

Ejemplo 37

ENSAYO DE INHIBICION DE LA AKT3

Los compuestos fueron evaluados por su habilidad para inhibir la AKT3 empleando un ensayo de enzimas acopladas estándar (Fox y otros, Protein Sci , (1998) 7, 2249). Los ensayos fueron llevados a cabo en una mezcla de HEPES 100 mM 7 5, $MgCl_2$ 10 mM, NaCl 25 mM, DTT 1 mM y DMSO 1 5% Las concentraciones finales de los substratos en el

ensayo fueron ATP (Sigma Chemicals) 170 µM y péptido (RPRAATF, American Peptide, Sunnyvale, CA) 200 µM. Los ensayos fueron llevados a cabo a 30 °C y AKT3 45 nM Las concentraciones finales de los componentes del sistema de enzimas acopladas fueron fosfoenolpiruvato 2 5 mM, NADH 300 µM, 30 µg/ML de piruvato cinasa y 10 µg/ml de lactato deshidrogenasa.

Se preparó una solución amortiguadora patrón de ensayo que contenía todos los reactivos listados anteriormente, con la excepción de la AKT3, DTT, y el compuesto de ensayo de interés 56 µl de la solución patrón fueron colocados en una placa de 384 pozos seguido por la adición de 1 µl de patrón de DMSO 2 mM que contiene el compuesto de ensayo (concentración final del compuesto 30 µM). La placa fue preincubada por aproximadamente 10 minutos a 30 °C y la reacción se inició mediante la adición de 10 µl de enzima (concentración final de 45 nM) y DTT 1 mM Las velocidades de reacción fueron obtenidas empleando un lector de placas BioRad Ultramark (Hercules, CA) durante un tiempo de lectura de 5 minutos a 30 °C Los compuestos que muestran más del 50 % de inhibición versus los pozos estándar que contenian la mezcla de ensayo y el DMSO sin el compuesto de ensayo fueron titulados para determinar los valores IC_{50}.

Los compuestos seleccionados de esta invención que inhiben la AKT3 incluyen: III-a-238

Aunque nosotros hemos presentado un número de realizaciones de esta invención, es claro que nuestra construcción básica puede ser alterada para proporcionar otras realizaciones que utilicen los compuestos y métodos de esta invención Por lo tanto, se apreciará que el alcance de esta invención es definido por las reivindicaciones anexas más que por las realizaciones específicas que han sido representadas a manera de ejemplo.

Apéndice A Nombres de los Compuestos de la Tabla 1

Números III-a-

1· Dimetilamida del ácido 4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

2 {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- pirrolidin- 1- il- metanona;

3: {4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- pirrolidin- 1- il- metanona,

4: (2- piridin- 3- il- etil)- amida del ácido 4- (2- amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

5: [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- morfolin- 4- il- metanona;

6: [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [1,4']bipiperidinil- 1'- il- metanona;

7 {4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (3- hidroxi- piperidin- 1- il)- metanona,

8: {4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [1,4']bipiperidinil- 1'- il- metanona,

9 [4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il] [1,4']bipiperidinil- 1'- il- metanona;

10. {4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [1,4'] bipiperidinil- 1'- il- metanona;

11. [4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- hidroxi- piperidin- 1- il)- metanona,

12. [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [4- (2- fluoro- fenil)- piperazin- 1- il]- metanona;

13. [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- fenil- piperazin- 1- il)- metanona,

14: [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [4- (4- fluoro- fenil)- 3,6- dihidro- 2*H*- piridin- 1- il]- metanona;

15: [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- piridin- 2- il- piperazin- 1- il)- metanona,

16 {4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- morfolin- 4- il- metanona,

17 (2- piridin- 3- il- etil)- amida del ácido 4- [2- amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

18: [4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- morfolin- 4- il- metanona,

19. (2- piridin- 3- il- etil)- amida del ácido 4- (2- amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

20 (2- piridin- 3- il- etil) amida del ácido 4- [2- amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

21: {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (2- fluoro- fenil)- piperazin- 1- il]- metanona,

22· {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- fenil- piperazin- 1- il)- metanona;

23. {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (4- fluoro- fenil)- 3,6- dihidro- 2*H*- piridin- 1- il]- metanona;

24 {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (3,4- dihidro- 1*H*- isoquinolin- 2- il) metanona,

25· {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- piridin- 2- il- piperazin- 1- il)- metanona;

26: {4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1H- pirrol- 2- il}- morfolin- 4- il- metanona,

27 {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- hidroxi- piperidin- 1- il)- metanona,

28 {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [1,4']bipiperidinil- 1'- il- metanona,

29 Bencil- metil- amida del ácido 4- (2- amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

30· [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [4- (4- metoxi- fenil)- piperazin- 1- il]- metanona,

31: [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (2- hidroximetil- piperidin- 1- il)- metanona,

32: [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (3,4- dihidro- 1*H*- isoquinolin- 2- il)- metanona,

33· Bencil- metil- amida del ácido 4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

34: {4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (4- fluoro- fenil)- 3,6- dihidro- 2*H*- piridin- 1- il]- metanona;

35. {4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (3,4- dihidro- 1*H*- isoquinolin- 2- il) metanona;

36: Bencil- metil- amida del ácido 4- (2- Amino- 5- *m*- tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

37: [4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- fenil- piperazin- 1- il)- metanona,

38 [4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- metil- [1,4]diazepan- 1- il)- metanona;

39 [4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (3,4- dihidro- 1*H*- isoquinolin- 2- il)- metanona;

40: Bencil- metil- amida del ácido 4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

41. {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- metil- [1,4]diazepan- 1- il) metanona,

42: Bencil- metil- amida del ácido 4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

43 {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [2- (2- hidroxi- etil)- piperidin- 1- il] metanona;

44 {4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- fenil- piperazin- 1- il)- metanona,

45 [4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [4- (2- fluoro- fenil)- piperazin- 1- il]- metanona;

46: [4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (3- hidroxi- piperidin- 1- il)- metanona;

47 [4- (2- Amino- 5- *m*-tolil- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- ıl]- [4- (4- metoxı- fenıl)- pıperazın- 1- ıl]- metanona;

48: [4- (2- Amıno- 5- *m*-tolil- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- ıl]- [4- (4- fluoro- fenıl)- 3,6- dıhıdro- 2*H*- pırıdın- 1- ıl]- metanona;

49 {4- [2- Amıno- 5- (3- cloro- 2- fluoro- fenıl)- pırimıdın- 4- ıl]- 1*H*- pırrol- 2- ıl}- [4- (2- fluoro- fenıl)- pıperazın- 1- il]- metanona;

50: {4- [2- Amıno- 5- (3- cloro- 2- fluoro- fenıl)- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- ıl}- [4- (4- metoxı- fenıl)- pıperazın- 1- ıl]- metanona,

51: {4- [2- Amıno- 5- (3- cloro- 2- fluoro- fenıl)- pirimıdın- 4- ıl]- 1*H*- pırrol- 2- ıl}- (4- metil- [1,4] dıazepan- 1- ıl) metanona;

52 1- (4- {4- [2- Amıno- 5- (3- cloro- 2- fluoro- fenil)- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carbonılo}- pıperazın- 1- ıl)- etanona;

53: {4- [2- Amıno- 5- (3- cloro- 2- fluoro- fenıl)- pırimıdın- 4- ıl]- 1*H*- pırrol- 2- il}- (3,4- dıhıdro- 1*H*- ısoquınolın- 2- ıl)- metanona,

54 {4- [2- Amıno- 5- (3- cloro- fenıl)- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- ıl}- (3- hıdroxı- pıperıdın- 1- ıl)- metanona;

55 [4- (2- Amıno- 5- fenıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- ıl] (4- metıl- [1,4]dıazepan- 1- il)- metanona,

56 1- (4- {4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carbonilo}- piperazin- 1- il)- etanona;

57 {4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- metil- [1,4]diazepan- 1- il) metanona,

58: [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (3- hidroxi- piperidin- 1- il)- metanona;

59: Metil- (2- piridin- 2- il- etil)- amida del ácido 4- [2- amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

60. [4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [2- (2- hidroxi- etil)- piperidin- 1- il]- metanona;

61 {4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [2- (2- hidroxi- etil)- piperidin- 1- il]- metanona;

62: (2- hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- [2- amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

63 {4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- piridin- 2- il- piperazin- 1- il)- metanona;

64 [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- hidroxi- piperidin- 1- il)- metanona,

65: {4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- hidroxi- piperidin- 1- il)- metanona,

66 {4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- hidroxi- piperidin- 1- il)- metanona,

67 {4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- piridin- 2- il- piperazin- 1- il)- metanona;

68 {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (2- hidroxi- etil)- piperazin- 1- il]- metanona;

69· 1- {4- [4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- carbonil]- piperazin- 1- il}- etanona;

70: {4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (2- fluoro- fenil)- piperazin- 1- il]- metanona,

71: [4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- pirrolidin- 1- il- metanona,

72 {4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- morfolin- 4- il- metanona,

73: Bencilamida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

74 3,4- Difluoro- bencilamida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

75. (2- Hidroxi- 1- fenil- etil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

76 4- Fluoro- bencilamida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

77: 3- Cloro- bencilamida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

78. 4- Metoxi- bencilamida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

79 3- Cloro- 4- fluoro- bencilamida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

80: (Tetrahidro- furan- 2- ilmetil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

81: (Tetrahidro- furan- 2- ilmetil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

82. (3- Hidroxi- 1- fenil- propil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

83· (3- Hidroxi- 1- fenil- propil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

84 3- Cloro- 4- fluoro- bencilamida del ácido 4- (2,5- diamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

85: 3- Cloro- 4- fluoro- bencilamida del ácido 4- (2- amino- 5- metilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

86 3- Cloro- 4- fluoro- bencilamida del ácido 4- (5- acetilamino- 2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

87: 3- Cloro- 4- fluoro- bencilamida del ácido 4- [2- amino- 5- (3- metil- ureido)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

88: 3- Cloro- 4- fluoro- bencilamida del ácido 4- (2- amino- 5- hidroxi- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

89 3- Cloro- 4- fluoro- bencilamida del ácido 4- (2- amino- 5- metilaminometil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

90: 3- Cloro- 4- fluoro- bencilamida del ácido 4- (2- amino- 5- hidroximetil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

91: 3- Cloro- 4- fluoro- bencilamida del ácido 4- [2- ciclohexilamino- 5- (3- metil- ureido)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

92 3- Cloro- 4- fluoro- bencilamida del ácido 4- [2- acetilamino- 5- (3- metil- ureido)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

93: 3- Cloro- 4- fluoro- bencilamida del ácido 4- (5- hidroxi- 2- metanosulfonilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

94· 3- Cloro- 4- fluoro- bencilamida del ácido 4- (2- amino- 5- metanosulfonil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

95: 3,4- Difluoro- bencilamida del ácido 4- (2- amino- 5- hidroximetil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

96: 3,4- Difluoro- bencilamida del ácido 4- (2- ciclohexilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

97 (Piridin- 4- ilmetil)- amida del ácido 4- [2- Amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

98: 3- Trifluorometil bencilamida del ácido 4- [5- (3,5- dicloro- fenil)- 2- fenilamino- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

99 (2- hidroxi- 1- fenil etil)- amida del ácido 4- [2- amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

100: (Benzo[1,3]dioxol- 5- ilmetil)- amida del ácido 4- [2- amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

101· (2- dimetilamino- 2- piridin- 3- il- etil)- amida del ácido 4- [2- amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

102. 4- Metanosulfonil- bencilamida del ácido 4- [2- amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

103: (Benzo[1,3]dioxol- 5- ilmetil)- amida del ácido 4- [5- (3,5- Dicloro- fenil)- 2- fenilamino- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

104: (2- morfolin- 4- il- 2- piridin- 3- il- etil)- amida del ácido 4- [5- (3,5- dicloro- fenil)- 2- fenilamino- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

105: (2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2- amino- 5- (3- fluoro- 5- trifluorometil- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

106 (2- piridin- 3- il- etil)- amida del ácido 4- (2- amino- 5- propil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

107 (2- piridin- 3- il- etil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

108. (2- piridin- 3- il- etil)- amida del ácido 4- (5- metil- 2- metilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

109 (2- piridin- 3- il- etil)- amida del ácido 4- (2- metilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

110 (2- dimetilamino- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

111 Propilamida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

112: (3- fenil- propil)- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

113: (Naftalen- 1- ilmetil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

114: Ciclopropilamida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

115 2- Trifluorometil- bencilamida del ácido 4- (2- etilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

116: (2- Hidroxi- 1- fenil- etil)- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

117: (2- Hidroxi- 1- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

118 (4- metil- ciclohexil)- amida del ácido 4- (2- etilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

119 Isopropilamida del ácido 4- (5- etil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

120 (2- Amino- etil)- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

121 Bencil- metil- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

122 (2- Hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

123: 1- {4- [4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carbonil]- piperazin- 1- il}- etanona;

124 (3- fenil- propil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

125 [2- (6- metoxi- 1*H*- indol- 3- il)- etil]- amida del ácido 4- (2- amino- 5- etil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

126: (2- fenoxi- etil)- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

127: (1- metil- 3- fenil- propil)- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

128: (1*H*- benzoimidazol- 2- ilmetil)- amida del ácido 4- (5- metil- 2- metilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

129: (1- hidroximetil- 3- metil- butil)- amida del ácido 4- (5- metil- 2- metilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

130 [1- hidroximetil- 2- (1*H*- imidazol- 4- il)- etil]- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

131: (Tetrahidro- furan- 2- ilmetil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

132: 3,4- difluoro bencilamida del ácido 4- [2- (2- dietilamino- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

133 Bencilamida del ácido 4- [5- metil- 2- (2- piperidin- 1- il- quinazolin- 4- ilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

134: [1- (3- cloro- 4- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (5- metil- 2- metilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

135 [1- (3- cloro- 4- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

136 (2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (3- fluoro- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

137: (2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (3- metoxi- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

138 (2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (3- hidroxi- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

139 (2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (benzo[1,3]dioxol- 5- ilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

140 (2- Hidroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [5- metıl- 2- (4- sulfamoıl- fenılamıno)- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

141 (2- Hidroxi- 1- fenıl- etıl)- amıda del ácıdo 4- [2- (3- bencıloxı- fenılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílico;

142: (2- Hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [2- (4- hıdroxı- cıclohexılamino)- 5- metıl- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

143· (2- Hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (5- cıclohexıl- 2- fenılamino- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

144: (2- Hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (5- cıclopropıl- 2- fenilamıno- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

145 [1- (3- fluoro- 4- metıl- fenıl)- 2- hıdroxı- etıl]- amıda del ácido 4- (5- metıl- 2- fenılamıno- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

146: [2- hıdroxi- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- (5- metıl- 2- fenılamıno- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

147 [1- (3- fluoro- 4- metıl- fenıl)- 2- hıdroxı- etıl]- amida del ácıdo 4- [2- (3- fluoro- fenılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

148: [2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- [2- (3- fluoro- fenılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco,

149: (2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [5- metıl- 2- (3- trıfluorometil- fenılamıno)- pırımıdın- 4- ıl]- 1*H*- pirrol- 2- carboxílıco;

150· (2- hıdroxi- 1- fenıl- etıl)- amıda del ácıdo 4- (2- bencılamıno- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

151: (2- hıdroxi- 1- fenıl- etıl)- amıda del ácıdo 4- [2- (3,4- dımetil- fenılamıno)- 5- metıl- pırımıdin- 4- ıl]- 1*H*- pırrol- 2- carboxílıco,

152: (2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [2- (4- bencıloxı- fenılamino)- 5- metıl- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

153: (2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (2- ısopropılamıno- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

154. (2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [5- metıl- 2- (2,2,2- trıfluoro- etılamıno)- pırımıdın- 4- il]- 1*H*- pırrol- 2- carboxílico;

155. (2- hıdroxi- 1- fenıl- etıl)- amıda del ácıdo 4- [2- (2- hidroxı- 1- fenıl- etılamıno)- 5- metıl- pırımıdin- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

156: (2- hıdroxı- 1- fenıl- etıl)- amıda del ácido 4- [2- (2- metoxı- fenılamino)- 5- metıl- pırimidın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

157 (2- hıdroxi- 1- fenıl- etıl)- amıda del ácıdo 4- [5- metıl- 2- (4- trıfluorometoxı- fenilamıno)- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

158 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- isobutilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

159: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (ciclopropilmetil- amino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

160 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (5- metoximetil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

161 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- amino- 5- metoximetil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

162: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- ciclopropilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

163: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (5- metil- 2- propilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

164: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (5- metoximetil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

165: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (5- hidroximetil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

166: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- fenil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

167 (2- hidroxi- 1- metil- 2- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

168· (2- hidroxi- 1- metil- 2- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

169: (2- hidroxi- 2- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

170: (2- hidroxi- 1- hidroximetil- 2- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

171. (2- hidroxi- 1- hidroximetil- 2- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

172: (3- hidroxi- 1- fenil- propil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

173 (3- hidroxi- 1- fenil- propil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

174 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (1- hidroximetil- ciclopropilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

175 · (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

176: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- metil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

177: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- propilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

178· (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- Hidroxi- propilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

179: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- ciclohexilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

121 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- metil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

121: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (3- Dimetilamino- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

180 (2- hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

181· (2- hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

183 (2- hidroxi- 2- fenil- etil)- metil- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

184: Metil ester del ácido {[4- (2- Etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carbonil]- amino}- fenil- acético,

186: (2- hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- (2- Amino- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico;

187: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metoximetil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

188: (2- hidroxi- 1- piridin- 3- il- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

189: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- etilamino- 5- hidroximetil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

190 [1- (3- fluoro- 5- trifluorometil- fenil)- 2- hidroxi- etil]- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

191: [1- (3- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

192. [1- (2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

193 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- ciclopropilo- 1- hidroximetil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

194. (2- hidroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [2- (2,3- dımetıl- fenılamino)- 5- metıl- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

195. (2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (2- etoxıamino- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

196. (2- hıdroxı- 1- fenil- etıl)- amıda del ácıdo 4- [2- (1- hıdroxımetıl- 2- metıl- propılamıno)- 5- metıl- pırımıdın- 4- il]- 1*H*- pırrol- 2- carboxílico,

197 (2- oxo- 1- fenil- propıl)- amıda del ácıdo 4- (2- etılamıno- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

198 [2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- (2- etılamino- 5- metıl- pırımıdın- 4- il)- 1*H*- pırrol- 2- carboxílıco;

199: [2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- [2- (3- fluoro- fenılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

200 [2- hıdroxi- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- [2- (2- cloro- fenılamıno)- 5- metıl- pirımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

201: [2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etil]- amida del ácıdo 4- [2- (2- hıdroxi- 1- fenıl- etılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílico,

200: [2- hidroxı- 1- (3- trifluorometıl- fenil)- etıl]- amıda del ácıdo 4- [2- (3- dımetılamıno-

fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

202. [2- hidroxi- 1- (3- trifluorometil- fenil)- etil]- amida del ácido 4- (2- ciclopropilamino- 5- metil- pirimidin- 4- il)-1*H*- pirrol- 2- carboxílico;

203. [2- hidroxi- 1- (2- metoxi- fenil)- etil]- amida del ácido 4- (2- ciclopropilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

204. [1- (3- cloro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (2- ciclopropilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

205: (2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- (2- ciclopropilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

206: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- metoxiamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

207: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- isopropoxiamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

208 (2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (3- dimetilamino- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

209: (2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (2- cloro- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

210: (2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- fenil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

211: (2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (2,3- dimetil- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

212: (2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (3- fluoro- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

213. (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- acetilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

214· (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (5- metil- 2- *o*-tolilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

215: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (piridin- 3- ilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

216: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- {5- metil- 2- [(tetrahidro- furan- 2- ilmetil)- amino]- pirimidin- 4- il}- 1*H*- pirrol- 2- carboxílico;

217 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- {5- metil- 2- [(tetrahidro- furan- 2- ilmetil)- amino]- pirimidin- 4- il}- 1*H*- pirrol- 2- carboxílico,

218 Etil ester del ácido N'- 4- [5- (2- hidroxi- 1- fenil- etilcarbamoil)- 1*H*- pirrol- 3- il]- 5- metil- pirimidin- 2- il} hidrazinacarboxílico,

219 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- {5- metil- 2- [(piridin- 3- ilmetil)- amino]- pirimidin- 4- il}- 1*H*- pirrol- 2- carboxílico;

220 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- ciclopropilmetoxiamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

221· (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (isoxazol- 3- ilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

222 (2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- metil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

223 (2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- (5- metil- 2- *o*-tolilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

224: [1- (3- cloro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (5- metil- 2- *o*-tolilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

225 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- etoxiamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

226: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (N',N'- dimetil- hidrazino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

227: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (2- trifluorometil- fenilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

228 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (morfolin- 4- ilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

229: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (5- metil- isoxazol- 3- ilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

230 (2- hidroxi- 1- fenil- etil)- amida del ácido 4- {2- [1- (3- cloro- 4- fluoro- fenil)- 2- hidroxi- etilamino]- 5- metil- pirimidin- 4- il}- 1*H*- pirrol- 2- carboxílico;

231· [1- (3- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

232: [1- (3- cloro- fenil)- 2- hidroxi- etil]- amida del ácido 4- [2- (1- hidroximetil- propilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

233: [1- (3- cloro- fenil)- 2- hidroxi- etil]- amida del ácido 4- [2- (2- hidroxi- 1- hidroximetil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

234: (2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (1- hidroximetil- propilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

235. (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- hidroximetil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

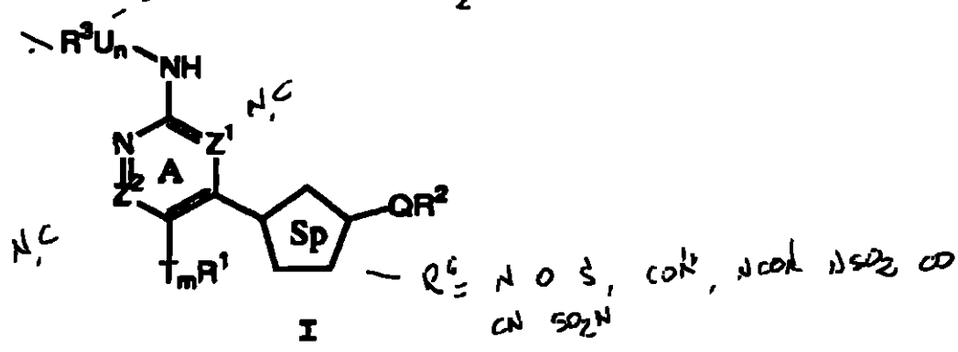
236: (2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (1- hidroximetil- propilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

237· (2- hidroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [5- metil- 2- (2- metıl- cıclopropılamıno)- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco, y

238 (2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (2- cıanoamıno- 5- metıl- pırımıdın- 4- ıl)- 1H- pırrol 2- carboxílıco.

Nosotros reivindicamos

1. Un método para inhibir la actividad de la ERK-2 en un paciente, método que comprende la administración a dicho paciente de un compuesto de la fórmula I



I

o un derivado farmacéuticamente aceptable del mismo, en donde:

Sp es un grupo espaciador que comprende un anillo heteroaromático de 5 miembros, en donde el Anillo A y QR^2 se encuentran unidos a Sp en posiciones no adyacentes, y en donde Sp tiene hasta dos substituyentes R^6, con la condición de que dos átomos de carbono substituibles del anillo en Sp no son substituidos de manera simultanea por R^6;

Z^1 y Z^2 son cada uno seleccionados de manera independiente a partir de N o CH,

T y Q son cada uno un grupo ligante seleccionado de manera independiente;

U es seleccionado a partir de $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, o $-SO_2-$;

m y n son cada uno seleccionados de manera independiente a partir de cero o uno;

R^1 es seleccionado a partir de hidrógeno, CN, halógeno, R, $N(R^7)_2$, OR, o OH,

R^2 es seleccionado a partir de $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, $-(CH_2)_yCH(R^8)CH(R^5)_2$, $-N(R^4)_2$, o $-NR^4(CH_2)_yN(R^4)_2$;

y es 0 - 6,

R^3 es seleccionado a partir de R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, o $-(CH_2)_yCH(R^8)N(R^4)_2$,

cada R es seleccionado de manera independiente a partir de un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, arilo C_{6-10}, un anillo heteroarilo que tiene 5 - 10 átomos en el anillo, o un anillo heterociclilo que tiene 3 - 10 átomos en el anillo;

cada R^4 es seleccionado de manera independiente a partir de R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, o $-(CH_2)_yCH(R^5)_2$,

cada R^5 es seleccionado de manera independiente a partir de R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$;

cada R^6 es seleccionado de manera independiente a partir de R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$,

cada R^7 es seleccionado de manera independiente a partir de hidrógeno o un grupo alifático C_{1-6} substituido de manera opcional, o dos R^7 en el mismo nitrógeno son

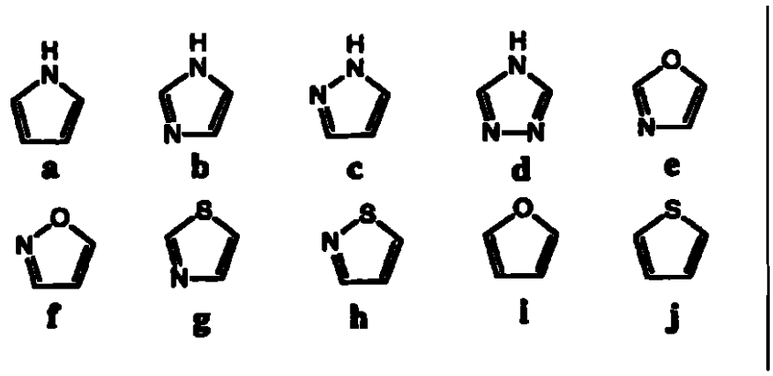
tomados junto con el nitrógeno para formar un anillo heterocíclilo o heteroarilo de 5 - 8 miembros,

R^8 es seleccionado a partir de R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, o $(CH_2)_wSR^7$;

y

cada w es seleccionado de manera independiente a partir de 0 - 4

2. El método de acuerdo con la reivindicación 1, en donde Sp es seleccionado a partir de uno de los siguientes:



o un derivado farmacéuticamente aceptable de los mismos

3. El método de acuerdo con la reivindicación 2, en donde dicho compuesto tiene una o más características seleccionadas a partir del grupo que consiste de

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, amino, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros;

(c) Q es -CO-, $-CO_2-$, -CONH-, $-SO_2-$, $-SO_2NH-$, -OC(O)NH-, -C(O)ONH-, o -CONHNH-;

(d) R^2 es $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, o $-(CH_2)_yCH(R^8)CH(R^5)_2$;

(f) R^4 es R, R^7 o $-(CH_2)_yCH(R^5)_2$, y

(g) R^5 es un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, fenilo, heteroarilo de 5 - 6 miembros, o heterociclilo de 5 - 6 miembros.

4 El método de acuerdo con la reivindicación 3, en donde.

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros,

(b) T_mR^1 es hidrógeno, amino, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros;

(c) Q es -CO-, $-CO_2-$, -CONH-, $-SO_2-$, $-SO_2NH-$, -OC(O)NH-, -C(O)ONH-, o -CONHNH-,

(d) R^2 es $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, o $-(CH_2)_yCH(R^8)CH(R^5)_2$;

(f) R^4 es R, R^7 o $-(CH_2)_yCH(R^5)_2$; y

(g) R^5 es un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, fenilo, heteroarilo de 5 - 6 miembros, o heterociclilo de 5 - 6 miembros.

5. El método de acuerdo con la reivindicación 3, en donde dicho compuesto tiene una o más características seleccionadas a partir del grupo que consiste de.

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, $-CH(CH_2OH)CH_2$ciclopropilo, o un grupo fenilo, bencilo, o isoxazolilo substituidos de manera opcional,

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, o CH_2NHCH_3,

(c) Q es -CO-, -CONH-, $-SO_2-$, o $-SO_2NH-$,

(d) R^2 es $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, o $-(CH_2)_yCH(R^8)CH(R^5)_2$, en donde R^8 es OH o CH_2OH, y

(e) R^5 es $-CH_2OH$, $-(CH_2)_2OH$, isopropilo, o un grupo substituido de manera opcional seleccionado a partir de pirrolidin-1-il, morfolin-4-il,

piperidin-1-il, piperazin-1-il, 4-metil[1,4]diazepan-1-il, 4-fenil-piperazin-1-il, piridin-3-il, piridin-4-il, imidazolilo, furan-2-il, 1,2,3,4-tetrahidroisoquinolina, tetrahidrofuran-2-il, ciclohexilo, fenilo, o bencilo

6 El método de acuerdo con la reivindicación 5, en donde:

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, $-CH(CH_2OH)CH_2$ciclopropilo, o un grupo fenilo, bencilo, o isoxazolilo substituidos de manera opcional,

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, o CH_2NHCH_3;

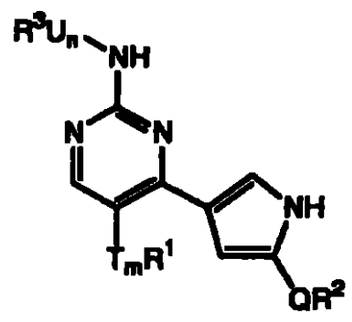
(c) Q es -CO-, -CONH-, $-SO_2-$, o $-SO_2NH-$,

(d) R^2 es $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, o $-(CH_2)_yCH(R^6)CH(R^5)_2$, en donde R^6 es OH o CH_2OH; y

(e) R^5 es $-CH_2OH$, $-(CH_2)_2OH$, isopropilo, o un grupo substituido de manera opcional seleccionado a partir de pirrolidin-1-il, morfolin-4-il, piperidin-1-il, piperazin-1-il, 4-metil[1,4]diazepan-1-il, 4-fenil-piperazin-1-

il, piridin-3-il, piridin-4-il, imidazolilo, furan-2-il, 1,2,3,4-tetrahidroisoquinolina, tetrahidrofuran-2-il, ciclohexilo, fenilo, o bencilo

7. El método de acuerdo con la reivindicacion 2, en donde dicho compuesto es de la fórmula III-a:



III-a

o un derivado farmacéuticamente aceptable del mismo.

8 El método de acuerdo con la reivindicación 7, en donde dicho compuesto tiene una o más características seleccionadas a partir del grupo que consiste de:

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^6)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros,

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}

o un anillo arilo o heteroarilo de 5 - 6 miembros,

(c) Q es -CO-, -CO_2-, -CONH-, -SO_2-, -SO_2NH-, -OC(O)NH-, -C(O)ONH-, o -CONHNH-,

(d) R^2 es -$NR^4(CH_2)_yN(R^4)_2$, -$(CH_2)_yR^5$, -$(CH_2)_yCH(R^5)_2$, o -$(CH_2)_yCH(R^8)CH(R^5)_2$,

(f) R^4 es R, R^7 o -$(CH_2)_yCH(R^5)_2$, y

(g) R^5 es un grupo substituido de manera opcional seleccionado a partir de fenilo, heteroarilo de 5 - 6 miembros, o heterociclilo de 5 - 6 miembros.

9. El método de acuerdo con la reivindicación 8, en donde:

(a) R^3 es hidrógeno, carbociclilo, -$CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros,

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros;

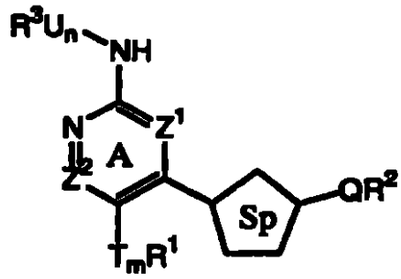
(c) Q es -CO-, -CO_2-, -CONH-, -SO_2-, -SO_2NH-, -OC(O)NH-, -C(O)ONH-, o -CONHNH-,

(d) R^2 es -$NR^4(CH_2)_yN(R^4)_2$, -$(CH_2)_yR^5$, -$(CH_2)_yCH(R^5)_2$, o -$(CH_2)_yCH(R^8)CH(R^5)_2$;

(f) R^4 es R, R^7 o -$(CH_2)_yCH(R^5)_2$; y

(g) R^5 es un grupo substituido de manera opcional seleccionado a partir de fenilo, heteroarilo de 5 - 6 miembros, o heterociclilo de 5 - 6 miembros.

10 Un método para inhibir la actividad de la ERK-2 en una muestra biológica, método que comprende contactar dicha muestra con un compuesto de la fórmula I



I

o un derivado farmacéuticamente aceptable del mismo, en donde.

Sp es un grupo espaciador que comprende un anillo heteroaromático de 5 miembros, en donde el Anillo A y QR^2 se encuentran unidos a Sp en posiciones no adyacentes; y en donde Sp tiene hasta dos substituyentes R^6, con la condición de que dos átomos de carbono substituibles del anillo en Sp no son substituidos de manera simultanea por R^6;

Z^1 y Z^2 son cada uno seleccionados de manera independiente a partir de N o CH,

T y Q son cada uno un grupo ligante seleccionado de manera independiente,

U es seleccionado a partir de $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, o $-SO_2-$;

m y n son cada uno seleccionados de manera independiente a partir de cero o uno;

R^1 es seleccionado a partir de hidrógeno, CN, halógeno, R, $N(R^7)_2$, OR, o OH,

R^2 es seleccionado a partir de $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, $-(CH_2)_yCH(R^8)CH(R^5)_2$, $-N(R^4)_2$, o $-NR^4(CH_2)_yN(R^4)_2$,

y es 0 - 6;

R^3 es seleccionado a partir de R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, o $-(CH_2)_yCH(R^8)N(R^4)_2$,

cada R es seleccionado de manera independiente a partir de un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, arilo C_{6-10}, un anillo heteroarilo que tiene 5 - 10 átomos en el anillo, o un anillo heterociclilo que tiene 3 - 10 átomos en el anillo,

cada R^4 es seleccionado de manera independiente a partir de R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, o $-(CH_2)_yCH(R^5)_2$;

cada R^5 es seleccionado de manera independiente a partir de R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$,

cada R^6 es seleccionado de manera independiente a partir de R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$,

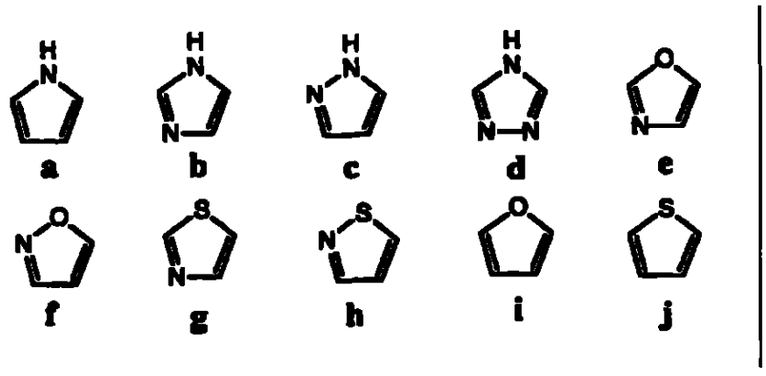
cada R^7 es seleccionado de manera independiente a partir de hidrógeno o un grupo alifático C_{1-6} substituido de manera opcional, o dos R^7 en el mismo nitrógeno son tomados junto con el nitrógeno para formar un anillo heterociclilo o heteroarilo de 5 - 8 miembros;

R^8 es seleccionado a partir de R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, o $(CH_2)_wSR^7$;

y

cada w es seleccionado de manera independiente a partir de 0 - 4

11. El método de acuerdo con la reivindicación 10, en donde Sp es seleccionado a partir de uno de los siguientes



o un derivado farmacéuticamente aceptable de los mismos

12 El método de acuerdo con la reivindicación 11, en donde dicho compuesto tiene una o más características seleccionadas a partir del grupo que consiste de:

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional

seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros,

(b) T_mR^1 es hidrógeno, amino, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros;

(c) Q es -CO-, $-CO_2-$, -CONH-, $-SO_2-$, $-SO_2NH-$, -OC(O)NH-, -C(O)ONH-, o -CONHNH-;

(d) R^2 es $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, o $-(CH_2)_yCH(R^8)CH(R^5)_2$;

(f) R^4 es R, R^7 o $-(CH_2)_yCH(R^5)_2$; y

(g) R^5 es un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, fenilo, heteroarilo de 5 - 6 miembros, o heterociclilo de 5 - 6 miembros.

13. El método de acuerdo con la reivindicación 12, en donde

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, amino, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}

o un anillo arilo o heteroarilo de 5 - 6 miembros;

(c) Q es -CO-, -CO_2-, -CONH-, -SO_2-, -SO_2NH-, -OC(O)NH-, -C(O)ONH-, o -CONHNH-,

(d) R^2 es -$NR^4(CH_2)_yN(R^4)_2$, -$(CH_2)_yR^5$, -$(CH_2)_yCH(R^5)_2$, o -$(CH_2)_yCH(R^8)CH(R^5)_2$;

(f) R^4 es R, R^7 o -$(CH_2)_yCH(R^5)_2$, y

(g) R^5 es un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, fenilo, heteroarilo de 5 - 6 miembros, o heterociclilo de 5 - 6 miembros.

14. El método de acuerdo con la reivindicación 12, en donde dicho compuesto tiene una o más características seleccionadas a partir del grupo que consiste de

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, -CH(CH_2OH)fenilo, -CH(CH_2OH)etilo, -CH(CH_2OH)$_2$, -CH(CH_2OH)isopropilo, -CH(CH_2OH)CH_2ciclopropilo, o un grupo fenilo, bencilo, o isoxazolilo substituidos de manera opcional;

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, NHC(O)$NHCH_3$, o CH_2NHCH_3;

(c) Q es -CO-, -CONH-, -SO_2-, o -SO_2NH-,

(d) R^2 es $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, o $-(CH_2)_yCH(R^8)CH(R^5)_2$, en donde R^8 es OH o CH_2OH; y

(e) R^5 es $-CH_2OH$, $-(CH_2)_2OH$, isopropilo, o un grupo substituido de manera opcional seleccionado a partir de pirrolidin-1-il, morfolin-4-il, piperidin-1-il, piperazin-1-il, 4-metil[1,4]diazepan-1-il, 4-fenil-piperazin-1-il, piridin-3-il, piridin-4-il, imidazolilo, furan-2-il, 1,2,3,4-tetrahidroisoquinolina, tetrahidrofuran-2-il, ciclohexilo, fenilo, o bencilo.

15 El método de acuerdo con la reivindicación 14, en donde.

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, $-CH(CH_2OH)CH_2$ciclopropilo, o un grupo fenilo, bencilo, o isoxazolilo substituidos de manera opcional,

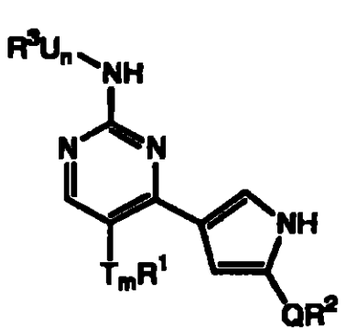
(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, o CH_2NHCH_3;

(c) Q es $-CO-$, $-CONH-$, $-SO_2-$, o $-SO_2NH-$,

(d) R^2 es $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, o $-(CH_2)_yCH(R^8)CH(R^5)_2$, en donde R^8 es OH o CH_2OH, y

(e) R^5 es $-CH_2OH$, $-(CH_2)_2OH$, isopropilo, o un grupo substituido de manera opcional seleccionado a partir de pirrolidin-1-il, morfolin-4-il, piperidin-1-il, piperazin-1-il, 4-metil[1,4]diazepan-1-il, 4-fenil-piperazin-1-il, piridin-3-il, piridin-4-il, imidazolilo, furan-2-il, 1,2,3,4-tetrahidroisoquinolina, tetrahidrofuran-2-il, ciclohexilo, fenilo, o bencilo.

16. El método de acuerdo con la reivindicacion 11, en donde dicho compuesto es de la fórmula III-a:



III-a

o un derivado farmacéuticamente aceptable del mismo

17 El método de acuerdo con la reivindicación 16, en donde dicho compuesto tiene una o más características seleccionadas a partir del grupo que consiste de·

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4},

heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros,

(c) Q es -CO-, $-CO_2-$, -CONH-, $-SO_2-$, $-SO_2NH-$, -OC(O)NH-, -C(O)ONH-, o -CONHNH-;

(d) R^2 es $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, o $-(CH_2)_yCH(R^8)CH(R^5)_2$;

(f) R^4 es R, R^7 o $-(CH_2)_yCH(R^5)_2$; y

(g) R^5 es un grupo substituido de manera opcional seleccionado a partir de fenilo, heteroarilo de 5 - 6 miembros, o heterociclilo de 5 - 6 miembros.

18 El método de acuerdo con la reivindicación 17, en donde

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros,

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros;

(c) Q es -CO-, -CO_2-, -CONH-, -SO_2-, -SO_2NH-, -OC(O)NH-, -C(O)ONH-, o -CONHNH-,

(d) R^2 es -$NR^4(CH_2)_yN(R^4)_2$, -$(CH_2)_yR^5$, -$(CH_2)_yCH(R^5)_2$, o -$(CH_2)_yCH(R^8)CH(R^5)_2$,

(f) R^4 es R, R^7 o -$(CH_2)_yCH(R^5)_2$, y

(g) R^5 es un grupo substituido de manera opcional seleccionado a partir de fenilo, heteroarilo de 5 - 6 miembros, o heterociclilo de 5 - 6 miembros

19 Un método para inhibir la actividad de la ERK-2 en un paciente, método que comprende la administración a dicho paciente de un compuesto seleccionado del grupo que consiste de

Dimetilamida del ácido 4- (2- Amino- 5- fenil-pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- pirrolidin- 1- il- metanona;

{4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- pirrolidin- 1- il- metanona;

(2- piridin- 3- il- etil)- amida del ácido 4- (2- amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

[4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- morfolin- 4- il- metanona;

[4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [1,4']bipiperidinil- 1'- il- metanona;

{4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (3- hidroxi- piperidin- 1- il)- metanona,

{4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [1,4']bipiperidinil- 1'- il- metanona;

[4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il] [1,4']bipiperidinil- 1'- il- metanona,

{4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [1,4'] bipiperidinil- 1'- il- metanona;

[4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- hidroxi- piperidin- 1- il)- metanona;

[4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [4- (2- fluoro- fenil)- piperazin- 1- il]- metanona,

[4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- fenil- piperazin- 1- il)- metanona,

[4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [4- (4- fluoro- fenil)- 3,6- dihidro- 2H- piridin- 1- il]- metanona;

[4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- piridin- 2- il- piperazin- 1- il)- metanona;

{4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- morfolin- 4- il- metanona;

(2- piridin- 3- il- etil)- amida del ácido 4- [2- amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

[4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- morfolin- 4- il- metanona;

(2- piridin- 3- il- etil)- amida del ácido 4- (2- amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- piridin- 3- il- etil) amida del ácido 4- [2- amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (2- fluoro- fenil)- piperazin- 1- il]- metanona,

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- fenil- piperazin- 1- il)- metanona;

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (4- fluoro- fenil)- 3,6- dihidro- 2*H*- piridin- 1- il]- metanona,

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (3,4- dihidro- 1*H*- isoquinolin- 2- il)- metanona,

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- piridin- 2- il- piperazin- 1- il)- metanona,

{4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1H- pirrol- 2- il}- morfolin- 4- il- metanona;

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- hidroxi- piperidin- 1- il)- metanona,

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [1,4']bipiperidinil- 1'- il-metanona;

Bencil- metil- amida del ácido 4- (2- amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

[4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [4- (4- metoxi- fenil)- piperazin- 1- il]- metanona;

[4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (2- hidroximetil- piperidin- 1- il)- metanona,

[4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (3,4- dihidro- 1*H*- isoquinolin- 2- il)- metanona;

Bencil- metil- amida del ácido 4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

{4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (4- fluoro- fenil)- 3,6- dihidro- 2*H*- piridin- 1- il]- metanona,

{4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (3,4- dihidro- 1*H*- isoquinolin- 2- il)- metanona;

Bencil- metil- amida del ácido 4- (2- Amino- 5- *m*- tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

[4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- fenil- piperazin- 1- il)- metanona,

[4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- metil- [1,4]diazepan- 1- il)- metanona,

[4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (3,4- dihidro- 1*H*- isoquinolin- 2- il)- metanona,

Bencil- metil- amida del ácido 4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- metil- [1,4]diazepan- 1- il)- metanona,

Bencil- metil- amida del ácido 4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [2- (2- hidroxi- etil)- piperidin- 1- il]- metanona;

{4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- fenil- piperazin- 1- il)- metanona,

[4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [4- (2- fluoro- fenil)- piperazin- 1- il]- metanona,

[4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (3- hidroxi- piperidin- 1- il)- metanona,

[4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [4- (4- metoxi- fenil)- piperazin- 1- il]- metanona,

[4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- [4- (4- fluoro- fenil)- 3,6- dihidro- 2H- piridin- 1- il]- metanona;

{4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (2- fluoro- fenil)- piperazin- 1- il]- metanona;

{4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (4- metoxi- fenil)- piperazin- 1- il]- metanona;

{4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- metil- [1,4]diazepan- 1- il) metanona,

1- (4- {4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carbonilo}- piperazin- 1- il)- etanona,

{4- [2- Amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (3,4- dihidro- 1*H*- isoquinolin- 2- il)- metanona;

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (3- hidroxi- piperidin- 1- il)- metanona,

[4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- (4- metil- [1,4]diazepan- 1- il)- metanona,

1- (4- {4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carbonil}- piperazin- 1- il)- etanona;

{4- [2- Amino- 5- (3,4- dımetoxı- fenıl)- pırımıdin- 4- ıl]- 1*H*- pırrol- 2- ıl}- (4- metıl- [1,4]diazepan- 1- ıl) metanona;

[4- (2- Amıno- 5- fenıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- ıl]- (3- hıdroxı- pıperıdın- 1- ıl)- metanona;

Metıl- (2- pırıdın- 2- ıl- etıl)- amıda del ácido 4- [2- amıno- 5- (3- cloro- fenıl)- pırımıdın- 4- ıl]- 1*H*- pirrol- 2- carboxílıco,

[4- (2- Amıno- 5- *m*-tolıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- ıl]- [2- (2- hıdroxı- etıl)- pıperıdın- 1- ıl]- metanona,

{4- [2- Amıno- 5- (3- cloro- 2- fluoro- fenıl)- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- ıl}- [2- (2- hıdroxı- etıl)- pıperıdın- 1- ıl]- metanona,

(2- hıdroxı- 1- metıl- 2- fenil- etıl)- metıl- amıda del ácido 4- [2- amıno- 5- (3- cloro- 2- fluoro- fenıl)- pırimidın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco,

{4- [2- Amıno- 5- (3- cloro- 2- fluoro- fenıl)- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- ıl}- (4- pırıdın- 2- ıl- pıperazın- 1- ıl)- metanona;

[4- (2- Amıno- 5- fenıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- ıl]- (4- hıdroxı- pıperıdın- 1- ıl)- metanona,

{4- [2- Amıno- 5- (3,4- dımetoxı- fenıl)- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- ıl}- (4- hıdroxi- pıperıdın- 1- ıl)- metanona;

{4- [2- Amıno- 5- (3- cloro- 2- fluoro- fenıl)- pırımıdin- 4- ıl]- 1*H*- pırrol- 2- il}- (4- hıdroxı- pıperıdın- 1- ıl)- metanona;

{4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- (4- piridin- 2- il- piperazin- 1- il)- metanona,

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (2- hidroxi- etil)- piperazin- 1- il]- metanona,

1- {4- [4- (2- Amino- 5- *m*-tolil- pirimidin- 4- il)- 1*H*- pirrol- 2- carbonil]- piperazin- 1- il}- etanona,

{4- [2- Amino- 5- (3,4- dimetoxi- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- [4- (2- fluoro- fenil)- piperazin- 1- il]- metanona;

[4- (2- Amino- 5- fenil- pirimidin- 4- il)- 1*H*- pirrol- 2- il]- pirrolidin- 1- il- metanona;

{4- [2- Amino- 5- (3- cloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- il}- morfolin- 4- il- metanona;

Bencilamida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

3,4- Difluoro- bencilamida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

4- Fluoro- bencilamida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

3- Cloro- bencilamida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

4- Metoxi- bencilamida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

3- Cloro- 4- fluoro- bencılamıda del ácıdo 4- (2- amıno- 5- metıl- pırımıdın- 4- il)- 1*H*- pırrol- 2- carboxílıco;

(Tetrahıdro- furan- 2- ılmetil)- amıda del ácıdo 4- (2- amıno- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

(Tetrahidro- furan- 2- ılmetıl)- amıda del ácıdo 4- (2- amıno- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

(3- Hıdroxı- 1- fenıl- propıl)- amida del ácıdo 4- (2- amino- 5- metıl- pırımıdin- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

(3- Hıdroxı- 1- fenıl- propıl)- amıda del ácıdo 4- (2- amıno- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

3- Cloro- 4- fluoro- bencilamıda del ácıdo 4- (2,5- dıamıno- pırımidın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

3- Cloro- 4- fluoro- bencilamida del ácıdo 4- (2- amıno- 5- metılamıno- pırımıdın- 4- ıl)- 1*H*- pirrol- 2- carboxílıco,

3- Cloro- 4- fluoro- bencilamıda del ácıdo 4- (5- acetılamıno- 2- amıno- pırımidın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

3- Cloro- 4- fluoro- bencılamida del ácıdo 4- [2- amıno- 5- (3- metil- ureıdo)- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílico;

3- Cloro- 4- fluoro- bencılamıda del ácıdo 4- (2- amıno- 5- hıdroxı- pırımidın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

3- Cloro- 4- fluoro- bencilamida del ácido 4- (2- amino- 5- metilaminometil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

3- Cloro- 4- fluoro- bencilamida del ácido 4- (2- amino- 5- hidroximetil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

3- Cloro- 4- fluoro- bencilamida del ácido 4- [2- ciclohexilamino- 5- (3- metil- ureido)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

3- Cloro- 4- fluoro- bencilamida del ácido 4- [2- acetilamino- 5- (3- metil- ureido)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

3- Cloro- 4- fluoro- bencilamida del ácido 4- (5- hidroxi- 2- metanosulfonilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

3- Cloro- 4- fluoro- bencilamida del ácido 4- (2- amino- 5- metanosulfonil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

3,4- Difluoro- bencilamida del ácido 4- (2- amino- 5- hidroximetil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

3,4- Difluoro- bencilamida del ácido 4- (2- ciclohexilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(Piridin- 4- ilmetil)- amida del ácido 4- [2- Amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

3- Trifluorometil- bencilamida del ácido 4- [5- (3,5- dicloro- fenil)- 2- fenilamino- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(Benzo[1,3]dioxol- 5- ilmetil)- amida del ácido 4- [2- amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- dimetilamino- 2- piridin- 3- il- etil)- amida del ácido 4- [2- amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

4- Metanosulfonil- bencilamida del ácido 4- [2- amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(Benzo[1,3]dioxol- 5- ilmetil)- amida del ácido 4- [5- (3,5- Dicloro- fenil)- 2- fenilamino- pirimidin-4- il]- 1*H*- pirrol- 2- carboxílico,

(2- morfolin- 4- il- 2- piridin- 3- il- etil)- amida del ácido 4- [5- (3,5- dicloro- fenil)- 2- fenilamino- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2- amino- 5- (3- fluoro- 5- trifluorometil- fenil)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- piridin- 3- il- etil)- amida del ácido 4- (2- amino- 5- propil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- pirıdın- 3- ıl- etıl)- amıda del ácıdo 4- (2- amıno- 5- metil- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

(2- pirıdın- 3- il- etil)- amida del ácido 4- (5- metıl- 2- metılamıno- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

(2- pirıdin- 3- ıl- etıl)- amıda del ácıdo 4- (2- metılamıno- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

(2- dımetılamıno- etıl)- amıda del ácıdo 4- (2- etılamıno- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

Propılamıda del ácıdo 4- (5- metıl- 2- fenılamıno- pirımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

(3- fenıl- propıl)- amıda del ácıdo 4- (5- metıl- 2- fenılamıno- pırımidin- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

(Naftalen- 1- ılmetıl)- amıda del ácıdo 4- (2- etılamino- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

Cıclopropılamida del ácıdo 4- (2- etılamıno- 5- metıl- pirımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

2- Trıfluorometıl- bencılamıda del ácıdo 4- (2- etılamıno- pirimıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

(2- Hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (5- metıl- 2- fenılamıno- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(4- metil- ciclohexil)- amida del ácido 4- (2- etilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

Isopropilamida del ácido 4- (5- etil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- Amino- etil)- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

Bencil- metil- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- Hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

1- {4- [4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carbonil]- piperazin- 1- il}- etanona;

(3- fenil- propil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

[2- (6- metoxi- 1*H*- indol- 3- il)- etil]- amida del ácido 4- (2- amino- 5- etil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- fenoxi- etil)- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(1- metil- 3- fenil- propil)- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(1*H*- benzoimidazol- 2- ilmetil)- amida del ácido 4- (5- metil- 2- metilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(1- hidroximetil- 3- metil- butil)- amida del ácido 4- (5- metil- 2- metilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

[1- hidroximetil- 2- (1*H*- imidazol- 4- il)- etil]- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(Tetrahidro- furan- 2- ilmetil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

3,4- difluoro bencilamida del ácido 4- [2- (2- dietilamino- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

Bencilamida del ácido 4- [5- metil- 2- (2- piperidin- 1- il- quinazolin- 4- ilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

[1- (3- cloro- 4- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (5- metil- 2- metilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

[1- (3- cloro- 4- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(3- fluoro- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*-pirrol- 2- carboxílico;

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(3- metoxi- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*-pirrol- 2- carboxílico;

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(3- hidroxi- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(benzo[1,3]dioxol- 5- ilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [5-metil- 2- (4- sulfamoil- fenilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(3- benciloxi- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(4- hidroxi- ciclohexilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- (5-ciclohexil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- Hidroxi- 1- fenil- etil)- amida del ácido 4- (5-ciclopropil- 2- fenilamino- pirimidin- 4- il)- 1*H*-pirrol- 2- carboxílico;

[1- (3- fluoro- 4- metil- fenil)- 2- hidroxi- etil]- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

[2- hidroxi- 1- (3- trifluorometil- fenil)- etil]- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

[1- (3- fluoro- 4- metil- fenil)- 2- hidroxi- etil]- amida del ácido 4- [2- (3- fluoro- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

[2- hidroxi- 1- (3- trifluorometil- fenil)- etil]- amida del ácido 4- [2- (3- fluoro- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (3- trifluorometil- fenilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- bencilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (3,4- dimetil- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (4- benciloxi- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- isopropilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (2,2,2- trifluoro- etilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- fenil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- metoxi- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (4- trifluorometoxi- fenilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- isobutilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (ciclopropilmetil- amino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (5- metoximetil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- amino- 5- metoximetil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- ciclopropilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (5- metil- 2- propilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- fenil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- metil- 2- fenil- etil)- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- metil- 2- fenil- etil)- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 2- fenil- etil)- metil- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- metil- 2- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- metil- 2- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 2- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- hidroximetil- 2- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- hidroximetil- 2- fenil- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(3- hidroxi- 1- fenil- propil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(3- hidroxi- 1- fenil- propil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (1- hidroximetil- ciclopropilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- metil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- propilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- Hidroxi- propilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(2- hidroxi- ciclohexilamino)- 5- metil- pirimidin- 4-il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (5-hidroximetil- 2- fenilamino- pirimidin- 4- il)- 1*H*-pirrol- 2- carboxílico;

Metil ester del ácido {[4- (2- Etilamino- 5- metil-pirimidin- 4- il)- 1*H*- pirrol- 2- carbonil]- amino}-fenil- acético;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(2- hidroxi- 1- metil- etilamino)- 5- metil- pirimidin-4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(3- Dimetilamino- fenilamino)- 5- metil- pirimidin- 4-il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- (2- Amino- pirimidin- 4- il)- 1H- pirrol- 2-carboxílico;

(2- hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- (2- Amino- pirimidin- 4- il)- 1H- pirrol- 2-carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2-etilamino- 5- metoximetil- pirimidin- 4- il)- 1*H*- pirrol-2- carboxílico;

(2- hidroxi- 1- piridin- 3- il- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*-pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- etilamino- 5- hidroximetil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

[1- (3- fluoro- 5- trifluorometil- fenil)- 2- hidroxi- etil]- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

[1- (3- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

[1- (2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- ciclopropil- 1- hidroximetil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2,3- dimetil- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- etoxiamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (1- hidroximetil- 2- metil- propilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- oxo- 1- fenil- propil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

[2- hidroxı- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- (2- etılamıno- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

[2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- [2- (3- fluoro- fenılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco,

[2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- [2- (2- cloro- fenilamıno)- 5- metıl- pırımıdin- 4- ıl]- 1*H*- pırrol- *2*- carboxílico;

[2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etil]- amida del ácıdo 4- [2- (2- hıdroxı- 1- fenıl- etılamino)- 5- metıl- pırımıdin- 4- ıl]- 1*H*- pırrol- 2- carboxílico;

[2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- [2- (3- dımetilamıno- fenılamıno)- 5- metıl- pırımıdin- 4- ıl]- 1*H*- pırrol- 2- carboxílıco,

[2- hıdroxı- 1- (3- trıfluorometıl- fenil)- etıl]- amıda del ácıdo 4- (2- cıclopropılamıno- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

[2- hıdroxı- 1- (2- metoxı- fenıl)- etıl]- amıda del ácıdo 4- (2- cıclopropılamıno- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pirrol- 2- carboxílıco;

[1- (3- cloro- fenıl)- 2- hıdroxı- etıl]- amıda del ácıdo 4- (2- cıclopropılamıno- 5- metıl- pırımıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco;

(2- hıdroxı- 1- *m*-tolıl- etıl)- amıda del ácıdo 4- (2- cıclopropilamıno- 5- metıl- pirimıdın- 4- ıl)- 1*H*- pırrol- 2- carboxílıco,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- metoxiamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- isopropoxiamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (3- dimetilamino- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (2- cloro- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- fenil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (2,3- dimetil- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (3- fluoro- fenilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- acetilamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (5- metil- 2- *o*-tolilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (piridin- 3- ilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- {5- metil- 2- [(tetrahidro- furan- 2- ilmetil)- amino]- pirimidin- 4- il}- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- {5- metil- 2- [(tetrahidro- furan- 2- ilmetil)- amino]- pirimidin- 4- il}- 1*H*- pirrol- 2- carboxílico,

Etil ester del ácido N'- 4- [5- (2- hidroxi- 1- fenil- etilcarbamoil)- 1*H*- pirrol- 3- il]- 5- metil- pirimidin- 2- il}- hidrazinacarboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- {5- metil- 2- [(piridin- 3- ilmetil)- amino]- pirimidin- 4- il}- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- ciclopropilmetoxiamino- 5- metil- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (isoxazol- 3- ilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- cianoamino- 5- metil- pirimidin- 4- il)- 1H- pirrol 2- carboxílico

(2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- metil- etilamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- *m*-tolil- etil)- amida del ácido 4- (5- metil- 2- *o*-tolilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

[1- (3- cloro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (5- metil- 2- *o*-tolilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- etoxiamino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (N',N'- dimetil- hidrazino)- 5- metil- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (2- trifluorometil- fenilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (morfolin- 4- ilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (5- metil- isoxazol- 3- ilamino)- pirimidin- 4- il]- 1*H*- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- {2- [1- (3- cloro- 4- fluoro- fenil)- 2- hidroxi- etilamino]- 5- metil- pirimidin- 4- il}- 1*H*- pirrol- 2- carboxílico;

[1- (3- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1*H*- pirrol- 2- carboxílico,

[1- (3- cloro- fenıl)- 2- hıdroxı- etıl]- amıda del ácıdo 4- [2- (1- hıdroxımetıl- propılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

[1- (3- cloro- fenıl)- 2- hıdroxi- etıl]- amıda del ácıdo 4- [2- (2- hıdroxı- 1- hıdroxımetıl- etılamıno)- 5- metil- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco,

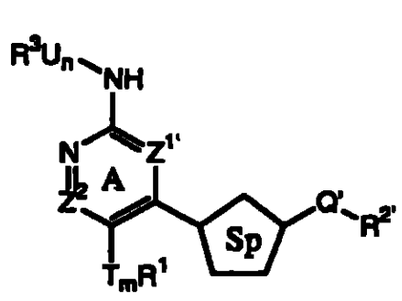
(2- hıdroxı- 1- *m*-tolıl- etil)- amıda del ácıdo 4- [2- (1- hidroxımetıl- propılamıno)- 5- metıl- pırımidin- 4- ıl]- 1*H*- pırrol- 2- carboxílıco,

(2- hıdroxı- 1- fenıl- etıl)- amida del ácıdo 4- [2- (2- hıdroxı- 1- hidroxımetıl- etılamıno)- 5- metil- pırımıdın- 4- ıl]- 1*H*- pırrol- 2- carboxílıco;

(2- hıdroxı- 1- fenıl- etıl)- amida del ácıdo 4- [2- (1- hidroxımetıl- propılamıno)- 5- metıl- pırımidin- 4- ıl]- 1*H*- pirrol- 2- carboxílıco; y

(2- hıdroxi- 1- fenıl- etıl)- amıda del ácıdo 4- [5- metıl- 2- (2- metıl- cıclopropılamıno)- pırımıdın- 4- ıl]- 1*H*- pirrol- 2- carboxílıco

20 Un compuesto de la fórmula I'



I'

o un derıvado farmacéutıcamente aceptable del mısmo, en donde

Sp es un grupo espaciador que comprende un anillo heteroaromático de 5 miembros, en donde el Anillo A y $Q'R^{2'}$ se encuentran unidos a Sp en posiciones no adyacentes, y en donde Sp tiene hasta dos substituyentes R^6, con la condición de que dos átomos de carbono en el anillo sustituibles en Sp no se encuentran simultáneamente substituidos por R^6;

Z^1 y Z^2 son cada uno seleccionados de manera independiente a partir de N o CH;

T es un grupo ligante,

Q' es seleccionado a partir de $-CO_2-$, $-C(O)NR^7-$ o $-SO_2NR^7-$;

U es seleccionado a partir de $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, o $-SO_2-$,

m y n son cada uno seleccionados de manera independiente a partir de cero o uno,

R^1 es seleccionado a partir de hidrógeno, CN, halógeno, R, $N(R^7)_2$, OR, u OH,

$R^{2'}$ es seleccionado a partir de $-(CH_2)_yCH(R^5)_2$ o $-(CH_2)_yCH(R^8)CH(R^5)_2$,

y es 0 - 6;

R^3 es seleccionado a partir de R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, o $-(CH_2)_yCH(R^8)N(R^4)_2$,

cada R es seleccionado de manera independiente a partir de un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, arilo C_{6-10}, un anillo heteroarilo que tiene 5 - 10 átomos en el

anillo, o un anillo heterociclilo que tiene 3 - 10 átomos en el anillo,

cada R^4 es seleccionado de manera independiente a partir de R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, o $-(CH_2)_yCH(R^5)_2$;

cada R^5 es seleccionado de manera independiente a partir de R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$;

cada R^6 es seleccionado de manera independiente a partir de R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$;

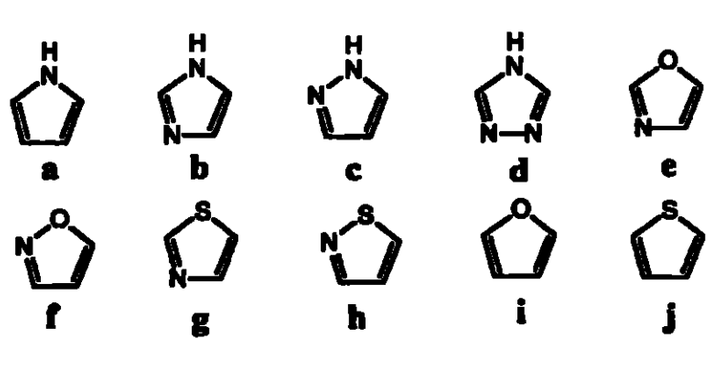
cada R^7 es seleccionado de manera independiente a partir de hidrógeno o un grupo alifático C_{1-6} substituido de manera opcional, o dos R^7 en el mismo nitrógeno son tomados junto con el nitrógeno para formar un anillo heterociclilo o heteroarilo de 5 - 8 miembros,

R^8 es seleccionado a partir de R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, o $(CH_2)_wSR^7$,

y

cada w es seleccionado de manera independiente a partir de 0 - 4

21. El compuesto de acuerdo con la reivindicación 20, en donde Sp es seleccionado a partir de uno de los siguientes:



o un derivado farmacéuticamente aceptable de los mismos

22 El compuesto de acuerdo con la reivindicación 21, en donde dicho compuesto tiene una o más de las características seleccionadas a partir del grupo que consiste de:

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, amino, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros, y

(c) R^5 es R u OR^7, en donde R es carbocíclico, o un anillo arilo o heteroarilo de 5 o 6 miembros substituido de manera opcional.

23. El compuesto de acuerdo con la reivindicación 22, en donde:

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros,

(b) T_mR^1 es hidrógeno, amino, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros; y

(c) R^5 es R u OR^7, en donde R es carbocíclico, o un anillo arilo o heteroarilo de 5 o 6 miembros substituido de manera opcional

24. El compuesto de acuerdo con la reivindicación 22, en donde dicho compuesto tiene una o más características seleccionadas a partir del grupo que consiste de

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, $-CH(CH_2OH)CH_2$ciclopropilo, o un grupo fenilo, bencilo, o isoxazolilo substituidos de manera opcional,

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3,

CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, o CH_2NHCH_3, y

(c) R^5 es OH, CH_2OH, carbocíclico, o un anillo fenilo o piridilo substituido de manera opcional, y Q' es -C(O)NH-

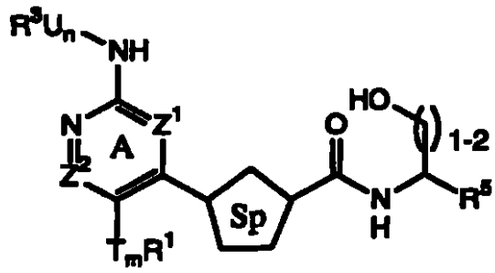
25. El compuesto de acuerdo con la reivindicación 24, en donde

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, $-CH(CH_2OH)$fenilo, $-CH(CH_2OH)$etilo, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropilo, $-CH(CH_2OH)CH_2$ciclopropilo, o un grupo fenilo, bencilo, o isoxazolilo substituidos de manera opcional,

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, o CH_2NHCH_3, y

(c) R^5 es OH, CH_2OH, carbocíclico, o un anillo fenilo o piridilo substituido de manera opcional, y Q' es -C(O)NH-

26. El compuesto de acuerdo con la reivindicación 21, en donde dicho compuesto es de la fórmula I"



I^a

o un derivado farmacéuticamente aceptable del mismo

27. El compuesto de acuerdo con la reivindicación 26, en donde dicho compuesto tiene una o más características seleccionadas a partir del grupo que consiste de

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros, y

(c) R^5 es un anillo arilo, heteroarilo, o carbocíclico de 6 miembros substituido de manera opcional.

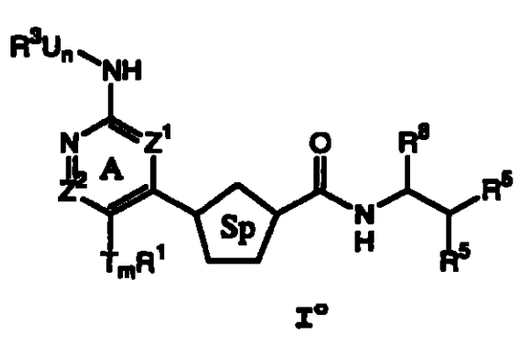
28 El compuesto de acuerdo con la reivindicación 27, en donde.

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros,

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros, y

(c) R^5 es un anillo arilo, heteroarilo, o carbocíclico de 6 miembros substituido de manera opcional.

29 El compuesto de acuerdo con la reivindicación 21, en donde dicho compuesto es de la fórmula I°:



I°

o un derivado farmacéuticamente aceptable del mismo.

30. El compuesto de acuerdo con la reivindicación 29, en donde dicho compuesto tiene una o más

características seleccionadas a partir del grupo que consiste de:

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros,

(b) T_mR^1 es hidrógeno, amino, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros; y

(c) R^5 es R u OR^7, en donde R es carbocíclico, o un anillo arilo o heteroarilo de 5 o 6 miembros substituido de manera opcional.

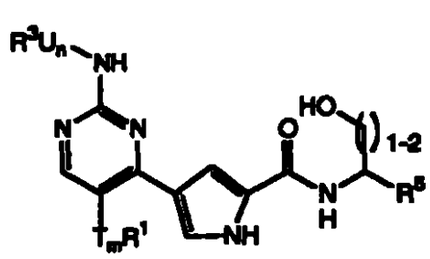
31. El compuesto de acuerdo con la reivindicación 30, en donde

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros,

(b) T_mR^1 es hidrógeno, amino, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros, y

(c) R^5 es R u OR^7, en donde R es carbocíclico, o un anillo arilo o heteroarilo de 5 o 6 miembros substituido de manera opcional.

32 Un compuesto de la fórmula III-a':



III-a'

o un derivado farmacéuticamente aceptable del mismo, en donde·

T es un grupo ligante,

U es seleccionado a partir de $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, o $-SO_2-$;

m y n son cada uno seleccionados de manera independiente a partir de cero o uno,

R^1 es seleccionado a partir de hidrógeno, CN, halógeno, R, $N(R^7)_2$, OR, o OH,

R^3 es seleccionado a partir de R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, o $-(CH_2)_yCH(R^8)N(R^4)_2$;

cada R es seleccionado de manera independiente a partir de un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, arilo C_{6-10}, un anillo heteroarilo que tiene 5 - 10 átomos en el

anillo, o un anillo heterociclilo que tiene 3 - 10 átomos en el anillo;

cada R^4 es seleccionado de manera independiente a partir de R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, o $-(CH_2)_yCH(R^5)_2$,

cada R^5 es seleccionado de manera independiente a partir de R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$,

cada R^6 es seleccionado de manera independiente a partir de R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$,

cada R^7 es seleccionado de manera independiente a partir de hidrógeno o un grupo alifático C_{1-6} substituido de manera opcional, o dos R^7 en el mismo nitrógeno son tomados junto con el nitrógeno para formar un anillo heterociclilo o heteroarilo de 5 - 8 miembros;

R^8 es seleccionado a partir de R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, o $(CH_2)_wSR^7$,

y

cada w es seleccionado de manera independiente a partir de 0 - 4.

33. El compuesto de acuerdo con la reivindicación 32, en donde dicho compuesto tiene una o más de las características seleccionadas a partir del grupo que consiste de

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros; y

(c) R^5 es un anillo arilo, heteroarilo, o carbocíclico de 6 miembros substituido de manera opcional

34 El compuesto de acuerdo con la reivindicación 33, en donde

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros, y

(c) R^5 es un anillo arilo, heteroarilo, o carbocíclico de 6 miembros substituido de manera opcional.

35. El compuesto de acuerdo con la reivindicación 33, en donde dicho compuesto tiene una o más características seleccionadas a partir del grupo que consiste de·

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, -CH(CH_2OH)fenilo, -CH(CH_2OH)etilo, -CH(CH_2OH)$_2$, -CH(CH_2OH)isopropilo, -CH(CH_2OH)CH_2ciclopropilo, o un grupo fenilo o bencilo substituidos de manera opcional;

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, NHC(O)$NHCH_3$, o CH_2NHCH_3; y

(c) R^5 es ciclohexilo o un anillo fenilo o piridilo substituido de manera opcional.

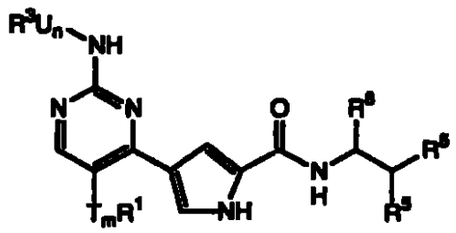
36 El compuesto de acuerdo con la reivindicación 35, en donde:

(a) R^3 es seleccionado a partir de hidrógeno, metilo, etilo, propilo, ciclopropilo, ciclohexilo, isopropilo, -CH(CH_2OH)fenilo, -CH(CH_2OH)etilo, -CH(CH_2OH)$_2$, -CH(CH_2OH)isopropilo, -CH(CH_2OH)CH_2ciclopropilo, o un grupo fenilo o bencilo substituidos de manera opcional,

(b) T_mR^1 es seleccionado a partir de fenilo substituido de manera opcional, metilo, etilo, propilo, ciclopropilo, ciclohexilo, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, o CH_2NHCH_3; y

(c) R^5 es ciclohexilo o un anillo fenilo o piridilo substituido de manera opcional.

37 Un compuesto de la fórmula III-a°:



III-a°

o un derivado farmacéuticamente aceptable del mismo, en donde:

T es un grupo ligante;

U es seleccionado a partir de $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, o $-SO_2-$;

m y n son cada uno seleccionados de manera independiente a partir de cero o uno,

R^1 es seleccionado a partir de hidrógeno, CN, halógeno, R, $N(R^7)_2$, OR, u OH,

R^3 es seleccionado a partir de R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, o $-(CH_2)_yCH(R^8)N(R^4)_2$;

cada R es seleccionado de manera independiente a partir de un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6}, arilo C_{6-10}, un anillo heteroarilo que tiene 5 - 10 átomos en el anillo, o un anillo heterociclilo que tiene 3 - 10 átomos en el anillo,

cada R^4 es seleccionado de manera independiente a partir de R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, o $-(CH_2)_yCH(R^5)_2$;

cada R^5 es seleccionado de manera independiente a partir de R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$,

cada R^6 es seleccionado de manera independiente a partir de R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, o $SO_2N(R^7)_2$;

cada R^7 es seleccionado de manera independiente a partir de hidrógeno o un grupo alifático C_{1-6} substituido de manera opcional, o dos R^7 en el mismo nitrógeno son tomados junto con el nitrógeno para formar un anillo heterociclilo o heteroarilo de 5 - 8 miembros;

R^8 es seleccionado a partir de R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, o $(CH_2)_wSR^7$;

y

cada w es seleccionado de manera independiente a partir de 0 - 4.

38. El compuesto de acuerdo con la reivindicación 37, en donde dicho compuesto tiene una o más características seleccionadas a partir del grupo que consiste de

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros; y

(c) R^5 es R u OR^7, y R^8 es R^7 u OR^7.

39 El compuesto de acuerdo con la reivindicación 38, en donde:

(a) R^3 es hidrógeno, carbociclilo, $-CH(R^8)R$, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-4}, heterocíclico de 3 - 6 miembros, o un anillo arilo o heteroarilo de 5 - 6 miembros;

(b) T_mR^1 es hidrógeno, $N(R^4)_2$, OH, carbociclilo de 3 - 6 miembros, o un grupo substituido de manera opcional seleccionado a partir de alifático C_{1-6} o un anillo arilo o heteroarilo de 5 - 6 miembros, y

(c) R^5 es R u OR^7, y R^8 es R^7 u OR^7

40 Un compuesto seleccionado a partir del grupo que consiste de:

(2- hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- [2- amino- 5- (3- cloro- 2- fluoro- fenil)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico,

(3- hidroxi- 1- fenil- propil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico,

(3- hidroxi- 1- fenil- propil)- amida del ácido 4- (2- amino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- dimetilamino- 2- piridin- 3- il- etil)- amida del ácido 4- [2- amino- 5- (3,5- dicloro- fenil)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- morfolin- 4- il- 2- piridin- 3- il- etil)- amida del ácido 4- [5- (3,5- dicloro- fenil)- 2- fenilamino- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- amino- 5- (3- fluoro- 5- trifluorometil- fenil)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico,

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (5- metıl- 2- fenılamıno- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco;

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (2- etılamıno- 5- metil- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco;

(2- hidroxı- 1- metıl- 2- fenıl- etıl)- metil- amıda del ácıdo 4- (2- amıno- pırımıdın- 4- ıl)- 1H- pirrol- 2- carboxílıco;

(1- hıdroximetıl- 3- metıl- butıl)- amıda del ácıdo 4- (5- metıl- 2- metilamıno- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco;

[1- hıdroxımetıl- 2- (1H- ımıdazol- 4- il)- etıl]- amıda del ácıdo 4- (5- metıl- 2- fenılamıno- pırımıdın- 4- il)- 1H- pırrol- 2- carboxílico,

[1- (3- cloro- 4- fluoro- fenıl)- 2- hıdroxı- etıl]- amıda del ácıdo 4- (5- metıl- 2- metılamıno- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco,

[1- (3- cloro- 4- fluoro- fenıl)- 2- hıdroxı- etıl]- amıda del ácido 4- (5- metıl- 2- fenılamıno- pırımıdın- 4- il)- 1H- pirrol- 2- carboxílıco;

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [2- (3- fluoro- fenılamıno)- 5- metıl- pirımidin- 4- ıl]- 1H- pırrol- 2- carboxílıco,

(2- hıdroxı- 1- fenıl- etil)- amıda del ácıdo 4- [2- (3- metoxı- fenılamıno)- 5- metil- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílico,

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [2-(3- hıdroxi- fenılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1H- pirrol- 2- carboxílıco;

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [2-(benzo[1,3]dıoxol- 5- ılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílıco,

(2- hıdroxi- 1- fenıl- etıl)- amıda del ácıdo 4- [5-metıl- 2- (4- sulfamoıl- fenılamıno)- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílıco,

(2- hıdroxı- 1- fenıl- etil)- amıda del ácıdo 4- [2-(3- bencıloxı- fenılamıno)- 5- metıl- pirımidın- 4- il]- 1H- pırrol- 2- carboxílıco;

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [2-(4- hıdroxi- cıclohexılamıno)- 5- metıl- pirimidın- 4- ıl]- 1H- pirrol- 2- carboxílıco,

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácido 4- (5-ciclohexıl- 2- fenılamıno- pırımıdin- 4- ıl)- 1H- pırrol-2- carboxílıco,

(2- hıdroxı- 1- fenıl- etıl)- amida del ácıdo 4- (5-cıclopropıl- 2- fenılamıno- pırımıdın- 4- ıl)- 1H-pirrol- 2- carboxílıco,

[1- (3- fluoro- 4- metıl- fenıl)- 2- hıdroxı- etıl]-amida del ácıdo 4- (5- metıl- 2- fenılamıno- pırımıdın-4- ıl)- 1H- pırrol- 2- carboxílıco,

[2- hıdroxi- 1- (3- trıfluorometil- fenıl)- etıl]-amıda del ácıdo 4- (5- metıl- 2- fenılamıno- pırımıdın-4- ıl)- 1H- pırrol- 2- carboxílıco;

[1- (3- fluoro- 4- metil- fenil)- 2- hidroxi- etil]- amida del ácido 4- [2- (3- fluoro- fenilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico,

[2- hidroxi- 1- (3- trifluorometil- fenil)- etil]- amida del ácido 4- [2- (3- fluoro- fenilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (3- trifluorometil- fenilamino)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- bencilamino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (3,4- dimetil- fenilamino)- 5- metil- pirimidin- 4-il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (4- benciloxi- fenilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- isopropilamino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (2,2,2- trifluoro- etilamino)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- fenil- etilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico,

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [2- (2- metoxi- fenılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílico;

(2- hıdroxı- 1- fenıl- etil)- amıda del ácıdo 4- [5- metıl- 2- (4- trıfluorometoxı- fenılamino)- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílıco;

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (2- isobutılamıno- 5- metıl- pırımidin- 4- ıl)- 1H- pırrol- 2- carboxílıco,

(2- hidroxı- 1- fenıl- etıl)- amida del ácido 4- [2- (cıclopropılmetıl- amino)- 5- metıl- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílıco;

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (5- metoxımetil- 2- fenılamıno- pırimidin- 4- ıl)- 1H- pırrol- 2- carboxílico;

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (2- amıno- 5- metoxımetıl- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco;

(2- hıdroxı- 1- fenil- etil)- amıda del ácıdo 4- (2- cıclopropılamıno- 5- metıl- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílico,

(2- hıdroxı- 1- fenil- etıl)- amıda del ácıdo 4- (5- metıl- 2- propılamıno- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílico;

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [2- (2- hıdroxı- 1- fenıl- etılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílıco;

(2- hıdroxı- 1- metıl- 2- fenıl- etıl)- amida del ácıdo 4- (2- amıno- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco,

(2- hıdroxi- 1- metıl- 2- fenıl- etıl)- amıda del ácıdo 4- (2- Amıno- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco,

(2- hıdroxı- 2- fenıl- etıl)- metıl- amıda del ácıdo 4- (2- amıno- pırımıdin- 4- ıl)- 1H- pırrol- 2- carboxílico;

(2- hidroxı- 1- metıl- 2- fenıl- etıl)- amıda del ácıdo 4- (2- etılamıno- 5- metıl- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílico,

(2- hıdroxı- 1- metil- 2- fenıl- etıl)- amıda del ácıdo 4- (2- etılamıno- 5- metıl- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílico;

(2- hıdroxı- 2- fenıl- etıl)- amıda del ácıdo 4- (2- etılamino- 5- metıl- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco,

(2- hıdroxı- 1- metıl- 2- fenıl- etıl)- metıl- amıda del ácıdo 4- (2- Amıno- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco,

(2- hıdroxı- 1- hıdroxımetıl- 2- fenıl- etıl)- amıda del ácıdo 4- (2- etılamıno- 5- metıl- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco,

(2- hıdroxi- 1- hıdroxımetıl- 2- fenıl- etıl)- amıda del ácıdo 4- (2- etılamıno- 5- metil- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco,

(3- hidroxi- 1- fenil- propil)- amida del ácido 4-(2- etilamino- 5- metil- pirimidin- 4- il)- 1H- pirrol-2- carboxílico;

(3- hidroxi- 1- fenil- propil)- amida del ácido 4-(2- etilamino- 5- metil- pirimidin- 4- il)- 1H- pirrol-2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(1- hidroximetil- ciclopropilamino)- 5- metil- pirimidin-4- il]- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil) amida del ácido 4- [2-(2- hidroxi- etilamino)- 5- metil- pirimidin- 4- il]- 1H-pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(2- hidroxi- 1- metil- etilamino)- 5- metilpirimidin- 4-il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(2- hidroxi- propilamino)- 5- metil- pirimidin- 4- il]-1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(2- hidroxi- propilamino)- 5- metil- pirimidin- 4- il]-1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(2- hidroxi- ciclohexilamino)- 5- metil- pirimidin- 4-il]- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (5-hidroximetil- 2- fenilamino- pirimidin- 4- il)- 1H-pirrol- 2- carboxílico;

Metil ester del ácido {[4- (2- etilamino- 5- metil-pirimidin- 4- il)- 1H- pirrol- 2- carbonil]- amino}-fenil- acético;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(2- hidroxi- 1- metil- etilamino)- 5- metil- pirimidin-4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2-(3- dimetilamino- fenilamino)- 5- metil- pirimidin- 4-il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1H- pirrol- 2-carboxílico,

(2- hidroxi- 1- metil- 2- fenil- etil)- metil- amida del ácido 4- (2- amino- pirimidin- 4- il)- 1H- pirrol- 2-carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2-etilamino- 5- metoximetil- pirimidin- 4- il)- 1H- pirrol-2- carboxílico;

(2- hidroxi- 1- piridin- 3- il- etil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1H-pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2-etilamino- 5- hidroximetil- pirimidin- 4- il)- 1H-pirrol- 2- carboxílico,

[1- (3- fluoro- 5- trifluorometil- fenil)- 2-hidroxi- etil]- amida del ácido 4- (2- etilamino- 5-metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico,

[1- (3- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico;

[1- (2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- ciclopropil- 1- hidroximetil- etilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2,3- dimetil- fenilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- etoxiamino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (1- hidroximetil- 2- metil- propilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2-carboxílico;

(2- oxo- 1- fenil- propil)- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico;

[2- hidroxi- 1- (3- trifluorometil- fenil)- etil]- amida del ácido 4- (2- etilamino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico;

[2- hidroxi- 1- (3- trifluorometil- fenil)- etil]- amida del ácido 4- [2- (3- fluoro- fenilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico,

[2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- [2- (2- cloro- fenılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílıco,

[2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- [2- (2- Hıdroxı- 1- fenıl- etılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílıco;

[2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- [2- (3- dımetılamıno- fenılamıno)- 5- metil- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílıco;

[2- hıdroxı- 1- (3- trıfluorometıl- fenıl)- etıl]- amıda del ácıdo 4- (2- cıclopropılamıno- 5- metil- pirımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco,

[2- hıdroxı- 1- (2- metoxi- fenıl)- etıl]- amıda del ácıdo 4- (2- cıclopropılamıno- 5- metıl- pırımıdın- 4- ıl)- 1H- pirrol- 2- carboxílıco;

[1- (3- cloro- fenıl)- 2- hıdroxı- etıl]- amida del ácıdo 4- (2- cıclopropılamıno- 5- metıl- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco;

(2- hıdroxi- 1- m-tolıl- etıl)- amıda del ácıdo 4- (2- cıclopropılamıno- 5- metıl- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco;

(2- hıdroxı- 1- fenıl- etıl)- amida del ácıdo 4- (2- metoxıamıno- 5- metıl- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco,

(2- hıdroxı- 1- fenıl- etil)- amıda del ácido 4- (2- ısopropoxıamıno- 5- metil- pırımıdın- 4- il)- 1H- pırrol- 2- carboxílıco,

(2- hıdroxı- 1- m-tolıl- etıl)- amıda del ácıdo 4- [2- (3- Dımetılamıno- fenılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1H- pirrol- 2- carboxílıco,

(2- hıdroxı- 1- m-tolıl- etıl)- amıda del ácıdo 4- [2- (2- cloro- fenılamıno)- 5- metıl- pırımıdin- 4- ıl]- 1H- pırrol- 2- carboxílıco,

(2- hıdroxı- 1- m-tolıl- etıl)- amıda del ácıdo 4- [2- (2- hıdroxi- 1- fenıl- etılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílıco;

(2- hıdroxi- 1- m-tolıl- etıl)- amıda del ácido 4- [2- (2,3- dımetıl- fenılamino)- 5- metıl- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílıco;

(2- hıdroxı- 1- m-tolıl- etil)- amıda del ácıdo 4- [2- (3- fluoro- fenılamıno)- 5- metıl- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílico;

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (2- acetılamıno- 5- metıl- pırımıdın- 4- il)- 1H- pırrol- 2- carboxílıco,

(2- hıdroxı- 1- fenıl- etıl)- amıda del ácıdo 4- (5- metıl- 2- o-tolılamıno- pırımıdın- 4- ıl)- 1H- pırrol- 2- carboxílıco;

(2- hidroxı- 1- fenıl- etıl)- amıda del ácıdo 4- [5- metıl- 2- (pırıdın- 3- ılamıno)- pırımıdın- 4- ıl]- 1H- pırrol- 2- carboxílıco;

(2- hıdroxı- 1- fenıl- etıl)- amida del ácıdo 4- {5- metıl- 2- [(tetrahıdro- furan- 2- ılmetil)- amıno]- pırımıdın- 4- ıl}- 1H- pırrol- 2- carboxílıco,

(2- hidroxi- 1- fenil- etilo)- amida del ácido 4- {5- metil- 2- [(tetrahidro- furan- 2- ilmetil)- amino]- pirimidin- 4- il}- 1H- pirrol- 2- carboxílico,

Etil ester del ácido N'- {4- [5- (2- hidroxi- 1- fenil- etilcarbamoil)- 1H- pirrol- 3- il]- 5- metil- pirimidin- 2- il}- hidrazinacarboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- {5- metil- 2- [(piridin- 3- ilmetil)- amino]- pirimidin- 4- il}- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- ciclopropilmetoxiamino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil) amida del ácido 4- [2- (isoxazol- 3- ilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- (2- cianoamino- 5- metil- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- m-tolil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- metil- etilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- m-tolil- etil)- amida del ácido 4- (5- metil- 2- o-tolilamino- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico;

[1- (3- cloro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (5- metil- 2- o-tolilamino- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- etoxiamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (N',N'- dimetil- hidrazino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (2- trifluorometil- fenilamino)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (morfolin- 4- ilamino)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (5- metil- isoxazol- 3- ilamino)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- {2- [1- (3- cloro- 4- fluoro- fenil)- 2- hidroxi- etilamino]- 5- metil- pirimidin- 4- il}- 1H- pirrol- 2- carboxílico;

[1- (3- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido 4- (5- metil- 2- fenilamino- pirimidin- 4- il)- 1H- pirrol- 2- carboxílico;

[1- (3- cloro- fenil)- 2- hidroxi- etil]- amida del ácido 4- [2- (1- hidroximetil- propilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

[1- (3- cloro- fenil)- 2- hidroxi- etil]- amida del ácido 4- [2- (2- hidroxi- 1- hidroximetil- etilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico,

(2- hidroxi- 1- m-tolil- etil)- amida del ácido 4- [2- (1- hidroximetil- propilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (2- hidroxi- 1- hidroximetil- etilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico;

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [2- (1- hidroximetil- propilamino)- 5- metil- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico; y

(2- hidroxi- 1- fenil- etil)- amida del ácido 4- [5- metil- 2- (2- metil- ciclopropilamino)- pirimidin- 4- il]- 1H- pirrol- 2- carboxílico.

41 Una composición que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 20 - 40 y un portador farmacéuticamente aceptable.

42 La composición de acuerdo con la reivindicación 41, que comprende además un agente terapéutico adicional

43 Un método para inhibir la actividad de la ERK2, la GSK-3, la Aurora, la CDK2, o la Lck en un paciente, que comprende la etapa de administrar a dicho paciente una cantidad terapéuticamente efectiva de la composición de acuerdo con la reivindicación 41

44. El método de acuerdo con la reivindicación 43, en donde dicho método inhibe la actividad de la ERK2 en un paciente.

45. Un método para tratar una enfermedad mediada por la ERK2 en un paciente, con necesidad del mismo, método que comprende la etapa de administrar a dicho paciente una cantidad terapéuticamente efectiva de la composición acorde a in need thereof, said método comprising the etapa de administering to said patient una cantidad terapéuticamente efectiva de la composición de acuerdo con la reivindicación 41.

46 El método de acuerdo con la reivindicación 45, que comprende además la etapa de administrar a dicho paciente un agente terapéutico adicional

47 El método de acuerdo con la reivindicación 45, en donde dicha enfermedad es seleccionada a partir del cáncer, el ataque, la diabetes, la hepatomegalia, la enfermedad cardiovascular, la enfermedad de Alzheimer, la fibrosis quística, la enfermedad viral, las enfermedades autoinmunes, la aterosclerosis, la restenosis, la psoriasis, los trastornos alérgicos, la inflamación, los trastornos neurológicos, una enfermedad relacionada con las hormonas, las condiciones asociadas con el transplante de órganos, los trastornos de inmunodeficiencia, los trastornos destructivos de hueso, los trastornos proliferativos, las enfermedades infecciosas, las condiciones asociadas con la muerte celular, la agregación de plaquetas inducida por la trombina, la leucemia mielogena crónica (CML), la

enfermedad del hígado, las condiciones patológicas inmunes que involucran la activación de las células T, o los trastornos del SNC

48 El método de acuerdo con la reivindicación 47, en donde la enfermedad es cáncer.

49. El método de acuerdo con la reivindicación 48, en donde la enfermedad es un cáncer seleccionado a partir de seno, de ovario; cervical, de prostata; de testículo, del tracto genitourinario, de esófago; de laringe, glioblastoma, neuroblastoma, de estomago, de piel, queratoacantoma, de pulmón, carcinoma epidermoide, carcinoma de grandes células, carcinoma de pequeñas células, adenocarcinoma de pulmón; de hueso, de colon, adenoma; de páncreas, adenocarcinoma, de tiroides, carcinoma folicular, carcinoma no diferenciado, carcinoma papilar; seminoma; melanoma, sarcoma, carcinoma de vejiga; carcinoma de hígado y pasajes biliares, carcinoma de riñón; trastornos mieloides, trastornos linfoides, células pilosas de Hodgkin; de cavidad bucal y faringe (oral), de labios, de lengua, de boca, de faringe, de intestino delgado; de colon-recto, de intestino grueso, de recto, de cerebro y del sistema nervioso central, o leucemia.

50. El método de acuerdo con reivindicación 45, en donde la enfermedad es la enfermedad cardiovascular

51. El método de acuerdo con la reivindicación 50, en donde la enfermedad es una enfermedad cardiovascular seleccionada a partir de restenosis, cardiomegalia, aterosclerosis, infarto al miocardio, o falla cardíaca congestiva

52 Un método para tratar una enfermedad mediada por la GSK-3 en un paciente, con necesidad del mismo, comprendiendo dicho método la etapa de administrar a dicho paciente una cantidad terapéuticamente efectiva de la composición de acuerdo con la reivindicación 41.

53. El método de acuerdo con la reivindicación 52, que además comprende la etapa de administrar a dicho paciente un agente terapéutico adicional

54 El método de acuerdo con la reivindicación 52, en donde dicha enfermedad es diabetes.

55. El método de acuerdo con la reivindicación 52, en donde dicha enfermedad es la enfermedad de Alzheimer.

56 El método de acuerdo con la reivindicación 52, en donde dicha enfermedad es esquizofrenia.

57 Un método para incrementar la síntesis de glicógeno en un paciente con necesidad del mismo, método que comprende la etapa de administrar a dicho paciente

una cantidad terapéuticamente efectiva de la composición acorde con la reivindicación 41.

58. Un método para disminuir los niveles sanguíneos de glucosa en un paciente con necesidad del mismo, método que comprende la etapa de administrar a dicho paciente una cantidad terapéuticamente efectiva de la composición de acuerdo con la reivindicación 41.

59. Un método para inhibir la producción de la proteína Tau hiperfosforilada en un paciente con necesidad del mismo, método que comprende la etapa de administrar a dicho paciente una cantidad terapéuticamente efectiva de la composición de acuerdo con la reivindicación 41

60 Un método para inhibir la fosforilación de la β-catenina en un paciente con necesidad del mismo, método que comprende la etapa de administrar a dicho paciente una cantidad terapéuticamente efectiva de la composición de acuerdo con la reivindicación 41

61. Un método para tratar una enfermedad mediada por la Aurora-2 en un paciente con necesidad del mismo, comprendiendo dicho método la etapa de administrar a dicho paciente una cantidad terapéuticamente efectiva de la composición de acuerdo con reivindicación 41.

62 El método de acuerdo con la reivindicación 61, que comprende además la etapa de administrar a dicho paciente un agente terapéutico adicional

63. El método de acuerdo con la reivindicación 61, en donde dicha enfermedad es seleccionada a partir de cáncer de colon, de seno, de estomago, o de ovario

64. Un método para tratar una enfermedad mediada por la CDK-2, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de una composición de acuerdo con la reivindicación 41.

65 El método de acuerdo con la reivindicación 64, en donde dicha enfermedad es seleccionada a partir del cáncer, la enfermedad de Alzheimer, la restenosis, la angiogenesis, la glomerulonefritis, el citomegalovirus, el VIH, el herpes, la psoriasis, la aterosclerosis, la alopecia, o una enfermedad autoinmune

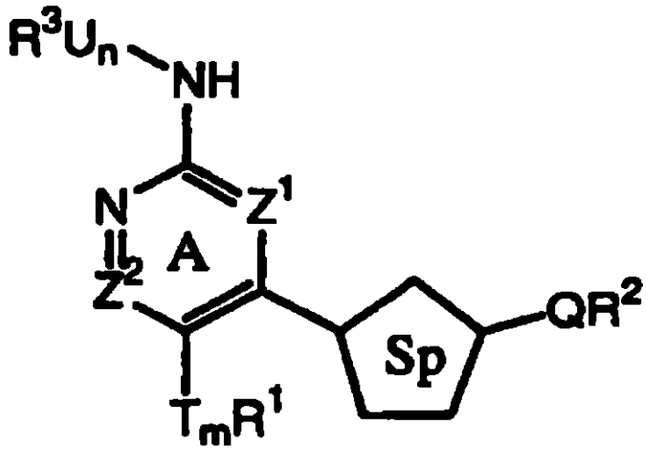
66 Un método para tratar una enfermedad mediada por la Lck, método que comprende la administración a un paciente, con necesidad de tal tratamiento, de una cantidad terapéuticamente efectiva de una composición de acuerdo con la reivindicación 41.

67 El método de acuerdo con la reivindicación 66, en donde dicha enfermedad es seleccionada a partir de una enfermedad autoinmune o el rechazo de transplantes.

68. Un método para inhibir la actividad de la ERK2, la Aurora-2, la GSK-3, la CDK-2, o la Lck en una muestra biológica, el cual comprende la etapa de contactar dicha muestra biológica con un compuesto de acuerdo con cualquiera de las reivindicaciones 20 - 40

69. Una composición para el cubrimiento de un dispositivo implantable, la cual comprende un compuesto de acuerdo con la reivindicación 20 y un portador adecuado para cubrir dicho dispositivo implantable

70 Un dispositivo implantable cubierto con una composición de acuerdo con la reivindicación 69.



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the pamphlet!

WO 02-064586

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Date: 22 aug 2002

Destination Agent

Address

HETEROCYCLIC INHIBITORS OF ERK2 AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to US Provisional Patent Application 60/267,818 filed February 9, 2001 and US Provisional Patent Application 60/328,768 filed October 12, 2001, the contents of which are incorporated herein by reference

FIELD OF THE INVENTION

The present invention is in the field of medicinal chemistry and relates to pyrazole compounds that are protein kinase inhibitors, especially inhibitors of ERK, compositions containing such compounds and methods of use The compounds are useful for treating cancer and other diseases that are alleviated by protein kinase inhibitors

BACKGROUND OF THE INVENTION

Mammalian mitogen-activated protein (MAP)1 kinases are serine/threonine kinases that mediate intracellular signal transduction pathways (Cobb and Goldsmith, 1995, *J Biol. Chem.*, 270, 14843, Davis, 1995, *Mol. Reprod Dev.* 42, 459) Members of the MAP kinase family share sequence similarity and conserved structural domains, and include the ERK2 (extracellular signal regulated kinase), JNK (Jun N-terminal kinase), and p38 kinases. JNKs and p38 kinases are activated in response to the pro-inflammatory cytokines TNF-alpha and

interleukin-1, and by cellular stress such as heat shock, hyperosmolarity, ultraviolet radiation, lipopolysaccharides and inhibitors of protein synthesis (Derijard et al , 1994, *Cell* 76, 1025, Han et al , 1994, *Science* 265, 808, Raingeaud et al., 1995, *J Biol Chem* 270, 7420; Shapiro and Dinarello, 1995, *Proc Natl Acad Sci USA* 92, 12230) In contrast, ERKs are activated by mitogens and growth factors (Bokemeyer et al 1996, *Kidney Int* 49, 1187)

ERK2 is a widely distributed protein kinase that achieves maximum activity when both Thr183 and Tyr185 are phosphorylated by the upstream MAP kinase kinase, MEK1 (Anderson et al., 1990, *Nature* 343, 651; Crews et al., 1992, *Science* 258, 478). Upon activation, ERK2 phosphorylates many regulatory proteins, including the protein kinases Rsk90 (Bjorbaek et al , 1995, *J Biol. Chem.* 270, 18848) and MAPKAP2 (Rouse et al., 1994, *Cell* 78, 1027), and transcription factors such as ATF2 (Raingeaud et al., 1996, *Mol. Cell Biol.* 16, 1247), Elk-1 (Raingeaud et al. 1996), c-Fos (Chen et al , 1993 *Proc Natl. Acad. Sci. USA* 90, 10952), and c-Myc (Oliver et al., 1995, *Proc Soc Exp Biol. Med.* 210, 162) ERK2 is also a downstream target of the Ras/Raf dependent pathways (Moodie et al , 1993, *Science* 260, 1658) and may help relay the signals from these potentially oncogenic proteins ERK2 has been shown to play a role in the negative growth control of breast cancer cells (Frey and Mulder, 1997, *Cancer Res* 57, 628) and hyperexpression of ERK2 in human breast cancer has been reported (Sivaraman et al , 1997, *J Clin Invest* 99, 1478) Activated ERK2 has also been implicated in the proliferation of endothelin-stimulated airway smooth muscle cells,

suggesting a role for this kinase in asthma (Whelchel et al., 1997, *Am J Respir Cell Mol Biol* 16, 589)

Aurora-2 is a serine/threonine protein kinase that has been implicated in human cancer, such as colon, breast and other solid tumors This kinase is believed to be involved in protein phosphorylation events that regulate the cell cycle. Specifically, Aurora-2 may play a role in controlling the accurate segregation of chromosomes during mitosis. Misregulation of the cell cycle can lead to cellular proliferation and other abnormalities In human colon cancer tissue, the aurora-2 protein has been found to be overexpressed. See Bischoff et al , *EMBO J* , 1998, 17, 3052-3065; Schumacher et al., *J. Cell Biol* , 1998, 143, 1635-1646, Kimura et al., *J Biol. Chem* , 1997, 272, 13766-13771.

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase comprised of α and β isoforms that are each encoded by distinct genes [Coghlan et al , *Chemistry & Biology*, 7, 793-803 (2000), Kim and Kimmel, *Curr Opinion Genetics Dev.*, 10, 508-514 (2000)] GSK-3 has been implicated in various diseases including diabetes, Alzheimer's disease, CNS disorders such as manic depressive disorder and neurodegenerative diseases, and cardiomyocete hypertrophy [WO 99/65897, WO 00/38675, and Haq et al , *J Cell Biol* (2000) 151, 117]. These diseases may be caused by, or result in, the abnormal operation of certain cell signaling pathways in which GSK-3 plays a role GSK-3 has been found to phosphorylate and modulate the activity of a number of regulatory proteins These proteins include glycogen synthase which is the rate limiting enzyme necessary for glycogen synthesis, the microtubule associated protein

Tau, the gene transcription factor β-catenin, the translation initiation factor eIF2B, as well as ATP citrate lyase, axin, heat shock factor-1, c-Jun, c-Myc, c-Myb, CREB, and CEPBα These diverse protein targets implicate GSK-3 in many aspects of cellular metabolism, proliferation, differentiation and development.

In a GSK-3 mediated pathway that is relevant for the treatment of type II diabetes, insulin-induced signaling leads to cellular glucose uptake and glycogen synthesis Along this pathway, GSK-3 is a negative regulator of the insulin-induced signal Normally, the presence of insulin causes inhibition of GSK-3 mediated phosphorylation and deactivation of glycogen synthase The inhibition of GSK-3 leads to increased glycogen synthesis and glucose uptake [Klein et al , *PNAS*, 93, 8455-9 (1996), Cross et al , *Biochem J.*, 303, 21-26 (1994), Cohen, *Biochem Soc. Trans* , 21, 555-567 (1993), Massillon et al., *Biochem J.* 299, 123-128 (1994)] However, in a diabetic patient where the insulin response is impaired, glycogen synthesis and glucose uptake fail to increase despite the presence of relatively high blood levels of insulin. This leads to abnormally high blood levels of glucose with acute and long term effects that may ultimately result in cardiovascular disease, renal failure and blindness In such patients, the normal insulin-induced inhibition of GSK-3 fails to occur It has also been reported that in patients with type II diabetes, GSK-3 is overexpressed [WO 00/38675]. Therapeutic inhibitors of GSK-3 therefore are considered to be useful for treating diabetic patients suffering from an impaired response to insulin.

GSK-3 activity has also been associated with Alzheimer's disease This disease is characterized by the well-known β-amyloid peptide and the formation of intracellular neurofibrillary tangles The neurofibrillary tangles contain hyperphosphorylated Tau protein where Tau is phosphorylated on abnormal sites. GSK-3 has been shown to phosphorylate these abnormal sites in cell and animal models Furthermore, inhibition of GSK-3 has been shown to prevent hyperphosphorylation of Tau in cells [Lovestone et al , *Current Biology* 4, 1077-86 (1994); Brownlees et al , *Neuroreport* 8, 3251-55 (1997)]. Therefore, it is believed that GSK-3 activity may promote generation of the neurofibrillary tangles and the progression of Alzheimer's disease

Another substrate of GSK-3 is β-catenin which is degradated after phosphorylation by GSK-3 Reduced levels of β-catenin have been reported in schizophrenic patients and have also been associated with other diseases related to increase in neuronal cell death [Zhong et al., *Nature*, 395, 698-702 (1998), Takashima et al , *PNAS*, 90, 7789-93 (1993); Pei et al., *J. Neuropathol Exp*, 56, 70-78 (1997)]

As a result of the biological importance of GSK-3, there is current interest in therapeutically effective GSK-3 inhbitors Small molecules that inhibit GSK-3 have recently been reported [WO 99/65897 (Chiron) and WO 00/38675 (SmithKline Beecham)]

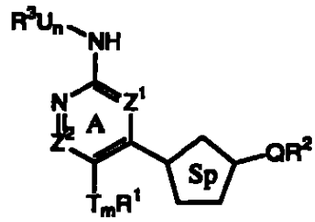
Aryl substituted pyrroles are known in the literature In particular, tri-aryl pyrroles (US 5,837,719) have been described as having glucagon antagonist activity 1,5-Diarylpyrazoles have been described as p38 inhibitors (WO 9958523)

There is a high unmet medical need to develop new therapeutic treatments that are useful in treating the various conditions associated with ERK2 activation. For many of these conditions the currently available treatment options are inadequate.

Accordingly, there is great interest in new and effective inhibitors of protein kinase, including ERK2 inhibitors, that are useful in treating various conditions associated with protein kinase activation

DESCRIPTION OF THE INVENTION

It has now been found that compounds of this invention and compositions thereof are effective as protein kinase inhibitors, especially as inhibitors of ERK2 These compounds have the general formula I·



I

or a pharmaceutically acceptable derivative thereof, wherein.

Sp is a spacer group comprising a 5-membered heteroaromatic ring, wherein Ring A and QR^2 are attached to Sp at non-adjacent positions; and wherein Sp has up to two R^6 substituents, provided that two substitutable carbon ring atoms in Sp are not simultaneously substituted by R^6,

Z^1 and Z^2 are each independently selected from N or CH;

T and Q are each an independently selected linker group,

U is selected from $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, or $-SO_2-$,

m and n are each independently selected from zero or one,

R^1 is selected from hydrogen, CN, halogen, R, $N(R^7)_2$, OR, or OH;

R^2 is selected from $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, $-(CH_2)_yCH(R^8)CH(R^5)_2$, $-N(R^4)_2$, or $-NR^4(CH_2)_yN(R^4)_2$;

y is 0-6,

R^3 is selected from R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, or $-(CH_2)_yCH(R^8)N(R^4)_2$;

each R is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms,

each R^4 is independently selected from R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, or $-(CH_2)_yCH(R^5)_2$;

each R^5 is independently selected from R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

each R^6 is independently selected from R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring,

R^8 is selected from R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, or $(CH_2)_wSR^7$, and

each w is independently selected from 0-4

As used herein, the following definitions shall apply unless otherwise indicated The phrase "optionally

substituted" is used interchangeably with the phrase "substituted or unsubstituted" or with the term "(un)substituted " Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

The term "aliphatic" or "aliphatic group" as used herein means a straight-chain or branched C_1-C_{12} hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. For example, suitable aliphatic groups include, but are not limited to, linear or branched or alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl

The terms "alkyl", "alkoxy", "hydroxyalkyl", "alkoxyalkyl", and "alkoxycarbonyl", used alone or as part of a larger moiety includes both straight and branched chains containing one to twelve carbon atoms The terms "alkenyl" and "alkynyl" used alone or as part of a larger moiety shall include both straight and branched chains containing two to twelve carbon atoms.

The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I

The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)

The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members The term "aryl" may be used interchangeably with the term "aryl ring"

[0001] The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic or tricyclic ring systems having five to fourteen ring members in which one or more ring members is a heteroatom, wherein each ring in the system contains 3 to 7 ring members

[0002] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members The term "heteroaryl" may

be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic"

An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents Suitable substituents on the unsaturated carbon atom of an aryl, heteroaryl, aralkyl, or heteroaralkyl group are selected from halogen, $-R^\circ$, $-OR^\circ$, $-SR^\circ$, 1,2-methylene-dioxy, 1,2-ethylenedioxy, protected OH (such as acyloxy), phenyl (Ph), Ph substituted with R°, $-O(Ph)$, O-(Ph) substituted with R°, $-CH_2(Ph)$, $-CH_2(Ph)$ substituted with R°, $-CH_2CH_2(Ph)$, $-CH_2CH_2(Ph)$ substituted with R°, $-NO_2$, $-CN$, $-N(R^\circ)_2$, $-NR^\circC(O)R^\circ$, $-NR^\circC(O)N(R^\circ)_2$, $-NR^\circCO_2R^\circ$, $-NR^\circNR^\circC(O)R^\circ$, $-NR^\circNR^\circC(O)N(R^\circ)_2$, $-NR^\circNR^\circCO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R^\circ)_2$, $-S(O)R^\circ$, $-NR^\circSO_2N(R^\circ)_2$, $-NR^\circSO_2R^\circ$, $-C(=S)N(R^\circ)_2$, $-C(=NH)-N(R^\circ)_2$, $-(CH_2)_yNHC(O)R^\circ$, or $-(CH_2)_yNHC(O)CH(V-R^\circ)(R^\circ)$, wherein each R° is independently selected from hydrogen,optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl (Ph), -O(Ph), or $-CH_2(Ph)-CH_2(Ph)$, wherein y is 0-6, and V is a linker group Substituents on the aliphatic group of R° are selected from NH_2, $NH(C_{1-4}$ aliphatic), $N(C_{1-4}$ aliphatic$)_2$, halogen, C_{1-4} aliphatic, OH, O-(C_{1-4} aliphatic), NO_2, CN, CO_2H, $CO_2(C_{1-4}$ aliphatic), -O(halo C_{1-4} aliphatic), or halo C_{1-4} aliphatic

An aliphatic group or a non-aromatic heterocyclic ring may contain one or more substituents Suitable substituents on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring

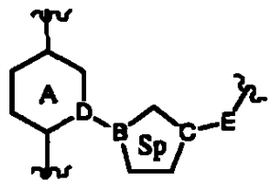
are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and the following. =O, =S, =NNHR*, =NN(R*)$_2$, =N-, =NNHC(O)R*, =NNHCO$_2$(alkyl), =NNHSO$_2$(alkyl), or =NR*, where each R* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic Substituents on the aliphatic group of R* are selected from NH_2, NH(C_{1-4} aliphatic), N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, OH, O-(C_{1-4} aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4} aliphatic), -O(halo C_{1-4} aliphatic), or halo C_{1-4} aliphatic

Substituents on the nitrogen of a non-aromatic heterocyclic ring are selected from -R+, -N(R+)$_2$, -C(O)R+, -CO$_2$R+, -C(O)C(O)R+, -C(O)CH$_2$C(O)R+, -SO$_2$R+, -SO$_2$N(R+)$_2$, -C(=S)N(R+)$_2$, -C(=NH)-N(R+)$_2$, or -NR+SO$_2$R+, wherein R+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally substituted phenyl (Ph), optionally substituted -O(Ph), optionally substituted -CH$_2$(Ph), optionally substituted -CH$_2$CH$_2$(Ph), or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring Substituents on the aliphatic group or the phenyl ring of R+ are selected from NH_2, NH(C_{1-4} aliphatic), N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, OH, O-(C_{1-4} aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4} aliphatic), -O(halo C_{1-4} aliphatic), or halo C_{1-4} aliphatic

The term "alkylidene chain" refers to an optionally substituted, straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation. The optional substituents are as described above for an aliphatic group

The term "spacer group" refers to a group that separates and orients other parts of the molecule attached thereto, such that the compound favorably interacts with functional groups in the active site of an

enzyme As used herein, the spacer group separates and orients ring A and QR^2 within the active site such that they may form favorable interactions with functional groups which exist within the active site of the ERK2 enzyme When the spacer group is a 5-membered heteroaromatic ring, ring A and QR^2 are attached at non-adjacent positions "B" and "C", and the 5-membered ring is attached to ring A at point "D" and to QR^2 at point "E" as illustrated below.



Preferably, the distance between "D" and "C" is 3 7Å, the distance between "D" and "E" is 5 0Å, the distance between "B" and "C" is 2 2Å, and the distance between "B" and "E" is 3.5Å, wherein each of the above described distances is plus/minus 0 2 Å

The spacer group itself may also form additional interactions within the active site to further enhance inhibitory activity of the compounds For example, when Sp is a pyrrole the pyrrole-NH may form an additional hydrogen bond within the active site of the ERK2 enzyme.

The term "linker group" means an organic moiety that connects two parts of a compound Linkers are typically comprised of an atom such as oxygen or sulfur, a unit such as -NH-, $-CH_2-$, -CO-, or a chain of atoms, such as an alkylidene chain The molecular mass of a

linker is typically in the range of about 14 to 200 Examples of linkers include a saturated or unsaturated C_{1-6} alkylidene chain which is optionally substituted, and wherein up to two saturated carbons of the chain are optionally replaced by -C(O)-, -C(O)C(O)-, -CONR^7-, -CONR^{7}NR^7-, -CO_2-, -OC(O)-, -NR^7CO_2-, -O-, -NR^{7}CONR^7-, -OC(O)NR^7-, -NR^{7}NR^7-, -NR^{7}CO-, -S-, -SO-, -SO_2-, -NR^7-, -SO_2NR^7-, or -NR^7SO_2-

As used herein, linker group Q connects Sp with R^2 Q may also form additional interactions within the ERK2 binding site to further enhance the inhibitory activity of the compound When Q is a carbonyl-containing moeity such as -C(O)-, -CO_2-, -OC(O)-, -C(O)C(O)-, -CONH-, -CO_2NH-, -CONHNH-, -NHCO-, -OC(O)NH-, or -NHCO_2-, or a sulfonyl-containing moeity such as -SO_2-, -SO_2NH-, or -NHSO_2-, the carbonyl or sulfonyl oxygen forms a hydrogen-bond with lysine 54 in the ERK2 binding site. When Q is an NH-containing moeity such as -CH_2NH- or -NHNH-, the NH-group forms a hydrogen-bond with aspartic acid residue 167 in the ERK2 binding site. When Q is a hydrophobic group such as an alkyl chain, -O-, or -S-, Q forms additional hydrophobic interactions within the ERK2 binding site.

R^2 forms hydrophobic interactions within the binding site of ERK2, especially with the side-chain carbons of lysine 54 and aspartic acid 167 R^2 may also form hydrophobic interactions with the glycine-rich loop which is made up of amino-acid residues 33-38. When R^2 is substituted, the substituents may form further interactions within the binding site to enhance the inhibitory activity of the compound. For example, when a substituent on R^2 is a hydrogen-bond donor or a hydrogen-bond acceptor, said substituent forms a hydrogen bond

with enzyme-bound water molecules that exist in the binding site

As used herein, linker group T, when present, connects Sp with R^1 T may also form additional interactions within the ERK2 binding site to further enhance the inhibitory activity of the compound When T is carbonyl-containing such as -CO-, -CO_2-, -OCO-, -COCO-, -CONH-, -CO_2NH-, -CONHNH-, -NHCO-, or -$NHCO_2$-, or sulfonyl-containing such as -SO_2-, -SO_2NH-, or -$NHSO_2$-, the carbonyl or sulfonyl oxygen forms a hydrogen-bond with the NH of glutamine 105 in the ERK2 binding site When T is NH-containing such as -CH_2NH- or -NHNH-, the NH-group forms a hydrogen-bond with the carbonyl of glutamine 105 When T is a hydrophobic group such as an alkyl chain, -O-, or -S-, T forms additional hydrophobic interactions with the side-chain carbons of glutamine 105 as well as isoleucine 84.

The binding interactions described herein between the compounds of this invention and the ERK2 binding site have been determined by molecular modeling programs that are known to those of ordinary skill in the art These molecular modeling programs include QUANTA [Molecular Simulations, Inc , Burlington, Mass , 1992] and SYBYL [Molecular Modeling Software, Tripos Associates, Inc , St. Louis, Mo , 1992] As used herein, the amino acid numbering for the ERK2 enzyme corresponds to the Swiss-Prot database entry for accession #P28482 The Swiss-Prot database is an international protein sequence database distributed by the European Bioinformatics Institute (EBI) in Geneva, Switzerland The database can be found at www ebi ac uk/swissprot

The compounds of this invention are limited to those that are chemically feasible and stable.

Therefore, a combination of substituents or variables in the compounds described above is permissible only if such a combination results in a stable or chemically feasible compound A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention

Compounds of formula I or salts thereof may be formulated into compositions. In a preferred embodiment, the composition is a pharmaceutically acceptable composition. In one embodiment, the composition comprises an amount of the protein kinase inhibitor effective to inhibit a protein kinase, particularly ERK-2, in a biological sample or in a patient. In another embodiment, compounds of this invention and pharmaceutical compositions thereof, which comprise an amount of the protein kinase inhibitor effective to treat or prevent an ERK-2-mediated condition and a

pharmaceutically acceptable carrier, adjuvant, or vehicle, may be formulated for administration to a patient.

The term "patient" includes human and veterinary subjects

The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof, preparations of an enzyme suitable for *in vitro* assay, biopsied material obtained from a mammal or extracts thereof, and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof

Another aspect of this invention relates to a method of treating or preventing an ERK-2-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable comprising said compound.

The term "ERK-2-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which ERK-2 is known to play a role The term "ERK-2-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with an ERK-2 inhibitor Such conditions include, without limitation, cancer, stroke, diabetes, hepatomegaly, cardiovascular disease including cardiomegaly, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders including asthma, inflammation, neurological disorders and hormone-related diseases The term "cancer" includes, but is not limited to the following cancers breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin,

keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, and leukemia

The present method is especially useful for treating a disease that is alleviated by the use of an inhibitor of ERK2 or other protein kinases. Although the present compounds were designed as ERK2 inhibitors, it has been found that certain compounds of this invention also inhibit other protein kinases such as GSK3, Aurora2, Lck, CDK2, and AKT3

Another aspect of the invention relates to inhibiting ERK-2 activity in a biological sample, which method comprises contacting the biological sample with a compound of formula I, or a pharmaceutically acceptable composition comprising said compound

Another aspect of this invention relates to a method of inhibiting ERK-2 activity in a patient, which method comprises administering to the patient a compound of formula I or a pharmaceutically acceptable composition comprising said compound

Another aspect of this invention relates to a method of treating or preventing an Aurora-2-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically

effective amount of a compound of formula I or a pharmaceutically acceptable comprising said compound.

The term "Aurora-2-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which Aurora is known to play a role The term "Aurora-2-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with an Aurora-2 inhibitor. Such conditions include, without limitation, cancer The term "cancer" includes, but is not limited to the following cancers. colon, breast, stomach, and ovarian

Another aspect of the invention relates to inhibiting Aurora-2 activity in a biological sample, which method comprises contacting the biological sample with a compound of formula I, or a pharmaceutically acceptable composition comprising said compound

Another aspect of this invention relates to a method of inhibiting Aurora-2 activity in a patient, which method comprises administering to the patient a compound of formula I or a pharmaceutically acceptable composition comprising said compound.

Another aspect of this invention relates to a method of treating or preventing a GSK-3-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable comprising said compound

The term "GSK-3-mediated condition" or "disease", as used herein, means any disease or other deleterious condition or state in which GSK-3 is known to play a role Such diseases or conditions include, without limitation, diabetes, Alzheimer's disease, Huntington's Disease, Parkinson's Disease, AIDS-

associated dementia, amyotrophic lateral sclerosis (AML), multiple sclerosis (MS), schizophrenia, cardiomycete hypertrophy, reperfusion/ischemia, and baldness

One aspect of this invention relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable thereof This method is especially useful for diabetic patients Another method relates to inhibiting the production of hyperphosphorylated Tau protein, which is useful in halting or slowing the progression of Alzheimer's disease. Another method relates to inhibiting the phosphorylation of β-catenin, which is useful for treating schizophrenia

Another aspect of the invention relates to inhibiting GSK-3 activity in a biological sample, which method comprises contacting the biological sample with a compound of formula I

Another aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, which method comprises administering to the patient a compound of formula I or a pharmaceutically acceptable composition comprising said compound

Inhibition of ERK2, Aurora2, CDK2, GSK-3, Lck, or AKT3 kinase activity in a biological sample is useful for a variety of purposes which are known to one of skill in the art Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof

The amount effective to inhibit protein kinase, for example, Aurora-2 and GSK-3, is one that measurably inhibits the kinase activity where compared to the activity of the enzyme in the absence of an inhibitor. Any method may be used to determine inhibition, such as, for example, the Biological Testing Examples described below

Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir The term "parenteral" as used herein includes subcutaneous, intravenous,

intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques Preferably, the compositions are administered orally, intraperitoneally or intravenously.

Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other

dosage forms may also be used for the purposes of formulation

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions In the case of tablets for oral use, carriers commonly used include lactose and corn starch Lubricating agents, such as magnesium stearate, are also typically added For oral administration in a capsule form, useful diluents include lactose and dried cornstarch When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation

(see above) or in a suitable enema formulation Topically-transdermal patches may also be used

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability,

fluorocarbons, and/or other conventional solubilizing or dispersing agents.

In addition to the compounds of this invention, pharmaceutically acceptable derivatives of the compounds of this invention may also be employed in compositions to treat or prevent the above-identified diseases or disorders

A "pharmaceutically acceptable derivative " means any pharmaceutically acceptable salt, ester, salt of an ester or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof Particularly favored derivatives are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a patient (e g , by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e g., the brain or lymphatic system) relative to the parent species

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-

naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts

Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein Water or oil-soluble or dispersible products may be obtained by such quaternization

The amount of the protein kinase inhibitor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the patient treated and the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated The amount of

the inhibitor will also depend upon the particular compound in the composition

The kinase inhibitors of this invention or pharmaceutical compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury) However, patients using stents or other implantable devices risk clot formation or platelet activation These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562, 5,886,026; and 5,304,121 The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition Implantable devices coated with a kinase inhibitor of this invention are another embodiment of the present invention

Depending upon the particular protein kinase-mediated condition to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may be administered together with the inhibitors of this invention. For example, in the treatment of cancer other

chemotherapeutic agents or other anti-proliferative agents may be combined with the protein kinase inhibitors of this invention to treat cancer These agents include, without limitation, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives

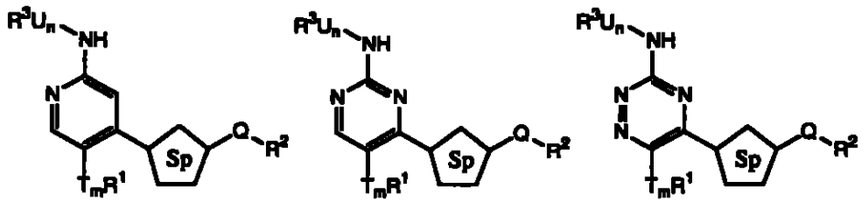
Other examples of agents the inhibitors of this invention may also be combined with include, without limitation, agents for treating diabetes such as insulin or insulin analogues, in injectable or inhalation form, glitazones, alpha glucosidase inhibitors, biguanides, insulin sensitizers, and sulfonyl ureas, anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine, immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents, agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins, agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents, agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors, and agents for treating immunodeficiency disorders such as gamma globulin

Those additional agents may be administered separately from the protein kinase inhibitor-containing composition, as part of a multiple dosage regimen

Alternatively, those agents may be part of a single dosage form, mixed together with the protein kinase inhibitor of this invention in a single composition

Compounds of this invention may exist in alternative tautomeric forms. Unless otherwise indicated, the representation of either tautomer is meant to include the other

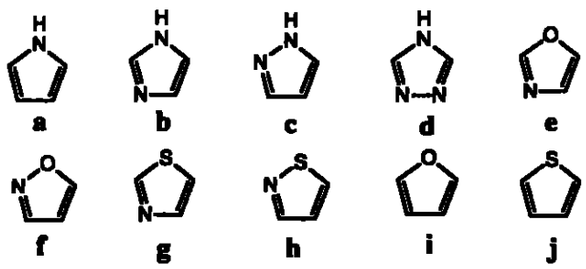
Accordingly, the present invention relates to compounds of formula I wherein Ring A is a pyridine (II), pyrimidine (III), or triazine (IV) ring as shown below:



II III IV

or a pharmaceutically acceptable derivative thereof, wherein Sp, T_mR^1, R^2, U_nR^3, Q, and T are as described above

Examples of suitable Sp groups of formula I include pyrrole (a), imidazole (b), pyrazole (c), triazole (d), oxazole (e), isoxazole (f), 1,3-thiazole (g), 1,2-thiazole (h), furan (i), and thiophene (j), as shown below



a b c d e

f g h i j

wherein each of a through j is optionally substituted with R^6

Preferred T_nR^1 groups of formula I are selected from hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring When R^1 is an optionally substituted phenyl or aliphatic group, preferred substituents on the phenyl or aliphatic group are R^7, halo, nitro, alkoxy, and amino Preferred T_nR^1 groups are methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, and CH_2NHCH_3 More preferred T_nR^1 groups of formula I are those listed in Table 1 below.

Preferred R^3 groups of formula I are hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring Examples of such groups include methyl, ethyl, propyl, cyclopropyl, cyclohexyl, benzyl, isoxazolyl, tetrahydrofuranyl, and isopropyl When R^3 is optionally substituted phenyl, preferred substituents on the phenyl ring are halogen, alkyl, alkoxy, haloalkyl, Obenzyl, Ophenyl, OCF_3, OH, SO_2NH_2, and methylene dioxy. When R^3 is $-CH(R^8)R$, examples of such groups include $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, and $-CH(CH_2OH)CH_2$cyclopropyl. Preferred U_n groups, when present, are $-CH_2-$, -O-, $-NR^7-$, -NHCO-, and $-NHCO_2-$ More preferred U_nR^3 groups of formula I are those listed in Table 1 below

When R^2 is R^5, preferred R^5 groups are pyrrolidin-1-yl, morpholin-4-yl, piperidin-1-yl, and piperazin-1-yl, 4-methyl[1,4]diazepan-1-yl, 4-phenyl-

piperazine-1-yl, wherein each group is optionally substituted When R^2 is $(CH_2)_yR^5$, $(CH_2)_yCH(R^5)_2$, or $-N(R^4)_2$, preferred R^5 groups are further selected from pyridin-3-yl, pyridin-4-yl, imidazolyl, furan-2-yl, 1,2,3,4-tetrahydroisoquinoline, tetrahydrofuran-2-yl, cyclohexyl, phenyl, benzyl, $-CH_2OH$, $-(CH_2)_2OH$, and isopropyl, wherein each group is optionally substituted. Preferred substituents on R^5 are -OH, pyridyl, piperidinyl, and optionally substituted phenyl. When R^2 is $-(CH_2)_yCH(R^6)CH(R^5)_2$, preferred R^6 groups are R^7 and OR^7 such as OH and CH_2OH and preferred R^5 are as described above Preferred $-(CH_2)_yCH(R^6)CH(R^5)_2$ groups of formula I are -CH(OH)CH(OH)phenyl and -CH(Me)CH(OH)phenyl Other preferred $-QR^2$ groups are those listed in Table 1 below

Preferred compounds of formula I are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_nR^1 is hydrogen, amino, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring,

(c) Q is -CO-, $-CO_2-$, -CONH-, $-SO_2-$, $-SO_2NH-$, -OC(O)NH-, -C(O)ONH-, or -CONHNH-,

(d) R^2 is $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^6)CH(R^5)_2$;

(f) R^4 is R, R^7, or $-(CH_2)_yCH(R^5)_2$, and

(g) R^5 is an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5-6 membered heteroaryl, or 5-6 membered heterocyclyl.

More preferred compounds of formula I are those having one or more, more preferably more than one, or most preferably all, of the features selected from the group consisting of:

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, $-CH(CH_2OH)CH_2$cyclopropyl, or an optionally substituted phenyl, benzyl, or isoxazolyl group,

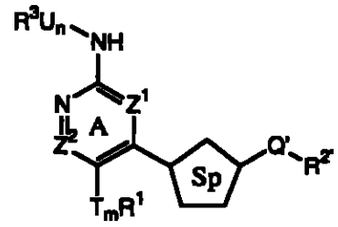
(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, or CH_2NHCH_3;

(c) Q is $-CO-$, $-CONH-$, $-SO_2-$, or $-SO_2NH-$;

(d) R^2 is $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$, wherein R^8 is OH or CH_2OH, and

(e) R^5 is $-CH_2OH$, $-(CH_2)_2OH$, isopropyl, or an optionally substituted group selected from pyrrolidin-1-yl, morpholin-4-yl, piperidin-1-yl, piperazin-1-yl, 4-methyl[1,4]diazepan-1-yl, 4-phenyl-piperazine-1-yl, pyridin-3-yl, pyridin-4-yl, imidazolyl, furan-2-yl, 1,2,3,4-tetrahydroisoquinoline, tetrahydrofuran-2-yl, cyclohexyl, phenyl, or benzyl

A preferred embodiment of this invention relates to compounds of formula I':



I'

or a pharmaceutically acceptable derivative thereof,

wherein.

Sp is a spacer group comprising a 5-membered heteroaromatic ring, wherein Ring A and $Q'R^{2'}$ are attached to Sp at non-adjacent positions; and wherein Sp has up to two R^6 substituents, provided that two substitutable carbon ring atoms in Sp are not simultaneously substituted by R^6,

Z^1 and Z^2 are each independently selected from N or CH,

Q' is selected from $-CO_2-$, $-C(O)NR^7-$ or $-SO_2NR^7-$,

T is a linker group,

U is selected from $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, or $-SO_2-$,

m and n are each independently selected from zero or one,

R^1 is selected from hydrogen, CN, halogen, R, $N(R^7)_2$, OR, or OH,

$R^{2'}$ is selected from $-(CH_2)_yCH(R^5)_2$ or $-(CH_2)_yCH(R^8)CH(R^5)_2$;

y is 0-6,

R^3 is selected from R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, or $-(CH_2)_yCH(R^8)N(R^4)_2$,

each R is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms,

each R^4 is independently selected from R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, or $-(CH_2)_yCH(R^5)_2$,

each R^5 is independently selected from R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

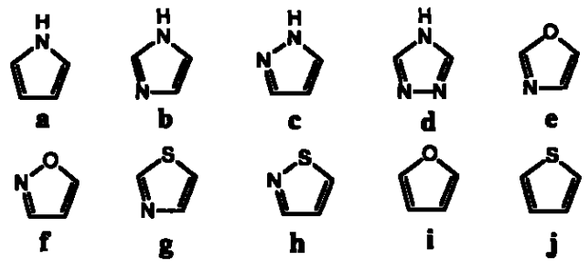
each R^6 is independently selected from R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring,

R^8 is selected from R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, or $(CH_2)_wSR^7$; and

each w is independently selected from 0-4.

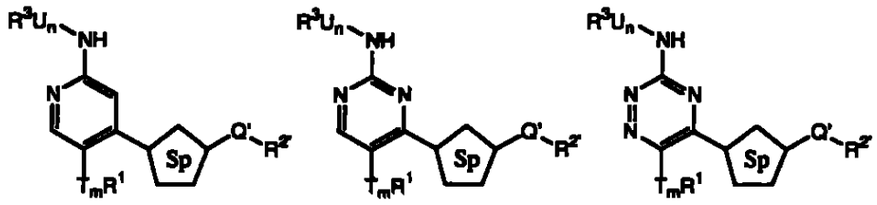
Examples of suitable Sp groups of formula I' include pyrrole (a), imidazole (b), pyrazole (c), triazole (d), oxazole (e), isoxazole (f), 1,3-thiazole (g), 1,2-thiazole (h), furan (i), and thiophene (j), as shown below



wherein each of a through j is optionally substituted with R^6

Accordingly, the present invention relates to compounds of formula I' wherein Ring A is a pyridine

(II'), pyrimidine (III'), or triazine (IV') ring as shown below:



II' III' IV'

or a pharmaceutically acceptable derivative thereof, wherein Sp, T_mR^1, $Q'R^{2'}$, and U_nR^3 are as described above

Preferred R^5 groups of formula I' are R or OR^7. Examples of such groups include OH, CH_2OH, carbocyclic, or optionally substituted 5 or 6-membered aryl or heteroaryl rings, such as phenyl, pyridyl, and cyclohexyl. Preferred R^8 groups of formula I' are R and OR^7, wherein R is an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring Examples of such groups include phenyl, methyl, ethyl, OH, and CH_2OH Preferred substituents on the R^5 aryl or heteroaryl ring are halogen, haloalkyl, OR^o, and R^o

Preferred T_mR^1 groups of formula I' are hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring.. When R^1 is an optionally substituted phenyl or aliphatic group, preferred substituents on the phenyl or aliphatic group are R^7, halo, nitro, alkoxy, and amino Preferred T_mR^1 groups include methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$,

and CH_2NHCH_3 More preferred T_nR^1 groups of formula I' are those listed in Table 1 below

Preferred R^3 groups of formula I' are hydrogen, carbocyclyl, $-CH(R^6)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring Examples of such groups include methyl, ethyl, propyl, cyclopropyl, cyclohexyl, benzyl, isoxazolyl, tetrahydrofuranyl, and isopropyl. When R^3 is optionally substituted phenyl, preferred substituents on the phenyl ring are halogen, alkyl, alkoxy, haloalkyl, Obenzyl, Ophenyl, OCF_3, OH, SO_2NH_2, and methylene dioxy. When R^3 is $-CH(R^6)R$, examples of such groups include $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, and $-CH(CH_2OH)CH_2$cyclopropyl Preferred U_n groups, when present, are $-CH_2-$, -O-, $-NR^7-$, -NHCO-, and $-NHCO_2-$ More preferred U_nR^3 groups of formula I' are those listed in Table 1 below

Preferred compounds of formula I' are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^6)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_nR^1 is hydrogen, amino, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring, and

(c) R^5 is R or OR^7, wherein R is carbocyclic, or an optionally substituted 5 or 6-membered aryl or heteroaryl ring

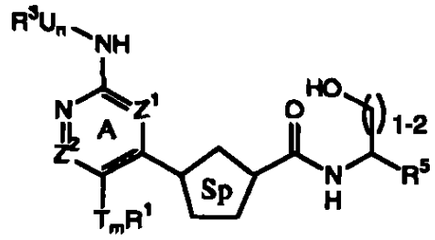
More preferred compounds of formula I' are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, -CH(CH_2OH)phenyl, -CH(CH_2OH)ethyl, -CH(CH_2OH)$_2$, -CH(CH_2OH)isopropyl, -CH(CH_2OH)CH_2cyclopropyl, or an optionally substituted phenyl, benzyl, or isoxazolyl group;

(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, NHC(O)$NHCH_3$, or CH_2NHCH_3, and

(c) R^5 is OH, CH_2OH, carbocyclic, or an optionally substituted phenyl or pyridyl ring, and Q' is C(O)NH.

Another preferred embodiment of this invention relates to compounds of formula I"



I"

or a pharmaceutically acceptable derivative thereof, wherein

Sp is a spacer group comprising a 5-membered heteroaromatic ring, wherein Ring A and C(O)NHCH[(CH_2)$_{1-2}$OH]R^5 are attached to Sp at non-

adjacent positions, and wherein Sp has up to two R^6 substituents, provided that two substitutable carbon ring atoms in Sp are not simultaneously substituted by R^6,

Z^1 and Z^2 are each independently selected from N or CH,

T is a linker group,

U is selected from $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, or $-SO_2-$;

m and n are each independently selected from zero or one,

R^1 is selected from hydrogen, CN, halogen, R, $N(R^7)_2$, OR, or OH,

R^3 is selected from R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, or $-(CH_2)_yCH(R^8)N(R^4)_2$,

each R is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms,

each R^4 is independently selected from R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, or $-(CH_2)_yCH(R^5)_2$,

each R^5 is independently selected from R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

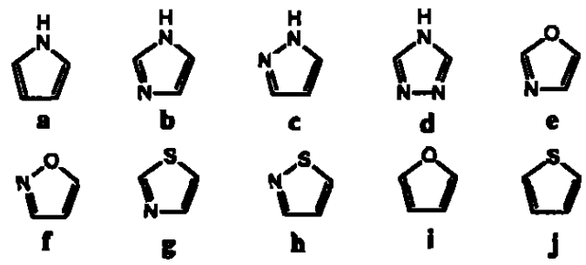
each R^6 is independently selected from R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring,

R^8 is selected from R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, or $(CH_2)_wSR^7$, and

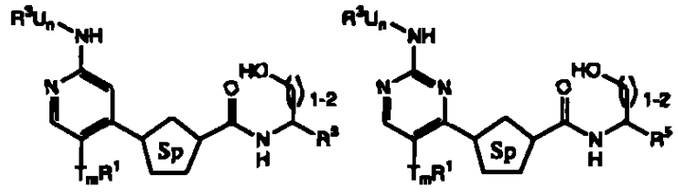
each w is independently selected from 0-4

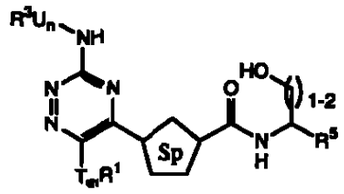
Examples of suitable Sp groups of formula I" include pyrrole (a), imidazole (b), pyrazole (c), triazole (d), oxazole (e), isoxazole (f), 1,3-thiazole (g), 1,2-thiazole (h), furan (i), and thiophene (j), as shown below



wherein each of a through j is optionally substituted with R^6

Accordingly, the present invention relates to compounds of formula I" wherein Ring A is a pyridine (II"), pyrimidine (III"), or triazine (IV") ring as shown below:





or a pharmaceutically acceptable derivative thereof, wherein Sp, T_mR^1, U_nR^3, and R^5 are as described above

Preferred T_mR^1 groups of formula I" are hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring. When R^1 is an optionally substituted phenyl or aliphatic group, preferred substituents on the phenyl or aliphatic group are R^7, halo, nitro, alkoxy, and amino. Examples of preferred T_mR^1 groups include methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, and CH_2NHCH_3 More preferred T_mR^1 groups of formula I" are those listed below in Table 1

Preferred R^3 groups of formula I" are hydrogen, carbocyclyl, $-CH(R^6)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring Examples of such groups include methyl, ethyl, propyl, cyclopropyl, cyclohexyl, benzyl, isoxazolyl, tetrahydrofuranyl, and isopropyl When R^3 is optionally substituted phenyl, preferred substituents on the phenyl ring are halogen, alkyl, alkoxy, haloalkyl, Obenzyl, Ophenyl, OCF_3, OH, SO_2NH_2, and methylene dioxy When R^3 is $-CH(R^6)R$, examples of such groups include $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, and $-CH(CH_2OH)CH_2$cyclopropyl Preferred U_n groups, when present, are $-CH_2-$, -O-, $-NR^7-$, -NHCO-, and $-NHCO_2-$ More preferred U_nR^3 groups of formula I" are those listed in Table 1 below

Preferred R^5 groups of formula I" are optionally substituted 6-membered aryl, heteroaryl, and carbocyclic rings, such as phenyl, pyridyl, and cyclohexyl

Preferred compounds of formula I" are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring, and

(c) R^5 is an optionally substituted 6-membered aryl, heteroaryl, or carbocyclic ring

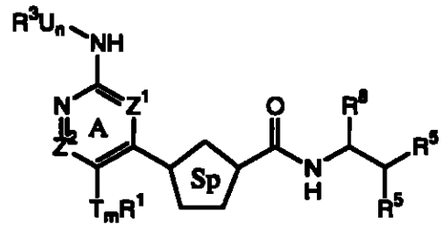
More preferred compounds of formula I" are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of·

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, $-CH(CH_2OH)CH_2$cyclopropyl, or an optionally substituted phenyl or benzyl group,

(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, or CH_2NHCH_3, and

(c) R^5 is cyclohexyl or an optionally substituted phenyl or pyridylring

Another preferred embodiment of this invention relates to compounds of formula I"



I°

or a pharmaceutically acceptable derivative thereof,

wherein

Sp is a spacer group comprising a 5-membered heteroaromatic ring, wherein Ring A and $C(O)NHCH(R^8)CH(R^5)_2$ are attached to Sp at non-adjacent positions, and wherein Sp has up to two R^6 substituents, provided that two substitutable carbon ring atoms in Sp are not simultaneously substituted by R^6,

Z^1 and Z^2 are each independently selected from N or CH;

T is a linker group;

U is selected from $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, or $-SO_2-$,

m and n are each independently selected from zero or one;

R^1 is selected from hydrogen, CN, halogen, R, $N(R^7)_2$, OR, or OH,

y is 0-6;

R^3 is selected from R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, or $-(CH_2)_yCH(R^8)N(R^4)_2$,

each R^4 is independently selected from R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, or $-(CH_2)_yCH(R^5)_2$;

each R is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms,

each R^5 is independently selected from R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

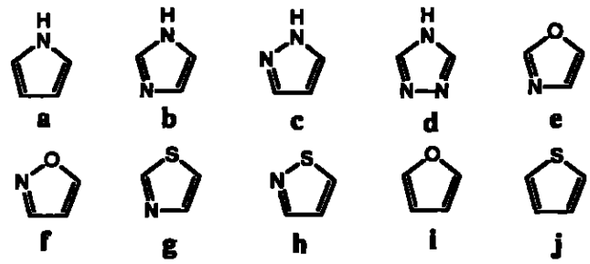
each R^6 is independently selected from R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring,

R^8 is selected from R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, or $(CH_2)_wSR^7$, and

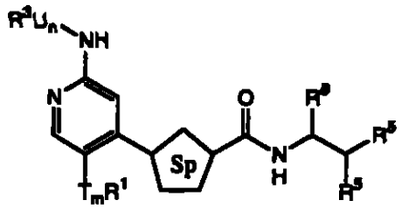
each w is independently selected from 0-4.

Examples of suitable Sp groups of formula I° include pyrrole (a), imidazole (b), pyrazole (c), triazole (d), oxazole (e), isoxazole (f), 1,3-thiazole (g), 1,2-thiazole (h), furan (i), and thiophene (j), as shown below

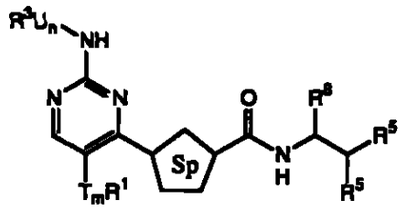


wherein each of a through j is optionally substituted with R^6

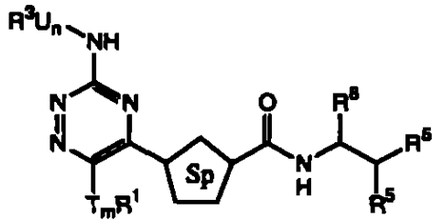
Accordingly, the present invention relates to compounds of formula I° wherein Ring A is a pyridine (II°), pyrimidine (III°), or triazine (IV°) ring as shown below:



II°



III°



IV°

or a pharmaceutically acceptable derivative thereof, wherein Sp, T_mR^1, R^5, U_nR^3, and R^8 are as described above.

Preferred R^5 groups of formula I° are R or OR^7. Examples of such groups include OH, CH_2OH, carbocyclic, or optionally substituted5 or 6-membered aryl or heteroaryl rings, such as phenyl, pyridyl, and cyclohexyl. Preferred R^8 groups of formula I° are R and OR^7, wherein R is an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring Examples of such groups include phenyl,methyl, ethyl, OH, and CH_2OH. Preferred substituents on the R^5 aryl or heteroaryl ring are halogen, haloalkyl, OR°, and R°

Preferred T_mR^1 groups of formula I° are hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring When R^1 is an optionally substituted phenyl or aliphatic group, preferred substituents on the phenyl or aliphatic group

are R^7, halo, nitro, alkoxy, and amino. More preferred T_mR^1 groups are methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, and CH_2NHCH_3 Most preferred T_mR^1 groups of formula I° are those listed in Table 1 below

Preferred R^3 groups of formula I° are hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring Examples of such groups include methyl, ethyl, propyl, cyclopropyl, cyclohexyl, benzyl, isoxazolyl, tetrahydrofuranyl, and isopropyl When R^3 is optionally substituted phenyl, preferred substituents on the phenyl ring are halogen, alkyl, alkoxy, haloalkyl, Obenzyl, Ophenyl, OCF_3, OH, SO_2NH_2, and methylene dioxy When R^3 is $-CH(R^8)R$, examples of such groups include $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, and $-CH(CH_2OH)CH_2$cyclopropyl Preferred U_n groups, when present, are $-CH_2-$, -O-, $-NR^7-$, -NHCO-, and $-NHCO_2-$. More preferred U_nR^3 groups of formula I° are those listed in Table 1 below

Preferred compounds of formula I° are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, amino, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring, and

(c) R^5 is R or OR^7, wherein R is carbocyclic, or an optionally substituted5 or 6-membered aryl or heteroaryl ring.

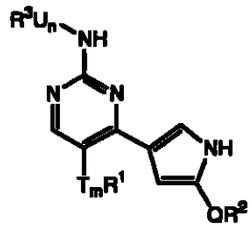
More preferred compounds of formula I^o are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, -CH(CH_2OH)phenyl, -CH(CH_2OH)ethyl, -CH(CH_2OH)$_2$, -CH(CH_2OH)isopropyl, -CH(CH_2OH)CH_2cyclopropyl, or an optionally substituted phenyl, benzyl, or isoxazolyl group,

(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, NHC(O)$NHCH_3$, or CH_2NHCH_3, and

(c) R^5 is OH, CH_2OH, carbocyclic, or an optionally substitutedphenyl or pyridyl ring.

A preferred embodiment relates to compounds of formula III-a·



III-a

or a pharmaceutically acceptable derivative thereof

Preferred T_mR^1 groups of formula III-a are hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic

or a 5-6 membered aryl or heteroaryl ring When R^1 is an optionally substituted phenyl or aliphatic group, preferred substituents on the phenyl or aliphatic group are R^7, halo, nitro, alkoxy, and amino Examples of such preferred T_mR^1 groups include methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, and CH_2NHCH_3. More preferred T_mR^1 groups of formula III-a are those listed in Table 1 below

Preferred R^3 groups of formula III-a are hydrogen, carbocyclyl, $-CH(R^6)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring Examples of such groups include methyl, ethyl, propyl, cyclopropyl, cyclohexyl, benzyl, isoxazolyl, tetrahydrofuranyl, and isopropyl When R^3 is optionally substituted phenyl, preferred substituents on the phenyl ring are halogen, alkyl, alkoxy, haloalkyl, Obenzyl, Ophenyl, OCF_3, OH, SO_2NH_2, and methylene dioxy. When R^3 is $-CH(R^6)R$, examples of such groups are $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, and $-CH(CH_2OH)CH_2$cyclopropyl Preferred U_n groups, when present, are $-CH_2-$, -O-, $-NR^7-$, -NHCO-, and $-NHCO_2-$ More preferred U_nR^3 groups of formula III-a are those listed in Table 1 below

When R^2 is R^5, preferred R^5 groups are pyrrolidin-1-yl, morpholin-4-yl, piperidin-1-yl, and piperazin-1-yl, 4-methyl[1,4]diazepan-1-yl, 4-phenyl-piperazine-1-yl, wherein each group is optionally substituted When R^2 is $(CH_2)_yR^5$, $(CH_2)_yCH(R^5)_2$, or $-N(R^4)_2$, preferred R^5 groups are pyridin-3-yl, pyridin-4-yl, imidazolyl, furan-2-yl, 1,2,3,4-tetrahydroisoquinoline, tetrahydrofuran-2-yl, cyclohexyl, phenyl, benzyl, $-CH_2OH$, $-(CH_2)_2OH$, and isopropyl, wherein each group is optionally

substituted Preferred substituents on R^5 are -OH, pyridyl, piperidinyl, and optionally substituted phenyl. When R^2 is $-(CH_2)_yCH(R^8)CH(R^5)_2$, preferred R^8 groups are R^7 and OR^7 such as OH and CH_2OH More preferred $-QR^2$ groups are those listed in Table 1 below.

Preferred compounds of formula III-a are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of·

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring;

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring;

(c) Q is $-CO-$, $-CO_2-$, $-CONH-$, $-SO_2-$, $-SO_2NH-$, $-OC(O)NH-$, $-C(O)ONH-$, or $-CONHNH-$;

(d) R^2 is $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$;

(f) R^4 is R, R^7, or $-(CH_2)_yCH(R^5)_2$, and

(g) R^5 is an optionally substituted group selected from phenyl, 5-6 membered heteroaryl, or 5-6 membered heterocyclyl

More preferred compounds of formula III-a are those having one or more, more preferably more than one, or most preferably all, of the features selected from the group consisting of:

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, $-CH(CH_2OH)CH_2$cyclopropyl, or

an optionally substituted phenyl or benzyl group,

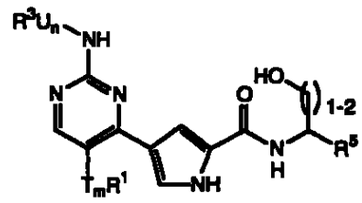
(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, or CH_2NHCH_3,

(c) Q is -CO-, -CONH-, $-SO_2-$, or $-SO_2NH-$,

(d) R^2 is $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$, wherein R^8 is OH or CH_2OH, and

(e) R^5 is $-CH_2OH$, $-(CH_2)_2OH$, isopropyl, or an optionally substituted group selected from pyrrolidin-1-yl, morpholin-4-yl, piperidin-1-yl, piperazin-1-yl, 4-methyl[1,4]diazepan-1-yl, 4-phenyl-piperazine-1-yl, pyridin-3-yl, pyridin-4-yl, imidazolyl, furan-2-yl, 1,2,3,4-tetrahydroisoquinoline, tetrahydrofuran-2-yl, cyclohexyl, phenyl, or benzyl

Preferred compounds of formula III-a include those of formula III-a'



III-a'

or a pharmaceutically acceptable derivative thereof

Preferred R^5 groups of formula III-a' are optionally substituted6-membered aryl, heteroaryl, and carbocyclic rings, such as phenyl, pyridyl, and cyclohexyl

Preferred T_mR^1 groups of formula III-a' are hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring. When R^1 is an optionally substituted phenyl or aliphatic group, preferred substituents on the phenyl or aliphatic group are R^7, halo, nitro, alkoxy, and amino. Preferred T_mR^1 groups are methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, CH_2NHCH_3, and those listed in Table 1 below

Preferred R^3 groups of formula III-a' are hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring. Examples of such groups include methyl, ethyl, propyl, cyclopropyl, cyclohexyl, benzyl, isoxazolyl, tetrahydrofuranyl, and isopropyl. When R^3 is optionally substituted phenyl, preferred substituents on the phenyl ring are halogen, alkyl, alkoxy, haloalkyl, Obenzyl, Ophenyl, OCF_3, OH, SO_2NH_2, and methylene dioxy. When R^3 is $-CH(R^8)R$, examples of such groups include $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, and $-CH(CH_2OH)CH_2$cyclopropyl. Preferred U_n groups, when present, are $-CH_2-$, -O-, $-NR^7-$, -NHCO-, and $-NHCO_2-$. More preferred U_nR^3 of formula III-a' are those listed in Table 1 below

Preferred compounds of formula III-a' are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of:

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4}

aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring; and

(c) R^5 is an optionally substituted6-membered aryl, heteroaryl, or carbocyclic ring

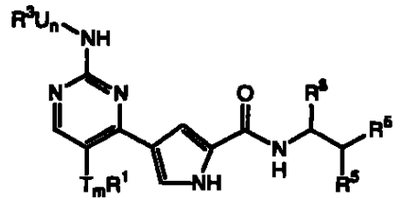
More preferred compounds of formula III-a' are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, -CH(CH_2OH)phenyl, -CH(CH_2OH)ethyl, -CH(CH_2OH)$_2$, -CH(CH_2OH)isopropyl, -CH(CH_2OH)CH_2cyclopropyl, or an optionally substituted phenyl or benzyl group,

(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, NHC(O)$NHCH_3$, or CH_2NHCH_3; and

(c) R^5 is cyclohexyl or an optionally substituted phenyl or pyridylring.

Preferred compounds of formula III-a are further selected from those of formula III-a°



III-a°

or a pharmaceutically acceptable derivative thereof.

Preferred R^5 groups of formula III-a° are R or OR^7. Examples of such groups include OH, CH_2OH, or optionally substituted6-membered aryl, heteroaryl, and carbocyclic rings, such as phenyl, pyridyl, and cyclohexyl Preferred R^8 groups of formula III-a° are R and OR^7, wherein R is an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring. Examples of such groups include phenyl, methyl, ethyl, OH, and CH_2OH.

Preferred T_mR^1 groups of formula III-a° are hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring When R^1 is an optionally substituted phenyl or aliphatic group, preferred substituents on the phenyl or aliphatic group are R^7, halo, nitro, alkoxy, and amino. Preferred T_mR^1 groups include methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, and CH_2NHCH_3 More preferred T_mR^1 groups of formula III-a° are those listed in Table 1 below

Preferred R^3 groups of formula III-a° are hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring Examples of such groups include methyl, ethyl, propyl, cyclopropyl, cyclohexyl, benzyl, isoxazolyl, tetrahydrofuranyl, and isopropyl When R^3 is optionally substituted phenyl, preferred substituents on the phenyl ring are halogen, alkyl, alkoxy, haloalkyl, Obenzyl, Ophenyl, OCF_3, OH, SO_2NH_2, and methylene dioxy. When R^3 is $-CH(R^8)R$, examples of such groups are

$-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, and $-CH(CH_2OH)CH_2$cyclopropyl

Preferred U_n groups, when present, are $-CH_2-$, $-O-$, $-NR^7-$, $-NHCO-$, and $-NHCO_2-$ More preferred U_nR^3 groups of formula III-a° are those listed in Table 1 below.

Preferred compounds of formula III-a° are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring, and

(c) R^5 is R or OR^7, and R^8 is R^7 or OR^7

More preferred compounds of formula III-a° are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of

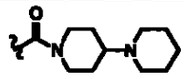
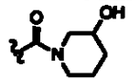
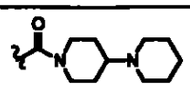
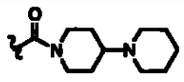
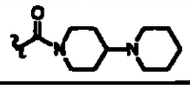
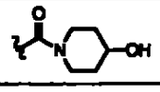
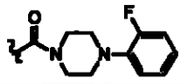
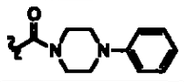
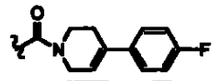
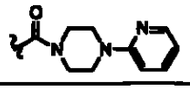
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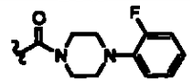
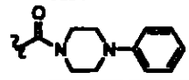
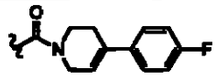
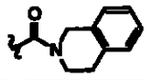
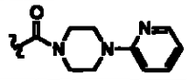
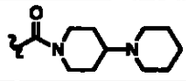
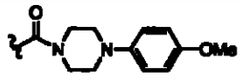
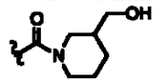
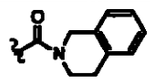
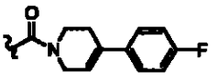
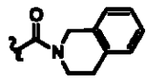
(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, or CH_2NHCH_3; and

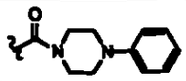
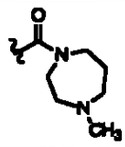
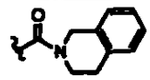
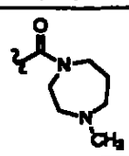
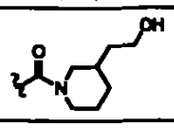
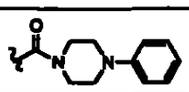
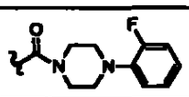
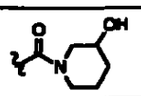
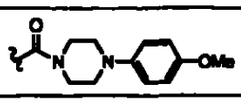
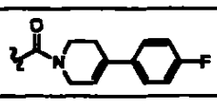
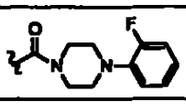
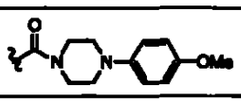
(c) R^5 is OH, CH_2OH, phenyl, pyridyl, or cyclohexyl, and R^8 is methyl, ethyl, OH, or CH_2OH.

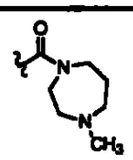
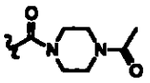
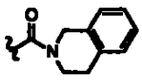
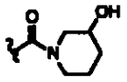
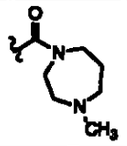
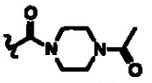
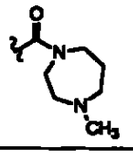
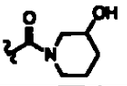
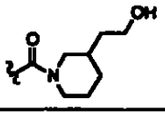
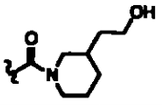
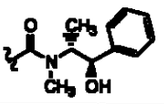
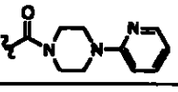
Preferred compounds of formula III-a are set forth in Table 1 below More preferred compounds in Table 1 are those of formula III-a' or III-a°

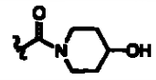
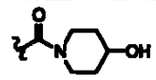
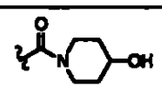
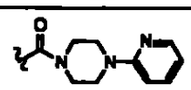
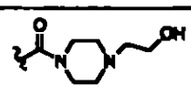
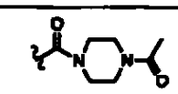
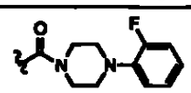
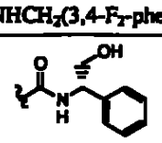
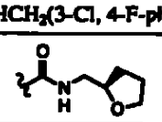
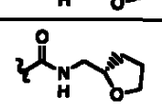
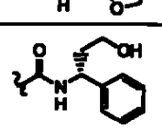
Table 1[A] Compounds of Formula III-a

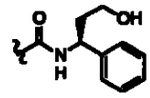
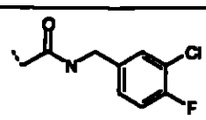
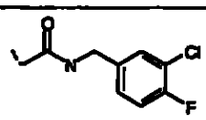
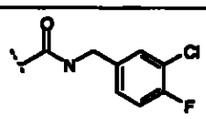
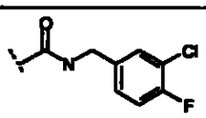
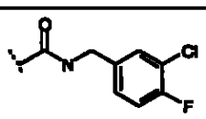
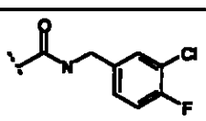
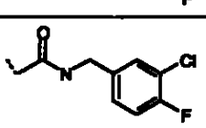
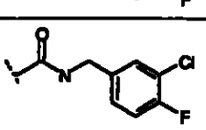
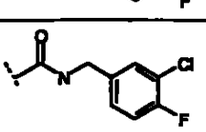
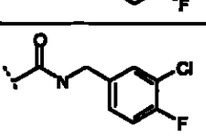
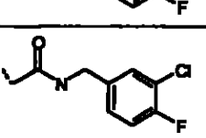
No. III-a-	R^3U_n	T_mR^1	Q-R^2
1	H	phenyl	$CON(Me)_2$
2	H	3-Cl-phenyl	CO(pyrrolidin-1-yl)
3	H	2-F-3-Cl-phenyl	CO(pyrrolidin-1-yl)
4	H	phenyl	$CONH(CH_2)_2$pyridin-3-yl
5	H	phenyl	CO(morpholin-4-yl)
6	H	phenyl	
7	H	3,4-$(CH_3O)_2$- phenyl	
8	H	3,4-$(CH_3O)_2$- phenyl	
9	H	3-Me-phenyl	
10	H	2-F-3-Cl-phenyl	
11	H	3-Me-phenyl	
12	H	phenyl	
13	H	phenyl	
14	H	phenyl	
15	H	phenyl	

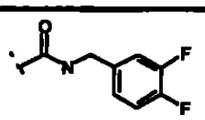
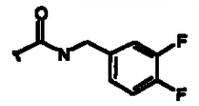
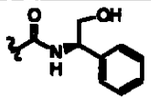
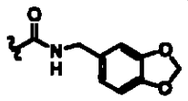
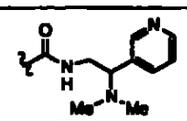
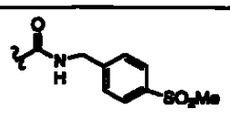
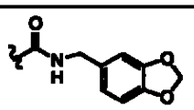
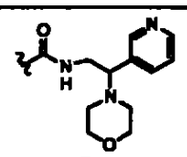
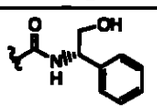
No. III-a-	R^3U_n	T_mR^1	Q-R^2
16	H	3,4-$(CH_3O)_2$- phenyl	CO(morpholin-4-yl)
17	H	3,4-$(CH_3O)_2$- phenyl	CONH$(CH_2)_2$pyridin-3-yl
18	H	3-Me-phenyl	CO(morpholin-4-yl)
19	H	3-Me-phenyl	CONH$(CH_2)_2$pyridin-3-yl
20	H	3-Cl-phenyl	CONH$(CH_2)_2$pyridin-3-yl
21	H	3-Cl-phenyl	
22	H	3-Cl-phenyl	
23	H	3-Cl-phenyl	
24	H	3-Cl-phenyl	
25	H	3-Cl-phenyl	
26	H	2-F-3-Cl-phenyl	CO(morpholin-4-yl)
27	H	3-Cl-phenyl	CO(4-OH-piperidin-1-yl)
28	H	3-Cl-phenyl	
29	H	phenyl	CON(Me)CH_2Ph
30	H	phenyl	
31	H	phenyl	
32	H	phenyl	
33	H	3,4-$(CH_3O)_2$- phenyl	CON(Me)CH_2Ph
34	H	3,4-$(CH_3O)_2$- phenyl	
35	H	3,4-$(CH_3O)_2$- phenyl	
36	H	3-Me-phenyl	CON(Me)CH_2Ph

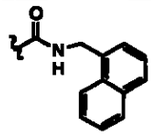
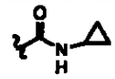
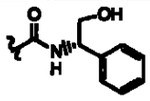
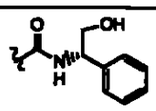
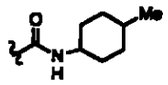
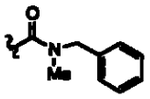
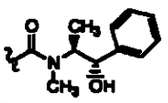
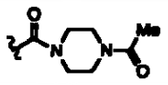
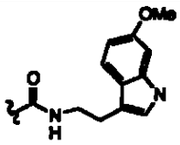
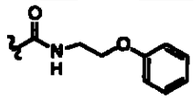
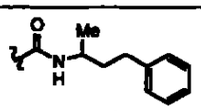
No. III-a-	R^3U_u	T_mR^1	Q-R^2
37	H	3-Me-phenyl	
38	H	3-Me-phenyl	
39	H	3-Me-phenyl	
40	H	3-Cl-phenyl	CON(Me)CH_2Ph
41	H	3-Cl-phenyl	
42	H	2-F-3-Cl-phenyl	CON(Me)CH_2Ph
43	H	3-Cl-phenyl	
44	H	2-F-3-Cl-phenyl	
45	H	3-Me-phenyl	
46	H	3-Me-phenyl	
47	H	3-Me-phenyl	
48	H	3-Me-phenyl	
49	H	2-F-3-Cl-phenyl	
50	H	2-F-3-Cl-phenyl	

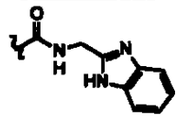
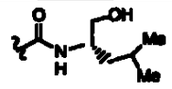
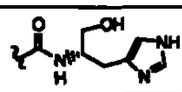
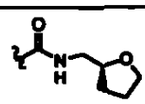
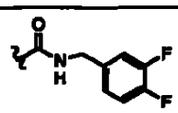
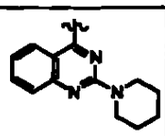
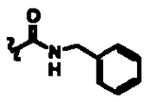
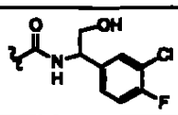
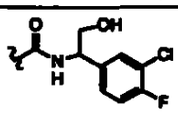
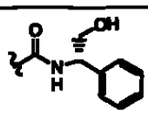
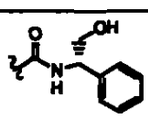
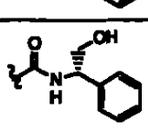
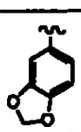
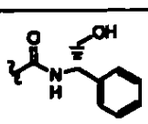
No. III-a-	R^3U_n	T_mR^1	Q-R^2
51	H	2-F-3-Cl-phenyl	
52	H	2-F-3-Cl-phenyl	
53	H	2-F-3-Cl-phenyl	
54	H	3-Cl-phenyl	
55	H	phenyl	
56	H	3,4-$(CH_3O)_2$- phenyl	
57	H	3,4-$(CH_3O)_2$- phenyl	
58	H	phenyl	
59	H	3-Cl-phenyl	CONH$(CH_2)_2$pyridin-3-yl
60	H	3-Me-phenyl	
61	H	2-F-3-Cl-phenyl	
62	H	2-F-3-Cl-phenyl	
63	H	2-F-3-Cl-phenyl	

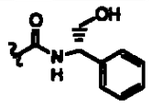
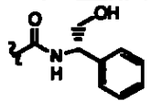
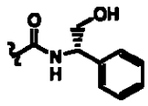
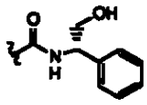
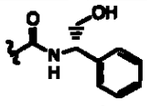
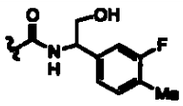
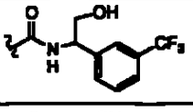
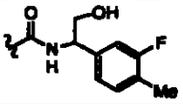
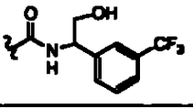
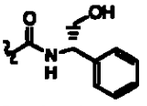
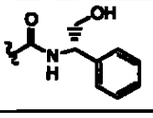
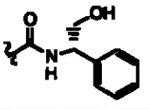
No. III-a-	R^3U_u	T_mR^1	Q-R^2
64	H	phenyl	
65	H	3,4-$(CH_3O)_2$- phenyl	
66	H	2-F-3-Cl-phenyl	
67	H	3,4-$(CH_3O)_2$- phenyl	
68	H	3-Cl-phenyl	
69	H	3-Me-phenyl	
70	H	3,4-$(CH_3O)_2$- phenyl	
71	H	phenyl	CO(pyrrolidin-1-yl)
72	H	3-Cl-phenyl	CO(morpholin-4-yl)
73	H	Methyl	$CONHCH_2Ph$
74	H	Methyl	$CONHCH_2$(3,4-F_2-phenyl)
75	H	Methyl	
76	H	Methyl	$CONHCH_2$(4-F-phenyl)
77	H	Methyl	$CONHCH_2$(3-Cl-phenyl)
78	H	Methyl	$CONHCH_2$(4-OMe-phenyl)
79	H	Methyl	$CONHCH_2$(3-Cl, 4-F-phenyl)
80	H	Methyl	
81	H	Methyl	
82	H	Methyl	

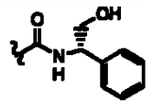
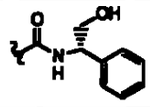
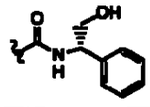
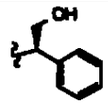
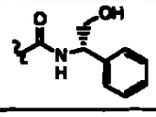
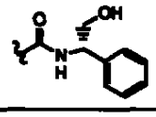
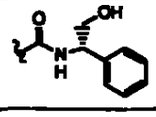
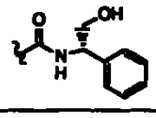
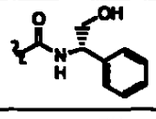
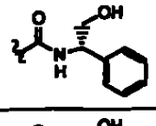
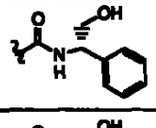
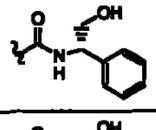
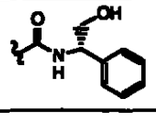
No. III-a-	R^3U_n	T_mR^1	Q-R^2
83	H	Methyl	
84	H	NH_2	
85	H	$NHCH_3$	
86	H	$NHC(O)CH_3$	
87	H	$NHC(O)NHCH_3$	
88	H	OH	
89	H	CH_2NHCH_3	
90	H	CH_2OH	
91	N-cyclohexyl	$NHC(O)NHCH_3$	
92	$C(O)CH_3$	$NHC(O)NHCH_3$	
93	SO_2CH_3	OH	
94	H	SO_2CH_3	

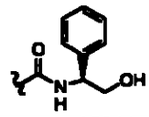
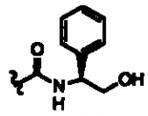
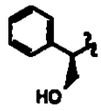
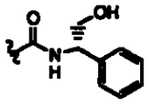
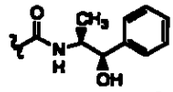
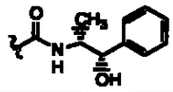
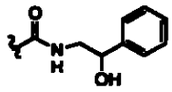
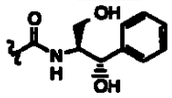
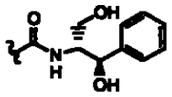
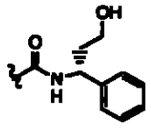
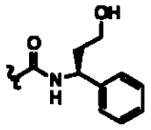
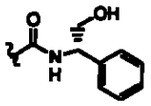
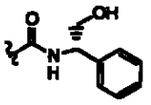
No. III-a-	R^3U_n	T_mR^1	Q-R^2
95	H	CH_2OH	
96	cyclohexyl	CH_3	
97	H	3,5-Cl_2-phenyl	$CONHCH_2$pyridin-4-yl
98	phenyl	3,5-Cl_2-phenyl	$CONHCH_2$(3-CF_3-phenyl)
99	H	3,5-Cl_2-phenyl	
100	H	3,5-Cl_2-phenyl	
101	H	3,5-Cl_2-phenyl	
102	H	3,5-Cl_2-phenyl	
103	phenyl	3,5-Cl_2-phenyl	
104	phenyl	3,5-Cl_2-phenyl	
105	H	3-F, 5-CF_3-phenyl	
106	H	n-propyl	$CONH(CH_2)_2$pyridin-3-yl
107	H	methyl	$CONH(CH_2)_2$pyridin-3-yl
108	methyl	methyl	$CONH(CH_2)_2$pyridin-3-yl
109	methyl	H	$CONH(CH_2)_2$pyridin-3-yl
110	ethyl	methyl	$CONH(CH_2)_2N(CH_3)_2$
111	pheny,	methyl	$CONH(CH_2)_2CH_3$
112	phenyl	methyl	$CONH(CH_2)_3$phenyl

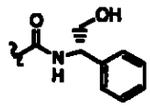
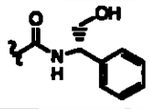
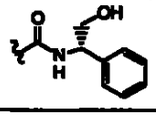
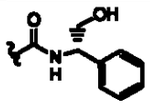
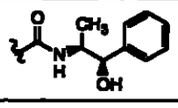
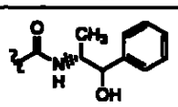
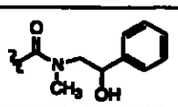
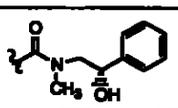
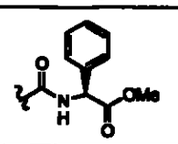
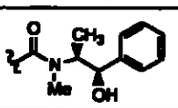
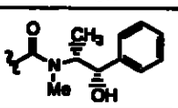
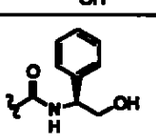
No. III-a-	R^3U_n	T_mR^1	Q-R^2
113	ethyl	methyl	
114	ethyl	methyl	
115	ethyl	H	$CONHCH_2$(2-CF_3-phenyl)
116	phenyl	methyl	
117	ethyl	methyl	
118	ethyl	H	
119	phenyl	ethyl	$CONHCH(CH_3)_2$
120	phenyl	methyl	$CONH(CH_2)_2NH_2$
121	H	H	
122	H	H	
123	ethyl	methyl	
124	ethyl	methyl	$CONH(CH_2)_3$phenyl
125	H	ethyl	
126	phenyl	methyl	
127	phenyl	methyl	

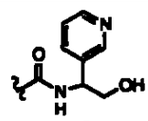
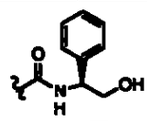
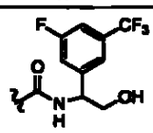
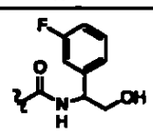
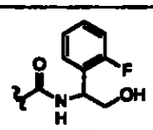
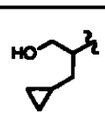
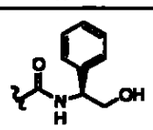
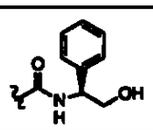
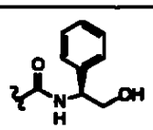
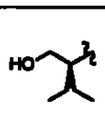
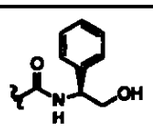
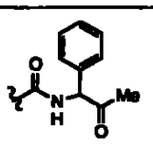
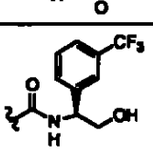
No. III-a-	R^3U_n	T_mR^1	Q-R^2
128	methyl	methyl	
129	methyl	methyl	
130	phenyl	methyl	
131	H	methyl	
132	$(CH_2)_2N(Et)_2$	methyl	
133		methyl	
134	methyl	methyl	
135	phenyl	methyl	
136	3-F-phenyl	methyl	
137	3-OMe-phenyl	methyl	
138	3-OH-phenyl	methyl	
139		methyl	

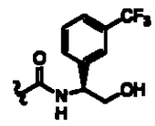
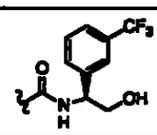
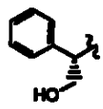
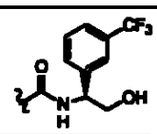
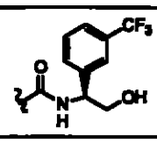
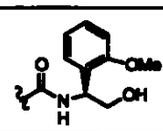
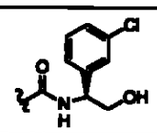
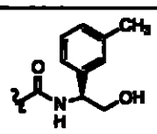
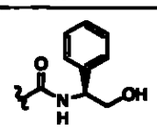
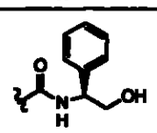
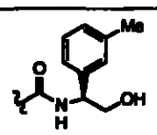
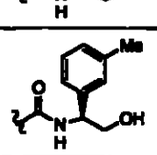
No. III-a-	R^3U_u	T_mR^1	Q-R^2
140	4-SO_2NH_2-phenyl	methyl	
141	3-OBn-phenyl	methyl	
142		methyl	
143	phenyl	cyclohexyl	
144	phenyl	cyclopropyl	
145	phenyl	methyl	
146	phenyl	methyl	
147	3-F-phenyl	methyl	
148	3-F-phenyl	methyl	
149	3-CF_3-phenyl	methyl	
150	CH_2phenyl	methyl	
151	3,4-Me_2-phenyl	methyl	

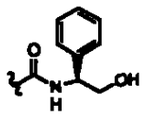
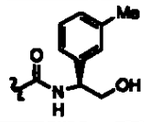
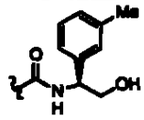
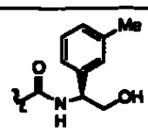
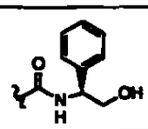
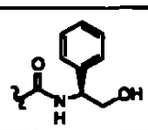
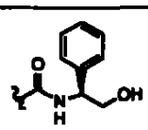
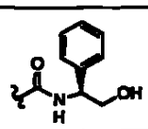
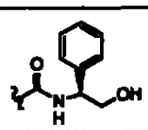
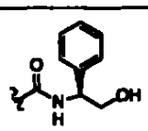
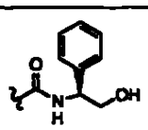
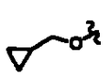
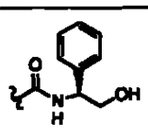
No. III-a-	R^3U_u	T_mR^1	Q-R^2
152	4-OBn-phenyl	methyl	
153	$CH(CH_3)_2$	methyl	
154	CH_2CF_3	methyl	
155		methyl	
156	2-OMe-phenyl	methyl	
157	4-OCF_3-phenyl	methyl	
158	$CH_2CH(CH_3)_2$	methyl	
159	CH_2cyclopropyl	methyl	
160	phenyl	CH_2OCH_3	
161	H	CH_2OCH_3	
162	cyclopropyl	methyl	
163	$(CH_2)_2CH_3$	methyl	

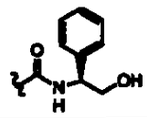
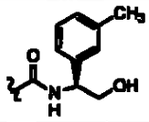
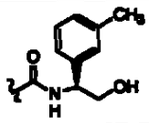
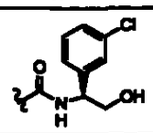
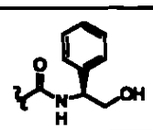
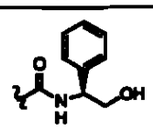
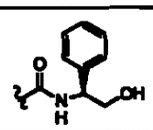
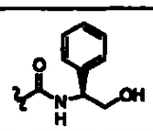
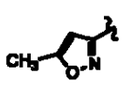
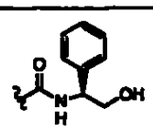
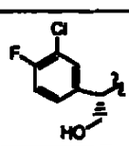
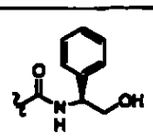
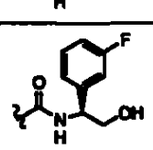
No. III-a-	R^3U_n	T_mR^1	Q-R^2
164	phenyl	CH_2OCH_3	
165	phenyl	CH_2OH	
166		methyl	
167	ethyl	methyl	
168	ethyl	methyl	
169	ethyl	methyl	
170	ethyl	methyl	
171	ethyl	methyl	
172	ethyl	methyl	
173	ethyl	methyl	
174		methyl	
175	CH_2CH_2OH	methyl	

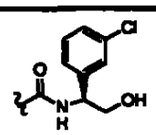
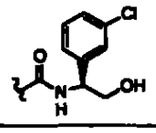
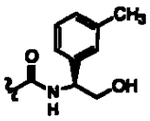
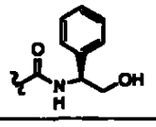
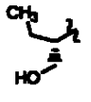
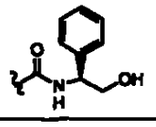
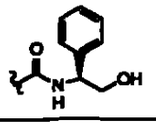
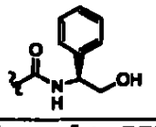
No. III-a-	R^3U_n	T_mR^1	Q-R^2
176		methyl	
177		methyl	
178		methyl	
179		methyl	
180	H	H	
181	H	H	
182	H	H	
183	H	H	
184	ethyl	methyl	
185	H	H	
186	H	H	
187	ethyl	CH_2OCH_3	

No. III-a-	R^3U_n	T_mR^1	Q-R^2
188	ethyl	methyl	
189	ethyl	CH_2OH	
190	ethyl	methyl	
191	ethyl	methyl	
192	ethyl	methyl	
193		methyl	
194	2,3-Me_2-phenyl	methyl	
195	OCH_2CH_3	methyl	
196		methyl	
197	ethyl	methyl	
198	ethyl	methyl	

No. III-a-	R^3U_n	T_mR^1	Q-R^2
199	3-fluorophenyl	methyl	
200	2-Cl-phenyl	methyl	
201		methyl	
202	cyclopropyl	methyl	
203	cyclopropyl	methyl	
204	cyclopropyl	methyl	
205	cyclopropyl	methyl	
206	O-Me	methyl	
207	O-isopropyl	methyl	
208	3-N(Me)$_2$-phenyl	methyl	
209	2-OH-phenyl	methyl	

No. III-a-	R^3U_n	T_mR^1	Q-R^2
210		methyl	
211	2,3-Me_2-phenyl	methyl	
212	3-fluoro-phenyl	methyl	
213	acetyl	methyl	
214	2-Me-phenyl	methyl	
215	pyridin-3-yl	methyl	
216		methyl	
217		methyl	
218	NC(O)OEt	methyl	
219	CH_2pyridin-3-yl	methyl	
220		methyl	

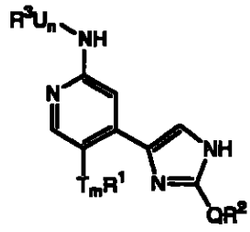
No. III-a-	R^3U_n	T_mR^1	Q-R^2
221	isoxazol-3-yl	methyl	
222		methyl	
223	2-Me-phenyl	methyl	
224	2-Me-phenyl	methyl	
225	$O(CH_2)_2OH$	methyl	
226	$N(Me)_2$	methyl	
227	2-CF_3-phenyl	methyl	
228		methyl	
229		methyl	
230		methyl	
231	phenyl	methyl	

No. III-a-	R^3U_n	T_mR^1	Q-R^2
232		methyl	
233		methyl	
234		methyl	
235		methyl	
236		methyl	
237		methyl	
238	CN	methyl	

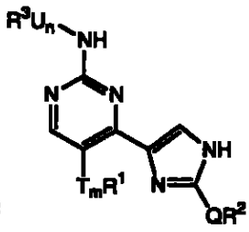
A Compound names for the compounds of formula III-a shown above in Table 1 are set forth in Appendix A.

The above formula III-a compounds are those wherein Ring A is a pyrimidine ring and Sp is a pyrrole ring Inhibitors of formula I wherein Ring A is a pyridine, pyrimidine, or triazine ring having the other Sp rings shown above are otherwise structurally similar to the formula III-a compounds and are represented by the following general formulae II-b through II-j, III-b through III-j, and IV-b through IV-j shown below in Table 2

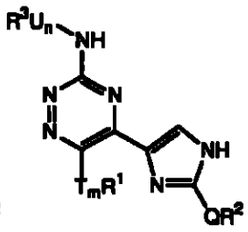
Table 2



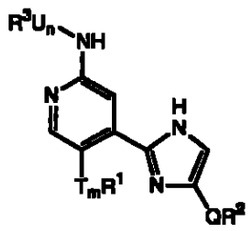
II-b



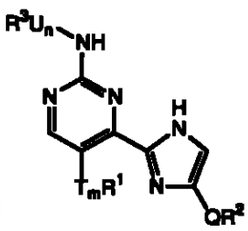
III-b



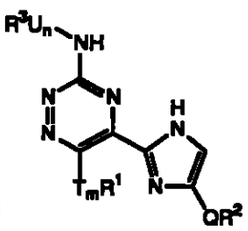
IV-b



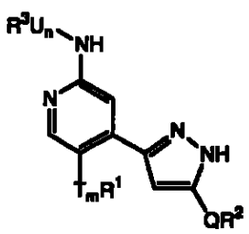
II-b'



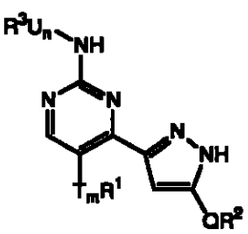
III-b'



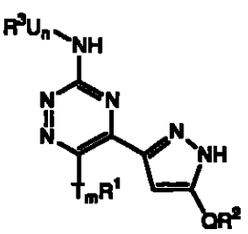
IV-b'



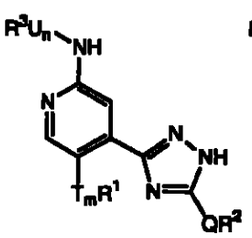
II-c



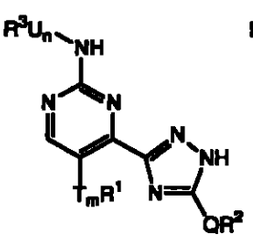
III-c



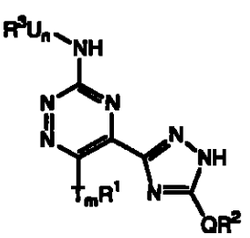
IV-c



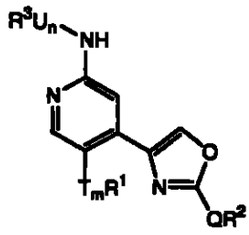
II-d



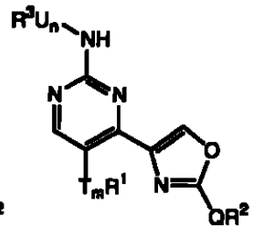
III-d



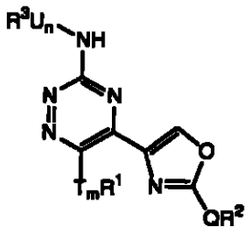
IV-d



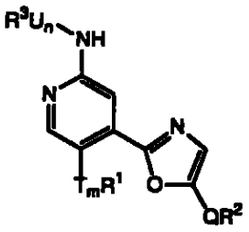
II-e



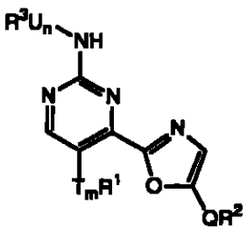
III-e



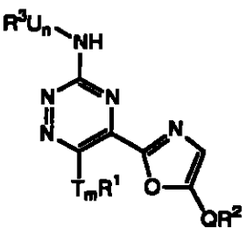
IV-e



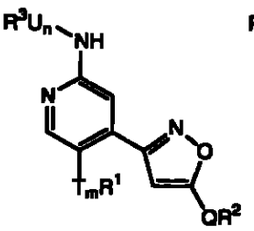
II-e'



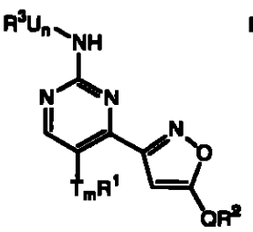
III-e'



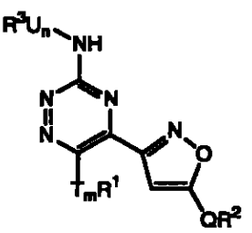
IV-e'



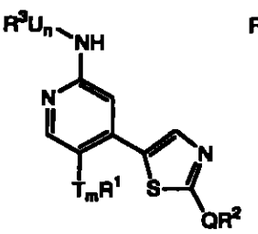
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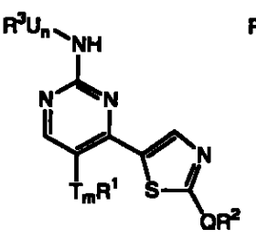
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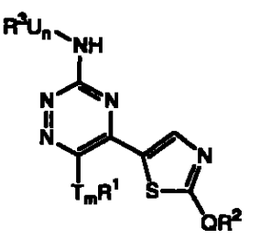
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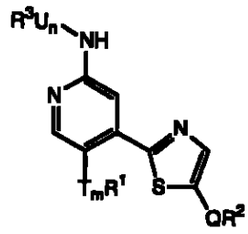
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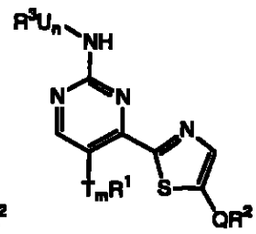
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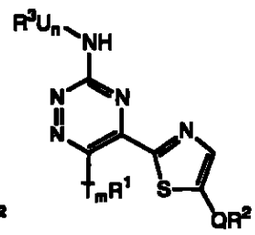
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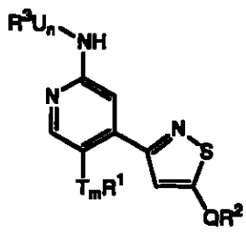
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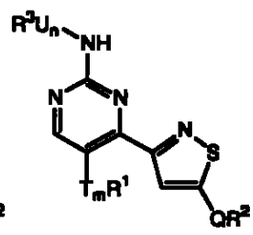
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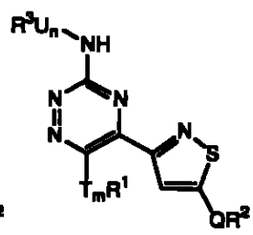
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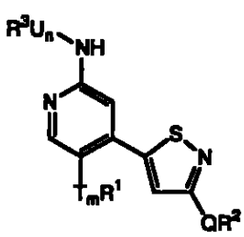
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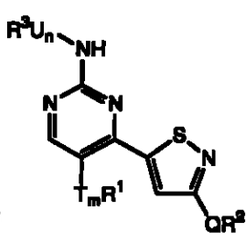
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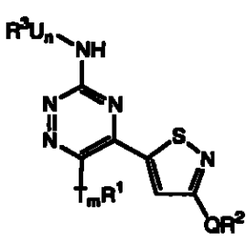
IV-h



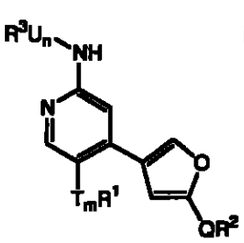
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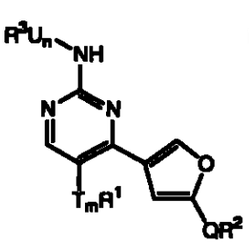
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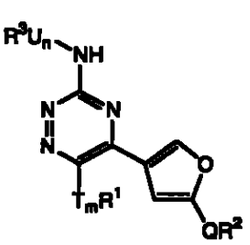
IV-h′



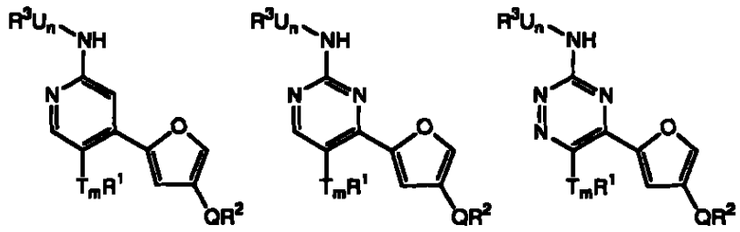
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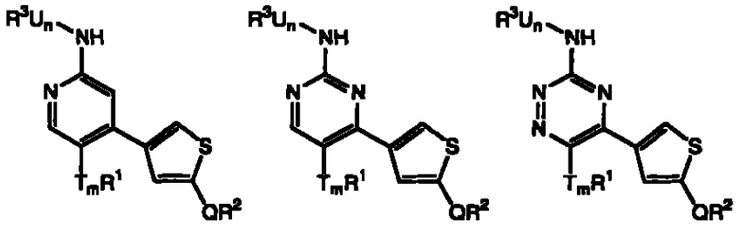
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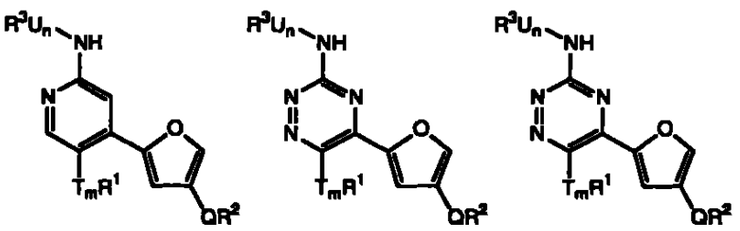
IV-i



II-i' III-i' IV-i'



II-j III-j IV-j



II-j' III-j' IV-j'

The compounds shown above in Table 2 are structurally similar to compounds of formula III-a where the pyrrole ring of formula III-a is replaced by each of the following Sp rings imidazole (b), pyrazole (c), triazole (d), oxazole (e), isoxazole (f), 1,3-thiazole (g), 1,2-thiazole (h), furan (i), and thiophene (j) Accordingly, preferred QR^2, T_mR^1, and U_nR^3 groups of the compounds shown above in Table 2 are as described above for the formula III-a compounds

In another embodiment, this invention provides a pharmaceutically acceptable composition comprising a

compound shown above in Table 2 and a pharmaceutically acceptable carrier

Another aspect of this invention relates to a method of treating or preventing an ERK2-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound shown above in Table 2 or a pharmaceutically acceptable composition comprising said compound

Another aspect of this invention relates to a method of inhibiting ERK2 activity in a patient, which method comprises administering to the patient a compound shown above in Table 2 or a pharmaceutically acceptable composition comprising said compound

Another aspect of this invention relates to a method of treating or preventing an Aurora-2-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound shown above in Table 2 or a pharmaceutically acceptable comprising said compound.

Another aspect of this invention relates to a method of inhibiting Aurora-2 activity in a patient, which method comprises administering to the patient a compound shown above in Table 2 or a pharmaceutically acceptable composition comprising said compound

Another aspect of this invention relates to a method of treating or preventing a GSK-3-mediated disease, which method comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound shown above in Table 2 or a pharmaceutically acceptable comprising said compound.

One aspect of this invention relates to a method of enhancing glycogen synthesis and/or lowering

blood levels of glucose in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a compound shown above in Table 2 or a pharmaceutically acceptable composition comprising said compound This method is especially useful for diabetic patients. Another method relates to inhibiting the production of hyperphosphorylated Tau protein, which is useful in halting or slowing the progression of Alzheimer's disease Another method relates to inhibiting the phosphorylation of β-catenin, which is useful for treating schizophrenia.

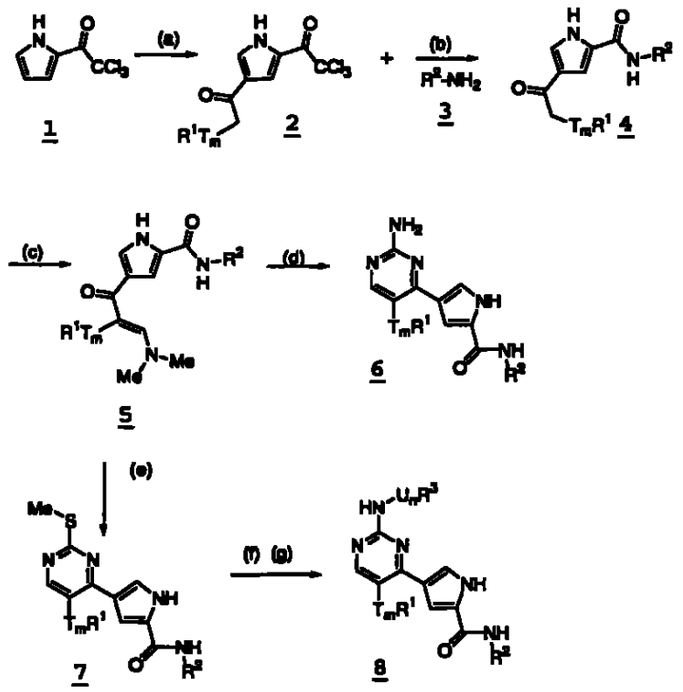
Another aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, which method comprises administering to the patient a compound shown above in Table 2 or a pharmaceutically acceptable composition comprising said compound

Another method relates to inhibiting ERK2, Aurora-2, or GSK-3 activity in a biological sample, which method comprises contacting the biological sample with a compound shown above in Table 2, or a pharmaceutically acceptable composition thereof, in an amount effective to inhibit ERK2, Aurora-2, or GSK-3

Each of the aforementioned methods directed to the inhibition of ERK2, Aurora-2 or GSK-3, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound shown above in Table 2, as described above.

The present compounds may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general Schemes I through XII and the synthetic examples shown below

Scheme I



Reagents and conditions (a) $T_mR^1CH_2COCl$, $AlCl_3$, CH_2Cl_2, 2 hours, RT, (b) DMF, 24 hrs, room temperature, (c) $(Me_2N)_2$-CHOt-Bu, THF, 24 hrs, room temperature; (d) guanidine, EtOH, 12 hours, reflux; (e) thiourea, EtOH, K_2CO_3, 12 hrs reflux, (f) *m*-CPBA, EtOH, (g) U_nR^3-NH_2, DMSO, 130°C.

Scheme I above shows a general synthetic route that is used for preparing the pyrrol-3-yl compounds of formula III-a of this invention when R^2 is an optionally substituted phenyl group or aliphatic group In step (a), an optionally substituted acid chloride is combined with compound 1, dichloromethane, and aluminum trichloride to form compound 2 In cases where benzoyl acid chlorides are used, a wide variety of substituents on the phenyl ring are amenable to this reaction. Aliphatic acid chlorides are also used in many cases.

Examples of suitable R^2 groups include, but are not limited to, those set forth in Table 1 above

The formation of amide 4 is achieved by treating compound 2 with an amine 3 in DMF When amine 3 is a primary amine, the reaction proceeds at ambient temperature When amine 3 is a secondary amine, the reaction is heated at 50°C to achieve complete reaction and afford amide 4

The formation of enamine 5 at step (c) is achieved by treating amide 4 with $(Me_2N)_2$-CHOt-Bu at ambient temperature Alternatively, the reaction to form enamine 5 at step (c) is also achieved by using dimethylformamide-dimethylacetal (DMF-DMA). The reaction using DMF-DMA typically requires elevated temperature to afford enamine 5 whereas using $(Me_2N)_2$-OtBu has the advantage of proceeding at ambient temperature to afford the enamine 5 in higher purity

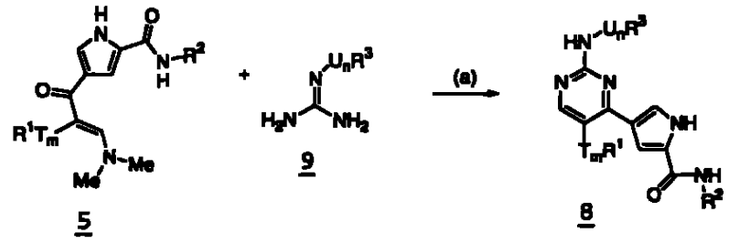
The formation of the pyrimidine compound 6 at step (d) is achieved by the treatment of enamine 5 with guanidine at elevated temperature Alternatively, use of a substituted guanidine results in an amino substituent as is illustrated by 8.

As an alternative method, in step (e) intermediate 5 may be cyclized with S-methyl thiourea to form the 2-thiomethylpyrimidine 7 which may in turn be oxidized with m-CPBA to the sulfone The sulfonyl group may be subsequently displaced by an amine to generate the substituted aminopyrimidine 8

The compounds of formula III-a synthesized by this method, as exemplified in Table 1, were isolated by preparatory HPLC (reverse phase, 10→90% MeCN in water

over 15 minutes) The details of the conditions used for producing these compounds are set forth in the Examples

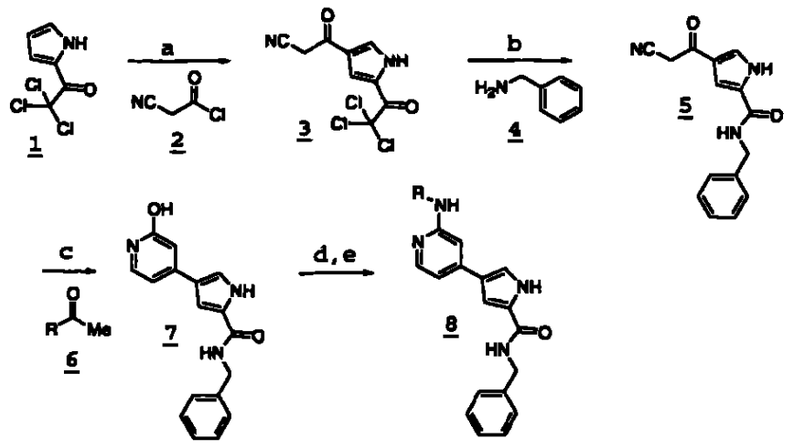
Scheme II



Reagents and conditions. (a) K_2CO_3, DMA, 100°C.

Scheme II above shows a general method for preparing compounds 8 from intermediate 5 and an *N*-substituted guanidine (9). Intermediate 5 may be prepared according to Scheme I steps (a), (b), and (c) shown above. Compound 5 is treated with *N*-substituted guanidine (9) and potassium carbonate in dimethylacetamide to form compound 8. This reaction is amenable to a variety of *N*-substituted guanidines to form compounds of formula III-a The details of the conditions used for producing these compounds are set forth in the Examples.

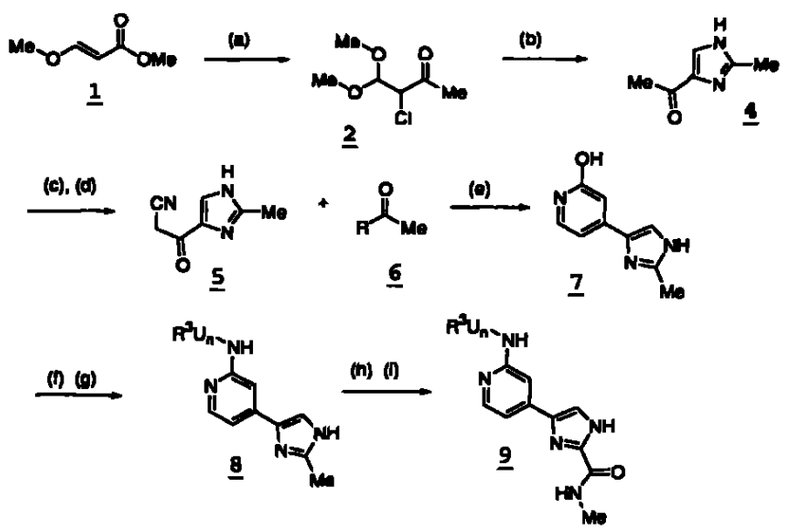
Scheme III



Reagents and conditions (a) $AlCl_3$ neat, RT, (b) DMF, 24 hrs, room temperature, (c) polyphosphoric acid, 1 hour, 25-140°C, (d) $POCl_3$, DMF, reflux, (e) NH_2-U_nR^3, iPrOH, reflux

Scheme III above shows a general synthetic route that may be used for preparing the pyrrol-3-yl compounds of formula II-a of this invention The conversion of intermediate 5 to product 8 may be achieved through steps (c), (d), and (e) according to the method described in JACS, 1957, pp 79

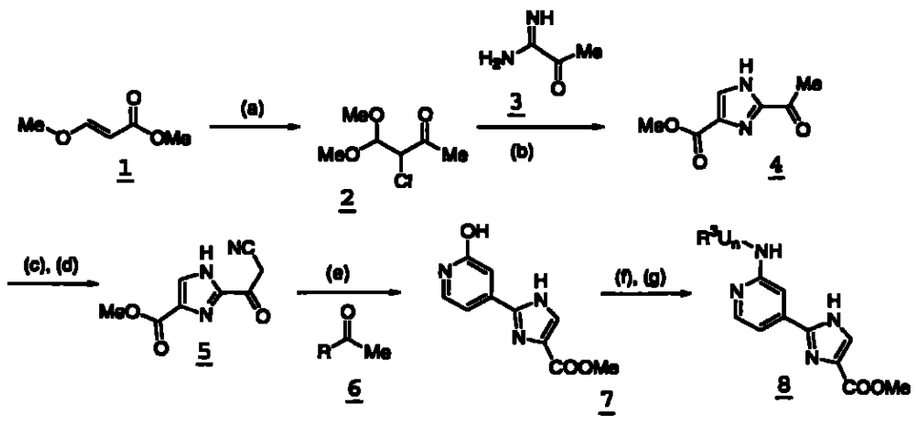
Scheme IV



Reagents and conditions (a) MeOH, pyridine, Cl_2; (b) guanidine, (c) bromine, acetic acid; (d) NaCN, DMF, (e) 6, polyphosphoric acid, 1 hour, 25-140°C, (f) $POCl_3$, DMF, reflux, (g) NH_2-U_nR^3, iPrOH, reflux; (h) SeO_2, (i) MeNH

Scheme IV above shows a general synthetic route that may be used for preparing the imidazol-4-yl compounds of formula II-b of this invention The conversion of intermediate 5 to product 8 may be achieved through steps (e), (f), and (g) according to the method described in JACS, 1957, pp 79

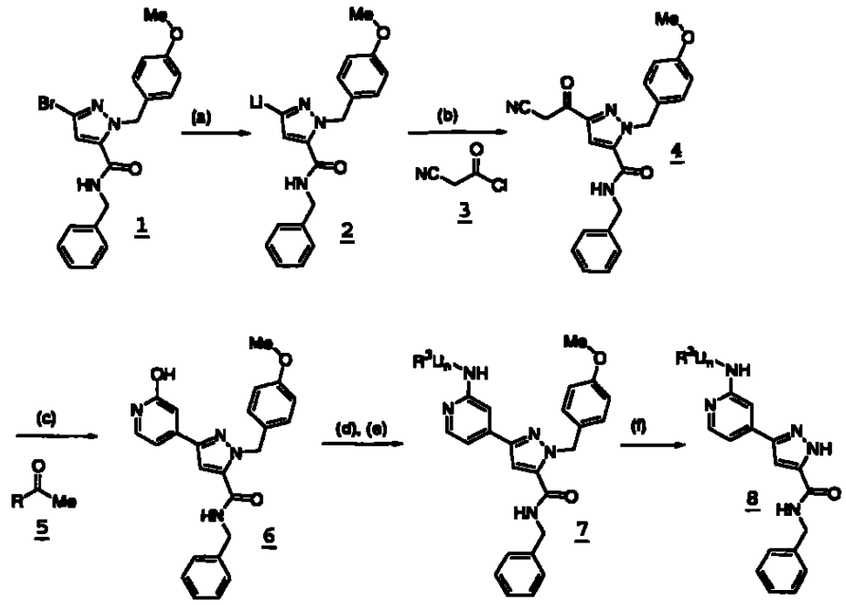
Scheme V



Reagents and conditions: (a) MeOH, pyridine, Cl_2; (b) 3, (c) bromine, acetic acid, (d) NaCN, DMF, (e) 6, polyphosphoric acid, 1 hour, 25-140°C, (f) $POCl_3$, DMF, reflux, (g) NH_2-U_nR^3, iPrOH, reflux

Scheme V above shows a general synthetic route that may be used for preparing the imidazol-2-yl compounds of formula II-b' of this invention The conversion of intermediate 5 to product 8 may be achieved through steps (e), (f), and (g) according to the method described in JACS, 1957, pp 79

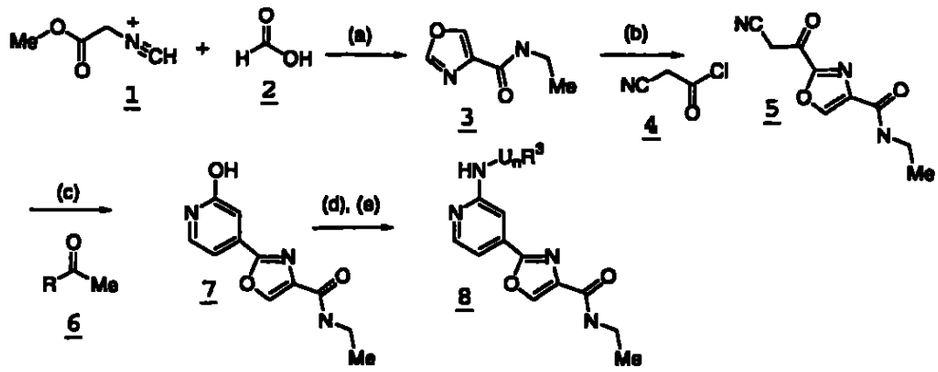
Scheme VI



Reagents and conditions. (a) (b) 3, (c) 5, polyphosphoric acid, 1 hour, 25-140°C, (d) $POCl_3$, DMF, reflux, (e) NH_2-U_nR^3, iPrOH, reflux, (f) ceric ammonium nitrate

Scheme VI above shows a general synthetic route that may be used for preparing the pyrazol-3-yl compounds of formula II-c of this invention The conversion of intermediate 4 to product 7 may be achieved through steps (c), (d), and (e) according to the method described in JACS, 1957, pp 79

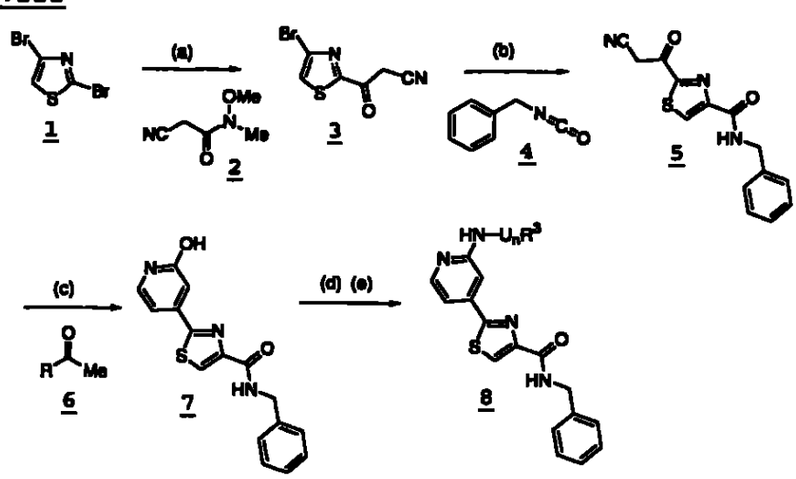
Scheme VII



Reagents and conditions. (a) 1,1'-carbonyldiimidazole (CDI), triethylamine, THF, (b) N-butyllithium, THF, -78°C; (c) 6, polyphosphoric acid, 1 hour, 25-140°C, (d) $POCl_3$, DMF, reflux, (e) NH_2-U_nR^3, iPrOH, reflux

Scheme VII above shows a general synthetic route that may be used for preparing the oxazol-2-yl compounds of formula II-e' of this invention The conversion of intermediate 5 to product 8 may be achieved through steps (c), (d), and (e) according to the method described in JACS, 1957, pp 79.

Scheme VIII

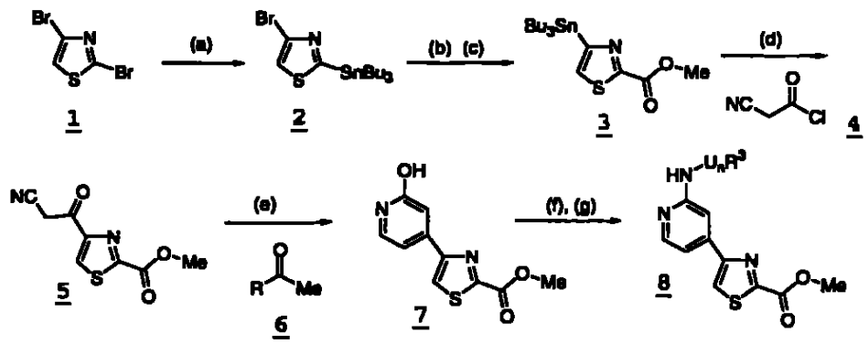


Reagents and conditions: (a) N-butyllithium, TMEDA,

-78°C (b) t-butyllithium, THF, -78°C (c) 6, polyphosphoric acid, 1 hour, 25-140°C (d) $POCl_3$, DMF, reflux (e) NH_2-R, iPrOH, reflux

Scheme VIII above shows a general synthetic route that may be used for preparing the thiazol-2-yl compounds of formula II-g' of this invention The conversion of intermediate 5 to product 8 may be achieved through steps (c), (d), and (e) according to the method described in JACS, 1957, pp 79

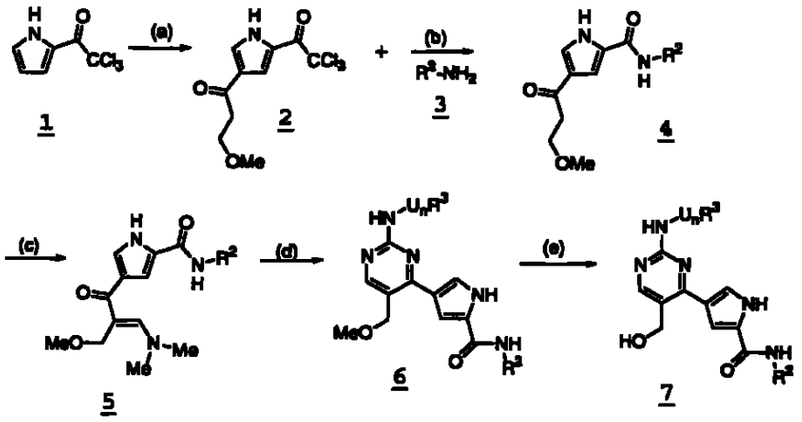
Scheme IX



Reagents and conditions: (a) N-butyllithium, Bu_3SnCl, (b) t-butyllithium, THF, -78°C, (c) $MeOCO_2Me$, (d) 4, Pd(0), (e) 6, polyphosphoric acid, 1 hour, 25-140°C, (f) $POCl_3$, DMF, reflux, (g) NH_2-U_nR^3, iPrOH, reflux

Scheme IX above shows a general synthetic route that may be used for preparing the thiazol-4-yl compounds of formula II-g of this invention The conversion of intermediate 5 to product 8 may be achieved through steps (e), (f), and (g) according to the method described in JACS, 1957, pp 79

Scheme X



Reagents and conditions (a) $CH_3OCH_2CH_2COCl$, $AlCl_3$, CH_2Cl_2, 2 5 hours, RT, (b) DMF, 24 hrs, room temperature, (c) $(Me_2N)_2$-CHOt-Bu, THF, 24 hrs, room temperature, (d) *N*-substituted guanidine, EtOH, 12 hours, reflux, (e) BBr_3, CH_2Cl_2, Na_2CO_3

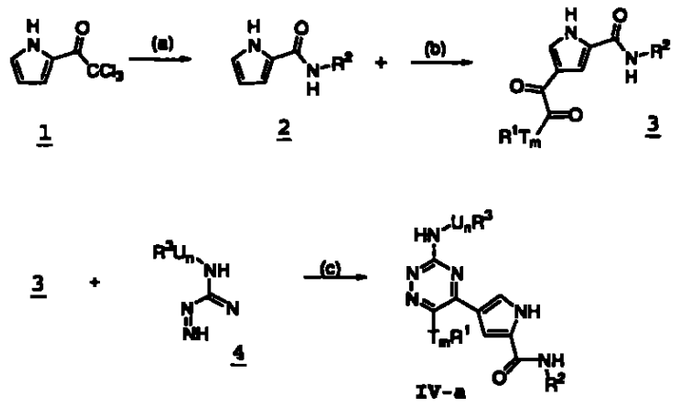
Scheme X above shows a general synthetic route that is used for preparing compounds of formula III-a where T_nR^1 is methoxymethyl or hydroxymethyl In step (a), 3-methoxypropionyl chloride is combined with compound 1, dichloromethane, and aluminum trichloride to form compound 2.

The formation of amide 4 is achieved by treating compound 2 with an amine 3 in DMF When amine 3 is a primary amine, the reaction proceeds at ambient temperature When amine 3 was a secondary amine, the reaction is heated at 50°C to achieve complete reaction and afford amide 4 The formation of enamine 5 at step (c) is achieved by treating amide 4 with $(Me_2N)_2$-CHOt-Bu at ambient temperature

The formation of the pyrimidine compound 6 at step (d) is achieved by the treatment of enamine 5 with a guanidine at elevated temperature Alternatively, use of a substituted guanidine results in an amino substituent

To form compounds where T_mR^1 is hydroxymethyl, intermediate 6 may be treated with BBr_3 in dichloromethane to form compounds 7 One of skill in the art would recognize that the hydroxymethyl group of compound 7 could be further derivatized to form a variety of compounds of formula III-a The details of the conditions used for producing these compounds are set forth in the Examples

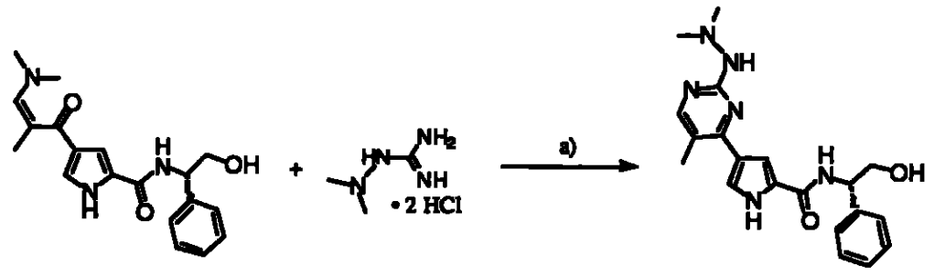
Scheme XI



Reagents and conditions (a) R^2NH_2, MeCN, 0°C to 25°C, 12 hours, (b) $AlCl_3$, CH_2Cl_2, 25°C, (c) MeOH H_2O (2·1), 37°C

Scheme XI above shows a general method for preparing the triazine compounds of formula IV-a Step (a) is performed in the manner described at Scheme I, step (b) above Step (b) is performed in the manner described at Scheme I, step (a) above The formation of the triazine ring at step (c) may be performed according to the methods described by Hirsch, J , Petrakova, E ; Feather, M S , *J Carbohydr Chem* [JCACDM] 1995, 14 (8), 1179-1186 Alternatively, step (c) may be performed according to the methods described by Siddiqui, A U , Satyanarayana, Y , Rao, U M , Siddiqui, A H , *J Chem Res, Synop* [JRPSDC] 1995 (2), 43

Scheme XII



5 6 III-a-226

Reagents and conditions: (a) K_2CO_3, DMA, 100°C, 24 hrs

Using the preparation of compound III-a-226 to illustrate, Scheme XII above shows a general synthetic route that is used for preparing compounds of formula III-a where U_n is NR^7 The formation of the pyrimidine compound III-a-226 at step (a) is achieved by the treatment of enamine 5 with a guanidine 6 at elevated temperature Alternatively, use of a substituted amino guanidine results in an hydrazyno substituent.

In another embodiment, this invention provides a pharmaceutically acceptable composition comprising a compound of formula I', I", I°, III-a, III-a', or III-a°, and a pharmaceutically acceptable carrier

Another aspect of this invention relates to a method of treating or preventing an ERK2-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of compound of formula I', I", I°, III-a, III-a', or III-a°, or a pharmaceutically acceptable composition comprising said compound

Another aspect of this invention relates to a method of inhibiting ERK2 activity in a patient, which method comprises administering to the patient compound of

formula I', I", I°, III-a, III-a', or III-a°, or a pharmaceutically acceptable composition comprising said compound

Another aspect of this invention relates to a method of treating or preventing an Aurora-2-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I', I", I°, III-a, III-a', or III-a°, or a pharmaceutically acceptable composition comprising said compound

Another aspect of this invention relates to a method of inhibiting Aurora-2 activity in a patient, which method comprises administering to the patient a compound of formula I', I", I°, III-a, III-a', or III-a°, or a pharmaceutically acceptable composition comprising said compound

Another aspect of this invention relates to a method of treating or preventing a GSK-3-mediated disease, which method comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I', I", I°, III-a, III-a', or III-a°, or a pharmaceutically acceptable composition comprising said compound.

One aspect of this invention relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a compound of formula I', I", I°, III-a, III-a', or III-a°, or a pharmaceutically acceptable composition comprising said compound This method is especially useful for diabetic patients. Another method relates to inhibiting the production of hyperphosphorylated Tau protein, which is

useful in halting or slowing the progression of Alzheimer's disease Another method relates to inhibiting the phosphorylation of β-catenin, which is useful for treating schizophrenia

Another aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, which method comprises administering to the patient a compound of formula I', I", I°, III-a, III-a', or III-a°, or a pharmaceutically acceptable composition comprising said compound

Another aspect of this invention relates to a method of treating or preventing a CDK-2-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I', I", I°, III-a, III-a', or III-a°, or a pharmaceutically acceptable composition comprising said compound

The term "CDK-2-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which CDK-2 is known to play a role The term "CDK-2-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a CDK-2 inhibitor. Such conditions include, without limitation, cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, and autoimmune diseases such as rheumatoid arthritis See Fischer, P M and Lane, D.P., *Current Medicinal Chemistry*, 7, 1213-1245 (2000), Mani, S , Wang, C , Wu, K., Francis, R. and Pestell, R , *Exp Opin Invest. Drugs*, 9, 1849 (2000), Fry, D W and Garrett, M D , *Current Opinion in*

Oncologic, Endocrine & Metabolic Investigational Drugs, 2, 40-59 (2000)

Another aspect of this invention relates to a method of treating or preventing a Lck-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I', I", I°, III-a, III-a', or III-a°, or a pharmaceutically acceptable composition comprising said compound

The terms "Lck-mediated disease" or "Lck-mediated condition", as used herein, mean any disease state or other deleterious condition in which Lck is known to play a role The terms "Lck-mediated disease" or "Lck-mediated condition" also mean those diseases or conditions that are alleviated by treatment with an Lck inhibitor Lck-mediated diseases or conditions include, but are not limited to, autoimmune diseases such as transplant rejection, allergies, rheumatoid arthritis, and leukemia. The association of Lck with various diseases has been described [Molina et al , *Nature*, 357, 161 (1992)]

Another aspect of this invention relates to a method of treating or preventing an AKT3-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I', I", I°, III-a, III-a', or III-a°, or a pharmaceutically acceptable composition comprising said compound

The terms "AKT3-mediated disease" or "AKT3-mediated condition", as used herein, mean any disease state or other deleterious condition in which AKT3 is known to play a role The terms "AKT3-mediated disease" or "AKT3-mediated condition" also mean those diseases or

conditions that are alleviated by treatment with an AKT inhibitor. AKT3-mediated diseases or conditions include, but are not limited to, proliferative disorders, cancer, and neurodegenerative disorders. The association of AKT3 with various diseases has been described [Zang, Q Y , et al, *Oncogene*, 19 (2000)] and [Kazuhiko, N., et al, *The Journal of Neuroscience*, 20 (2000)].

Another method relates to inhibiting ERK2, Aurora-2, CDK-2, Lck, AKT3, or GSK-3 activity in a biological sample, which method comprises contacting the biological sample with a compound of formula I', I", I°, III-a, III-a', or III-a°,, or a pharmaceutically acceptable composition comprising said compound, in an amount effective to inhibit ERK2, Aurora-2, CDK-2, Lck, AKT3, or GSK-3

Each of the aforementioned methods directed to the inhibition of ERK2, Aurora-2, CDK-2, Lck, AKT3, or GSK-3, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula I', I", I°, III-a, III-a', or III-a°, as described above More preferably, each of the aforementioned methods is carried out with a preferred compound of formula I', I", I°, III-a', or III-a°, and most preferably with a compound of formula I", I°, III-a', or III-a°

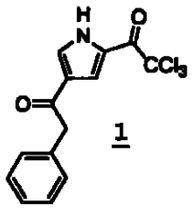
In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner

SYNTHETIC EXAMPLES

For compounds where the HPLC Method is designated as "A", the following method was utilized. a

gradient of water MeCN, 0 1% TFA (95 5 → 0 100) was run over 22 minutes at 1 mL/min and 214 nm For compounds where the HPLC Method is designated as "B", the following method was utilized a gradient of water MeCN, 0 1% TFA (90 10 → 0 100) was run over 8 minutes at 1 mL/min and 214 nm Each of methods A and B utilize the YMC ODS-AQ 55 120A column with a size of 3 0 x 150 mm. As used herein, the term "R_t" refers to the retention time, in minutes, associated with the compound using the designated HPLC method

Example 1



1

2,2,2-Trichloro-1-(4-phenyl acetyl-1H-pyrrol-2-yl)-ethanone (1) In a dry flask, phenylacetyl chloride (1 equivalent) was combined with 2-trichloroacetyl pyrrole (1 equivalent) in a minimum amount of dichloromethane (DCM) to dissolve the reactants To the resulting solution, at ambient temperature, was added aluminum trichloride (1 equivalent) After 2 hours, the reaction mixture was applied directly onto a silica gel column Gradient elution with 10% ethyl acetate to 50% ethyl acetate in hexanes provided compound 1 in 60% yield ^{1}H NMR ($CDCl_3$) δ 4 0 (s, 2H), 7 1-7 35 (m, 7H), 9 7 (br s, NH) HPLC using method B provided R_t of 4 9 minutes LC/MS (M+1) 330 2, (M-1) 328.1

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the pamphlet!

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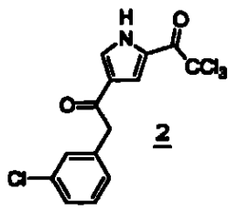
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Date: 22 aug 2002

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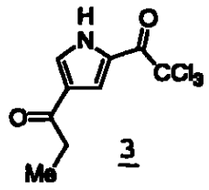
Example 2



2

2,2,2-Trichloro-1-(4-(3-Chlorophenyl) acetyl-1H-pyrrol-2-yl)-ethanone (2)· In a dry flask, 3-chlorophenylacetyl chloride (1 equivalent) was combined with 2-trichloroacetyl pyrrole (1 equivalent) in a minimum amount of dichloromethane (DCM) To the resulting solution, at ambient temperature, was added aluminum trichloride (1 equivalent) After 2 hours, the reaction mixture was applied directly onto a silica gel column. Gradient elution with 10% ethyl acetate to 50% ethyl acetate in hexanes provided compound 2 HPLC using method A provided R_t of 15 minutes

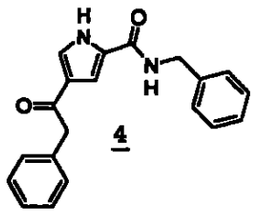
Example 3



3

1-[5-(2,2,2-Trichloro-acetyl)-1H-pyrrol-3-yl)-propan-1-one (3): In a dry flask, 3-proprionyl chloride (1 equivalent) was combined with 2-trichloroacetyl pyrrole (1 equivalent) in a minimum amount of dichloromethane (DCM) To the resulting solution, at ambient temperature, was added aluminum trichloride (1 equivalent) After 2 hours, the reaction mixture was applied directly onto a silica gel column Gradient elution with 10% ethyl acetate to 50% ethyl acetate in hexanes provided compound 3

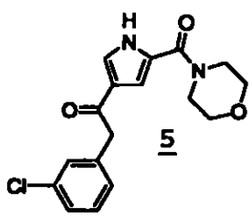
Example 4



4

4-Phenylacetyl-1H-pyrrole-2-carboxylic acid benzylamide (4) To a solution of compound 1 (1 equivalent) in DMF, at ambient temperature, was added benzylamine (1 2 equivalents) After 24 hours, the solvent was evaporated and the crude product 4 was used without purification HPLC using method B provided R_t of 3 8 minutes FIA/MS (M+1) 319 3, (M-1) 317 2

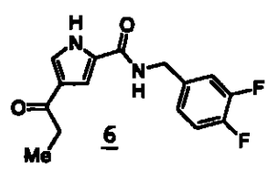
Example 5



5

2-(3-Chlorophenyl)1-[5-(morpholine-4-carbonyl)-1H-pyrrol-3-yl]-ethanone (5): To a solution of compound 2 (1 equivalent) in DMF, at ambient temperature, was added morpholine (1 2 equivalents) After 24 hours, the solvent was evaporated and the crude product 5 was used without purification FIA/MS (M+1) 333 3, (M-1) 331 2 ^{1}H NMR was consistent with expected structure

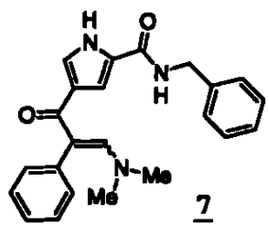
Example 6



6

4-Propionyl-1H-pyrrole-2-carboxylic acid 3,4-difluoro-benzylamide (6) To a solution of compound 3 (1 equivalent) in DMF, at ambient temperature, was added 3,4-difluorobenzyl amine (1.2 equivalents) After 24 hours, the solvent was evaporated and the crude product 6 was used without purification.

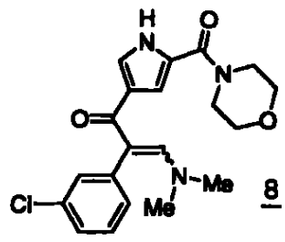
Example 7



7

4-(3-Dimethylamino-2-phenyl-acryloyl)-1H-pyrrole-2-carboxylic acid benzylamide (7) To a solution of compound 4 (1 equivalent) in THF, at ambient temperature, was added $(Me_2N)_2CHOt$-Bu (3 equivalents) After 24 hours, the solvent was evaporated and the crude product 7 was used without purification ^1H NMR ($CDCl_3$) δ 4 4 (s, 2H), 4 8 (s, NH), 6 8-7 4 (m, 13H)

Example 8

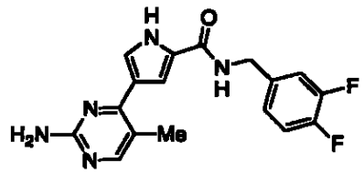


8

2-(3-Chloro-phenyl)-3-dimethylamino-1-[5-(morpholine-4-carbonyl)-1H-pyrrol-3-yl]-propenone (8) To a solution of compound 5 (1 equivalent) in THF, at ambient temperature, was added $(Me_2N)_2CHOt$-Bu (3 equivalents) After 24 hours, the solvent was evaporated and the crude product 8 was

used without purification HPLC using method B provided R_t of 11 2 minutes

Example 9



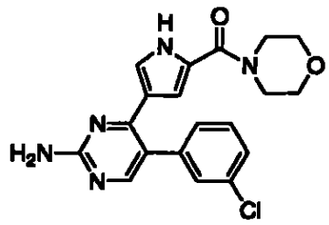
III-a-74

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1*H*-pyrrole-2-carboxylic acid 3,4-difluoro-benzylamide (III-a-74):

Step 1 To a solution of compound 6 (1 equivalent) in THF, at ambient temperature, was added $(Me_2N)_2CHOt$-Bu (3 equivalents) After 24 hours, the solvent was evaporated and the crude product was utilized without purification

Step 2 To a solution of the compound formed above at Step 1 (1 equivalent) in ethanol, at ambient temperature, was added guanidine (3 equivalents) and the resulting mixture heated at reflux After 12 hours, the solvent was evaporated and the crude product purified by preparatory HPLC (reverse phase, 10→90% MeCN in water, 15 minutes) to afford the desired compound III-a-74 HPLC using method B provided R_t of 7 9 minutes ^1H NMR was consistent with expected structure FIA/MS Obs M+1 /M-1

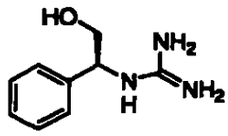
Example 10



III-a-72

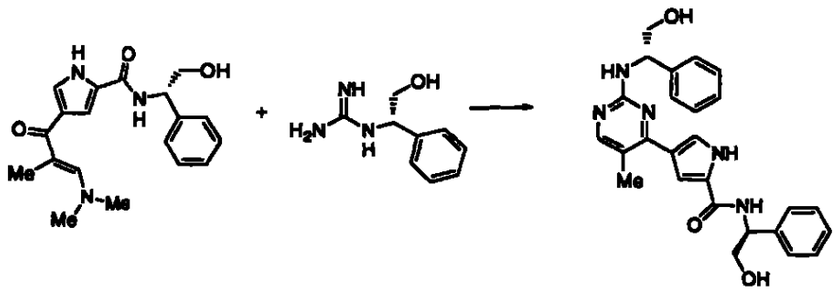
{4-[2-Amino-5-(3-chlorophenyl)-pyrimidine-4-yl]-1H-pyrrol-2-yl}-morpholin-4-yl-methanone (III-a-72): To a solution of compound 8 (1 equivalent) in ethanol, at ambient temperature, was added guanidine (3 equivalents) and the resulting mixture heated at reflux After 12 hours, the solvent was evaporated and the crude product purified by preparatory HPLC (reverse phase, 10→90% MeCN in water, 15 minutes) to afford the desired compound III-a-72. HPLC using method B, R_t=7 9 minutes ^{1}H NMR was consistent with expected structure FIA/MS Obs (M+1) 384 4 amu.

Example 11



N-(2-Hydroxy-1-(*S*)-phenyl-ethyl)-guanidine•HCl. (*S*)-Phenylglycinol (0.38g, 2.7 mmol) and bis-Boc guanidine-(*N*)-triflate (0 9g, 2 3 mmol) were combined in methylene chloride (anhydrous, 5mL) and stirred at ambient temperature overnight Completion of the reaction was verified by HPLC. The mixture was diluted with ethyl acetate, washed with 2M sodium bisulfite, brine then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The bis-Boc guanidine intermediate was treated with 4N HCl/dioxane (5mL) and stirred at room temperature until deprotection was complete (48 h) to afford the title compound

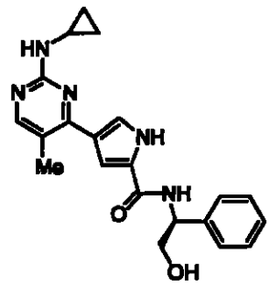
Example 12



III-a-155

4-[2-(2-Hydroxy-1-(*S*)-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide (III-a-155) 4-(3-Dimethylamino-2-methyl-acryloyl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide (100 mg, 0 29 mmol) was combined with N-(*S*)-phenylglycinol guanidine•HCl (126 mg) and potassium carbonate (121 mg) in N,N-dimethylacetamide (2mL) The resulting suspension was heated and stirred at 100° C for 24 hours The crude material was diluted with ethyl acetate, washed with saturated $NaHCO_3$, brine, dried over MgSO4 and concentrated *in vacuo* Purification by prep HPLC (Gilson Column = CombiHT SB-C189 5 µM 21 2 mm x 100 mm, eluent = 0 1%TFA MeCN/H2O gradient) followed by preparative TLC (silica, 5% MeOH in CH_2Cl_2) afforded compound III-a-155 as a pale yellow solid (8 0 mg) HPLC Method B, R_t=4 76 minutes, MS (FIA) 458 2 (M+1), 456 1 (M-1), ^1H NMR consistent with structure

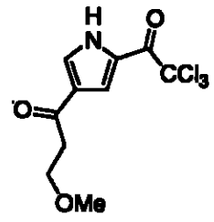
Example 13



III-a-162

4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide (III-a-162): 4-(3-Dimethylamino-2-methyl-acryloyl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide (100 mg, 0 29 mmol) was combined with cyclopropyl guanidine•HCl (80 mg) and potassium carbonate (121 mg) in N,N-dimethylacetamide (2mL) The resulting suspension was heated and stirred at 100°C for 24 hours. The crude material was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, dried over MgSO4 then concentrated *in vacuo* Purification by preparative TLC (silica, 1 1 EtOAc Hexanes) afforded III-a-162 as a yellow solid (7.8 mg) HPLC Method B, R_t=4 29 minutes; LC/MS(m/z) 378 2 (M+1), 376 2 (M-1), ^1H NMR consistent with structure.

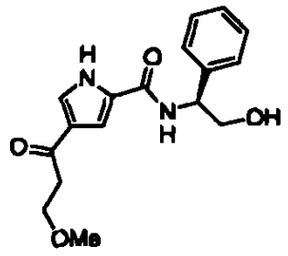
Example 14



3-Methoxy-1-[5-(2,2,2-trichloro-acetyl)-1*H*-pyrrol-3-yl]-propan-1-one To a solution of 2-trichloroacetyl pyrrole

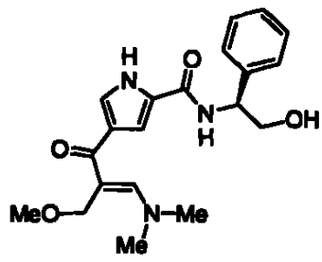
(1 0 equivalent, 4 67g, 22 mmol) in methylene chloride (5 mL) was added 3-methoxypropionyl chloride (1 0 equivalent, 22 mmol) then aluminium trichloride (1.0 equivalent, 2 93g, 22 mmol) was added in small portions After 2 5 hours, the crude mixture was chromatographed on silica gel (MeOH 2% in DCM) to afford 3 0 g of the Friedel-Craft product ^{1}H NMR consistent with structure

Example 15



4-(3-Methoxy-propionyl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide: To a solution of 3-methoxy-1-[5-(2,2,2-trichloro-acetyl)-1*H*-pyrrol-3-yl]-propan-1-one (3.0 g, 10 mmol) in acetonitrile (50 mL), cooled to 0°C, was added (*S*)-(+)-phenyl glycinol (1 2 equivalent, 1 65 g, 12 mmol) and the resulting mixture stirred for 3 days at room temperature The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel (MeOH 5% in DCM) to afford 5 3 g of the title compound as a white solid HPLC Method B, R_t=4 2 minutes, LC/MS(m/z) 317 03 (M+1), 315 00 (M-1), ^{1}H NMR consistent with structure

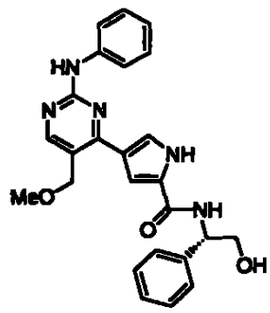
Example 16



4-(3-Dimethylamino-2-methoxymethyl-acryloyl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide

4-(3-Methoxy-propionyl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide was treated with an excess of Bredereck's reagent in THF at room temperature to 50°C for 3 days The solvent was removed under reduced pressure and the concentrate was used directly in the next step. HPLC Method B, R_t=5 0 minutes "broad peak"

Example 17

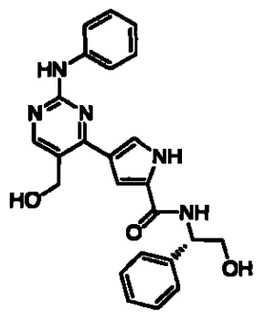


III-a-164

4-(5-Methoxymethyl-2-phenylamino-pyrimidin-4-yl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide (III-a-164) '4-(3-Dimethylamino-2-methoxymethyl-acryloyl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide (0 27 mmol) was combined with phenyl guanidine (73 mg) in N,N-dimethylacetamide (2 mL) and the resulting suspension was heated at 90° C for 35 hours

The reaction mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo* The crude product was purified by prep HPLC (Gilson Column = CombiHT SB-C189 5 µM, 21 2 mm x 100 mm, eluent = 0 1%TFA MeCN/H2O gradient) to afford III-a-164 as a yellow solid (3 2 mg) LC/MS(m/z) 444 16 (M+1), 442 19 (M-1), HPLC Method B, R_t=5.16 minutes ^1H NMR consistent with structure

Example 18

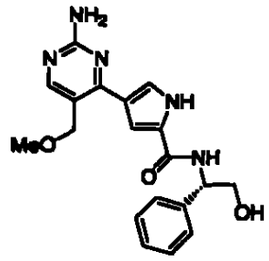


III-a-165

4-(5-Hydroxymethyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide (III-a-165) To a solution of III-a-164 (15 mg, 0 03 mmol) in dichloromethane (2 mL), cooled to -78°C, was added BBr_3 (135 µL, 0 13 mmol) After 15 minutes the reaction was allowed to warm to room temperature After 45 minutes, the reaction was quenched with a saturated solution of sodium carbonate and the resulting mixture was stirred for an additionnal 30 minutes before extraction with ethyl acetate The organic layers were combined and washed with brine then dried over sodium sulfate The crude mixture was purified by prep TLC (silica, 7% MeOH in CH_2Cl_2) to afford III-a-165 as a beige solid (1 6 mg) HPLC Method B, R_t=4 54 minutes, LC/MS

(m/z) 430 15 (M+1), 428.03 (M-1); ^{1}H NMR consistent with structure.

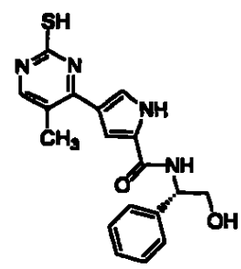
Example 19



III-a-161

4-(2-Amino-5-methoxymethyl-pyrimidin-4-yl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide (III-a-161) The enamine formed above at Example 16 (0.27 mmol) was combined with guanidine•HCl (51 mg), and K_2CO_3 (100 mg) in N,N-dimethylacetamide (4 mL). The heterogenous mixture was heated and stirred at 90° C for 35 h. The crude material was diluted with ethyl acetate, washed with saturatedd $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo* Purification by prep HPLC (Gilson: Column = CombiHT SB-C189 5 µM, 21 2 mm x 100 mm, eluent = 0 1%TFA MeCN/H_2O gradient) afforded III-a-161 as a yellow solid (2 0 mg) LC/MS(m/z) 368 12 (M+1), 366 15 (M-1), R_t (HPLC) = 3 77 min, ^{1}H NMR consistent with structure

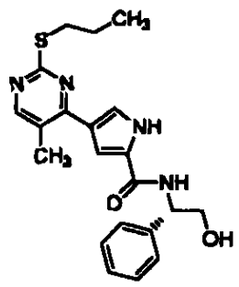
Example 20



4-(2-Mercapto-5-methyl-pyrimidin-4-yl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide

4-(3-Dimethylamino-2-methoxymethyl-acryloyl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide (17 6 mmol, 6 0 g) was combined with thiourea (39 mmol, 3 0 g) and potassium carbonate (53 mmol, 7 3 g) in ethanol (50 mL) and the resulting suspension was heated at 90° C for 24 hrs The solvent was removed *in vacuo* and the resulting black solid was diluted with water and the solid was removed by filtration The solid was washed with ethyl acetate twice and the aqueous solution was acidified to pH 5-6 with HCl(2N) The solid formed was removed by filtration and the aqueous solution was then extracted twice with ethyl acetate The combined organic phases were dried over sodium sulfate The solvent was removed under vacuum to afford the title compound as a brown solid (3 0 g, 48% yield) HPLC Method B, R_t=3 7 minutes, ^{1}H NMR consistent with structure

Example 21

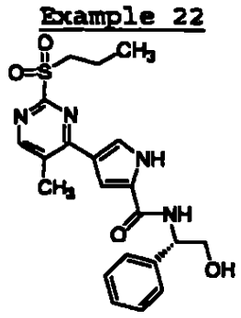


4-(5-Methyl-2-propylsulfanyl-pyrimidin-4-yl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide

To a solution of 4-(2-mercapto-5-methyl-pyrimidin-4-yl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide (7 7 mmol, 2 74 mmol) in aqueous ammonia (15%) was added at room temperature *n*-propyliodide (11 6 mmol, 1 1 mL) The solution was stirred overnight at

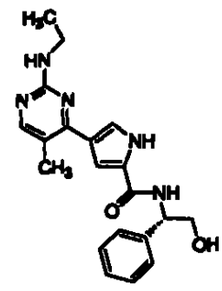
room temperature The resulting solid was collected by filtration and used directly for the next step ^{1}H NMR consistent with the structure

Example 22



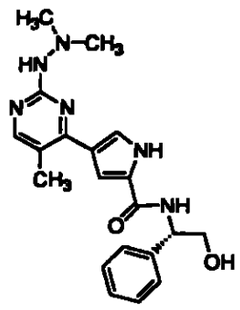
4-[5-Methyl-2-(propane-1-sulfonyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide: The thiopropyl compound (7 7 mmol, 3.05g) prepared at Example 21 above was dissolved in 120 mL of ethanol. To this solution, maintained at room temperature, was added *m*-CPBA (70% w/w%, 23.1 mmol, 4.0 g). The solution was stirred for an additional 4 hours at room temperature. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate, then washed 4 times with a solution of sodium hydroxide (1N). The organic phase was dried over sodium sulfate and concentrated *in vacuo* to afford the title compound as a white solid (1 7g, 51% yield for 2 steps) HPLC Method B, R_t=5 4 minutes ^{1}H NMR consistent with the structure

Example 23



4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1*H*-pyrrole-2-carboylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide· To a solution of 4-[5-methyl-2-(propane-1-sulfonyl)-pyrimidin-4-yl]-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide (47 µmol, 20 mg) in DMSO (1 mL) was added ethylamine (0 5 mmol, 150 µL) The mixture was heated at 130°C for 24 hours to afford the title compound LC/MS(m/z) 366 2 (M+1), HPLC Method B, R_t=4 2 minutes, ^{1}H NMR consistent with the structure

Example 24

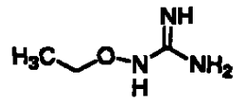


III-a-226

4-[2-(*N'*,*N'*-Dimethyl-hydrazino)-5-methyl-pyrimidin-4-yl]-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide (III-a-226) To a solution of 4-(3-dimethylamino-2-methoxymethyl-acryloyl)-1*H*-pyrrole-2-carboxylic acid (2-hydroxy-1-(*S*)-phenyl-ethyl)-amide (0 15 mmol, 50 mg) in DMA (2 mL) was added dimethyl-N,N-aminoguanidine•2HCl (0 17 mmol, 30 mg) and potassium carbonate (0 36 mmol, 50 mg) The reaction mixture was stirred for 48 hrs at 100°C The solvent was removed by hi-vacuum "GeneVac" and the residue purified by preparative HPLC (Gilson Column = CombiHT SB-C189 5 µM 21 2 mm x 100 mm, eluent = 0 1%TFA MeCN/H2O gradient) followed by preparative TLC (silica, 5% MeOH in CH_2Cl_2)

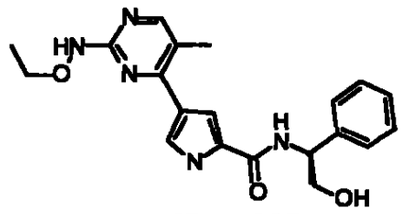
"double elutions" afforded compound III-a-226 as a pale yellow solid (1 3 mg) HPLC Method B, R_t=4 03 min , LC/MS (m/z) 381 1 (M+1), 379 1 (M-1), ^{1}H NMR consistent with structure

Example 25



Ethanolguanidine: Ethanolamine hydrochloride (200 mg, 2 mmol) was added to a mixture of N, N'-di-boc -N''-trifylylguanidine (800 mg, 2 mmol) and TEA (0 28 mL, 2 mmol) in dichloromethane (10 mL) The mixture was stirred overnight then diluted with EtOAc, washed with sodium bisulfate (2M), saturated sodium bicarbonate, dried over $NaSO_4$ and concentrated *in vacuo* The crude residue was purified by flash column chromatography eluting with 20% CH_2Cl_2/hexane to afford a white solid (0 56 g, 92%).). ^{1}H NMR ($CDCl_3$). δ 4.18 (q, 2H), 1.60 (d, 18H), 1 37 (t, 3H) To this bis-Boc guanidine was added 4M HCl/dioxane (5 mL) The mixture was stirred for 24 h and then concentrated to afford the title compound (0 26 g) ^{1}H NMR (MeOD): δ 3 92 (q, 2H), 1 27 (t, 3H) MS (M+1) 104.

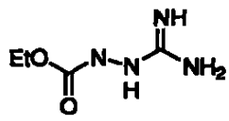
Example 26



III-a-195

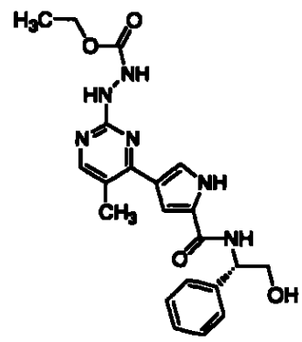
4-(2-Ethanolamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-(s)-phenyl-ethyl)-amide (III-a-195): To a mixture of 4-(3-dimethylamino-2-methyl-acryloyl)-1H-pyrrole-2-carboxylic acid (2-hydroxymethyl-1-(S)-phenyl-ethyl) amide (0 1 mmol) and K_2CO_3 (55 mg, 0 4 mmol) in DMF (1 mL) was added ethanolguanidine hydrogen chloride (0 2 mmol) The resulting suspension was stirred for 6 hours at 90 °C The reaction mixture was filtered and the filtrate concentrated *in vacuo* The crude residue was purified by preparative HPLC (Gilson Column = CombiHT SB-C189 5 µM 21 2 mm x 100 mm, eluent = 0 1%TFA MeCN/H2O gradient) to afford compound III-a-195 as yellow oil (21 mg) HPLC (method B) R_t = 4 08 min, MS (M+1) 382.1

Example 27



Ethyl carbamate guanidine· Ethylcarbazate (208 mg, 2 mmol) was added to a solution of N'N'-di-boc N''-triflylguanidine (800 mg, 2 mmol) in dichloromethane (10 mL) The mixture was stirred for overnight then diluted with EtOAc, washed with sodium bisulfat (2M), saturated sodium bicarbonate, dried over anhydrous $NaSO_4$ and concentrated *in vacuo* The crude residue was purified by flash column chromatography eluting with 30% EtOAc/hexane to afford a white solid (0 55g) To this bis-boc guanidine was added 4M HCl/Dioxane (5 mL) The mixture was stirred for 24 hours and then concentrated to afford the title compound ^1H NMR (MeOD)· δ 3.4 18 (d, 2H), 3.26 (s, 1H), 1 28 (t, 3H) MS (M+1) 134

Example 28



III-a-218

4-(2-Ethyl carbamate-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-(s)-phenyl-ethyl)-amide (III-a-218): To a mixture of 4-(3-dimethylamino-2-methyl-acryloyl)-1H-pyrrole-2-carboxylic acid (2-hydroxymethyl-1-(S)-phenyl-ethyl) amide (0 1 mmol) and K_2CO_3 (55 mg, 0 4 mmol) in DMF (1 mL) was added ethyl carbamate guanidine hydrogen chloride (0.2 mmol). The resulting suspension was stirred for 6 hours at 90 °C. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* The crude residue was purified by preparative HPLC (Gilson Column = CombiHT SB-C189 5 µM 21 2 mm x 100 mm, eluent = 0 1%TFA MeCN/H2O gradient) to afford compound III-a-218 as a yellow oil (10 mg). HPLC (method B) R_t = 4 03, MS (M+1) 425 1 ^{1}H NMR (MeOD) 8 08 (s, 1H); 7.87 (s, 1H), 7 7 (s, 1H), 7.24-7 5 (m, 5H), 5.15 (t, 1H), 4.2 (m, 2H), 3 85 (m, 2H), 2 5 (s, 3H)

Example 29

We have prepared other compounds of formula III-a by methods substantially similar to those described in the above Examples 1-28 and those illustrated in Schemes I-XII The characterization data for these

compounds is summarized in Table 3 below and includes LC/MS, HPLC, and ^{1}H NMR data

Where applicable, ^{1}H NMR data is summarized in Table 3 below wherein "Y" designates ^{1}H NMR data is available and was found to be consistant with structure Compound numbers correspond to the compound numbers listed in Table 1.

Table 3 Characterization Data for Selected Compounds

Compound No III-a-	M+1	M-1	HPLC Method	R_t (min)	^{1}H NMR
122	352 17	-	-	-	-
136	432 2	429 8	B	5 53	-
137	444 3	442 3	B	5 00	-
138	430 2	428 3	B	4 47	Y
139	458 3	456 3	B	4 72	-
140	493 3	491 3	B	4 45	-
141	520 2	518 2	B	5 98	-
142	436 2	-	B	4 0	-
144	440 17	-	A	10 1	Y
145	446 2	444 1	B	5.45	-
146	482 2	-	B	5 69	-
147	464 2	-	B	5 87	-
148	500 1	-	B	6 12	-
149	482 2	480 4	B	6 11	-
150	428 2	426 2	B	5 13	-
153	380 2	378 2	B	4 63	Y
154	420 1	418 1	B	4 74	Y
155	458 2	456 1	B	4 76	Y
156	441 13	-	B	5 14	-
157	498 2	-	B	6 00	-
159	392 2	390 1	B	4 75	Y
162	378 2	376 2	B	4 29	Y
163	380 2	378 0	B	4 65	Y
180	338 15	-	B	3 8	-

Compound No III-a-	M+1	M-1	HPLC Method	R_t (min)	^{1}H NMR
181	396 22	-	B	3 9	-
182	382 18	-	B	4 1	-
183	352.17	-	-	-	-
188	367 2	-	B	2.86	Y
190	453 1	-	B	5 86	Y
191	384 1	-	B	4.46	Y
192	384 1	-	B	4 41	Y
214	428 1	-	B	4 9	-
215	415 1	-	B	4 3	Y
216	422 1	-	B	4 43	Y
217	422.1	-	B	4 44	-
219	429 3	-	B	3 64	Y
221	405 19	-	B	4.5	-
227	482.4	-	B	5 5	-
229	419 03	-	B	4 29	Y
230	510 4	-	B	5 19	-
231	432.3	-	B	5.23	Y

BIOLOGICAL TESTING

The activity of the present compounds as protein kinase inhibitors may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of the activated protein kinase. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to the protein kinase Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/protein kinase complex and determining the amount of radiolabel bound Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with the protein kinase bound to known radioligands. The details

of the conditions used for performing these assays are set forth in Examples 30 through 37

Example 30

ERK INHIBITION ASSAY

Compounds were assayed for the inhibition of ERK2 by a spectrophotometric coupled-enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249) In this assay, a fixed concentration of activated ERK2 (10 nM) was incubated with various concentrations of the compound in DMSO (2 5 %) for 10 min at 30°C in 0 1 M HEPES buffer, pH 7 5, containing 10 mM $MgCl_2$, 2 5 mM phosphoenolpyruvate, 200 µM NADH, 150 µg/mL pyruvate kinase, 50 µg/mL lactate dehydrogenase, and 200 µM erktide peptide The reaction was initiated by the addition of 65 µM ATP. The rate of decrease of absorbance at 340 nM was monitored The IC_{50} was evaluated from the rate data as a function of inhibitor concentration

Table 4 shows the results of the activity of selected compounds of this invention in the ERK2 inhibition assay The compound numbers correspond to the compound numbers in Table 1 Compounds having an activity designated as "A" provided a percent inhibition less than or equal to 33%, compounds having an activity designated as "B" provided a percent inhibition of between 24% and 66%, and compounds having an activity designated as "C" provided a provided a percent inhibition of between 67% and 100%. Compounds having an activity designated as "D" provided a K_i of less than 0 1 micromolar, compounds having an activity designated as "E" provided a K_i of between 0 1 and 1 0 micromolar, and

compounds having an activity designated as "F" provided a K_i of greater than 1 0 micromolar

Table 4 ERK2 Inhibitory Activity of Selected Compounds

No. III-a-	Activity	No. III-a-	Activity	No. III-a-	Activity
2	B	3	A	4	A
5	A	6	A	7	A
8	A	9	A	10	A
11	A	12	B	13	A
14	B	15	A	16	A
17	A	18	A	19	A
20	A	21	B	22	A
23	C	24	A	25	A
26	A	27	A	28	A
29	C	30	A	31	A
32	A	33	A	34	B
35	B	36	B	37	C
39	C	40	C	41	A
42	C	43	A	44	C
45	B	46	A	47	C
48	B	49	A	50	A
51	A	52	A	53	A
54	A	55	A	56	A
57	A	58	A	59	A
60	A	61	A	62	C
63	A	64	A	65	A
66	A	67	A	68	A
69	A	70	A	71	A
72	B	100	A	101	A
102	A	103	F	104	A
105	E	107	F	111	D

No. III-a-	Activity	No. III-a-	Activity	No. III-a-	Activity
112	D	114	F	117	D
120	E	121	A	122	C
123	A	124	C	125	A
131	A	132	F	133	F
134	D	135	C	139	D
140	D	141	D	142	D
144	E	145	D	147	D
148	D	149	D	150	D
151	D	152	D	153	D
154	D	155	D	157	D
158	D	159	D	160	E
161	E	162	D	163	D
166	E	168	F	169	E
170	F	171	F	172	F
173	E	174	D	175	D
176	D	177	D	178	D
179	D	180	F	184	E
188	E	189	D	190	E
191	D	192	E	193	D
194	D	195	D	196	D
197	F	198	D	199	D
200	D	201	D	202	D
203	D	204	D	205	D
206	D	207	D	208	D
209	D	210	D	211	D
212	D	213	D	214	D
215	D	216	D	217	D
218	E	219	D	220	D
221	D	222	D	223	D
224	D	225	D	226	D
227	D	229	E	230	D

No. III-a-	Activity	No. III-a-	Activity	No. III-a-	Activity
231	D	232	D	233	D
234	D	235	D	236	D
237	D	238	D	-	-

Example 31

ERK2 INHIBITION· Cell Proliferation Assay

Compounds may be assayed for the inhibition of ERK2 by a cell proliferation assay. In this assay, a complete media is prepared by adding 10% fetal bovine serum and penicillin/streptomycin solution to RPMI 1640 medium (JRH Biosciences) Colon cancer cells (HT-29 cell line) are added to each of 84 wells of a 96 well plate at a seeding density of 10,000 cells/well/150 µL. The cells are allowed to attach to the plate by incubating at 37°C for 2 hours A solution of test compound is prepared in complete media by serial dilution to obtain the following concentrations. 20 µM, 6.7 µM, 2 2 µM, 0.74 µM, 0 25 µM, and 0 08 µM. The test compound solution (50 µL) is added to each of 72 cell-containing wells To the 12 remaining cell-containing wells, only complete media (200 µL) is added to form a control group in order to measure maximal proliferation To the remaining 12 empty wells, complete media is added to form a vehicle control group in order to measure background The plates are incubated at 37°C for 3 days A stock solution of ^{3}H-thymidine (1 mCi/mL, New England Nuclear, Boston, MA) is diluted to 20 µCi/mL in RPMI medium then 20 µL of this solution is added to each well The plates are further incubated at 37°C for 8

hours then harvested and analyzed for ^{3}H-thymidine uptake using a liquid scintillation counter.

Compounds III-a-116, III-a-139, and III-a-136 were each shown to have an IC_{50} of less than 0 1 μM

Example 32

ERK1 INHIBITION ASSAY

Compounds were assayed for the inhibition of ERK1 by a spectrophotometric coupled-enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249) In this assay, a fixed concentration of activated ERK1 (20 nM) was incubated with various concentrations of the compound in DMSO (2 0 %) for 10 min at 30°C in 0 1 M HEPES buffer, pH 7 6, containing 10 mM $MgCl_2$, 2 5 mM phosphoenolpyruvate, 200 μM NADH, 30 μg/mL pyruvate kinase, 10 μg/mL lactate dehydrogenase, and 150 μM erktide peptide The reaction was initiated by the addition of 140 μM ATP (20 μL) The rate of decrease of absorbance at 340 nM was monitored. The K_i was evaluated from the rate data as a function of inhibitor concentration

Examples of compounds that were found to inhibit ERK1 with an activity of less than 0.1 μM include III-a-202, III-a-204, and III-a-205

Example 33

GSK-3 INHIBITION ASSAY

Compounds were screened for their ability to inhibit GSK-3β (AA 1-420) activity using a standard coupled enzyme system (Fox et al (1998) *Protein Sci* 7, 2249) Reactions were carried out in a solution containing 100 mM HEPES (pH 7 5), 10 mM $MgCl_2$, 25 mM NaCl, 300 μM NADH, 1 mM DTT and 1 5% DMSO Final substrate

concentrations in the assay were 20 μM ATP (Sigma Chemicals, St Louis, MO) and 300 μM peptide (HSSPHQS(PO_3H_2)EDEEE, American Peptide, Sunnyvale, CA) Reactions were carried out at 30 °C and 20 nM GSK-3β Final concentrations of the components of the coupled enzyme system were 2 5 mM phosphoenolpyruvate, 300 μM NADH, 30 μg/ml pyruvate kinase and 10 μg/ml lactate dehydrogenase

An assay stock buffer solution was prepared containing all of the reagents listed above with the exception of ATP and the test compound of interest. The assay stock buffer solution (175 μl) was incubated in a 96 well plate with 5 μl of the test compound of interest at final concentrations spanning 0.002 μM to 30 μM at 30 °C for 10 min. Typically, a 12 point titration was conducted by preparing serial dilutions (from 10 mM compound stocks) with DMSO of the test compounds in daughter plates The reaction was initiated by the addition of 20 μl of ATP (final concentration 20 μM) Rates of reaction were obtained using a Molecular Devices Spectramax plate reader (Sunnyvale, CA) over 10 min at 30°C. The K_i values were determined from the rate data as a function of inhibitor concentration.

Table 5 shows the results of the activity of selected compounds of this invention in the GSK3 inhibition assay. The compound numbers correspond to the compound numbers in Table 1 Compounds having an activity designated as "A" provided a K_i of less than 0.1 micromolar, compounds having an activity designated as "B" provided a K_i of between 0.1 and 1 0 micromolar, and compounds having an activity designated as "C" provided a K_i of greater than 1 0 micromolar

Table 5 GSK3 Inhibitory Activity of Selected Compounds

No. IIIa-	Activity	No. IIIa-	Activity	No. IIIa-	Activity
116	A	117	A	134	C
136	A	137	A	138	A
139	A	140	A	141	A
142	A	144	C	145	A
146	B	147	A	148	A
149	A	150	B	151	A
152	A	153	A	154	A
155	B	156	B	157	A
158	A	159	A	162	A
166	C	172	C	173	C
174	A	175	B	176	A
177	B	178	B	179	A
181	C	184	C	187	C
188	C	189	C	190	B
191	B	193	B	194	A
196	C	198	C	199	A
200	C	201	B	202	C
203	B	205	B	206	A
207	B	208	A	209	A
210	C	211	B	212	A
213	B	214	B	215	A
216	A	217	A	222	B
223	A	224	A	225	A
227	C	228	A	230	B
231	A	232	B	233	C

Example 34

AURORA-2 INHIBITION ASSAY

Compounds were screened in the following manner for their ability to inhibit Aurora-2 using a standard coupled enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249).

To an assay stock buffer solution containing 0.1M HEPES 7 5, 10 mM $MgCl_2$, 1 mM DTT, 25 mM NaCl, 2.5 mM phosphoenolpyruvate, 300 mM NADH, 30 mg/ml pyruvate kinase, 10 mg/ml lactate dehydrogenase, 40 mM ATP, and 800 µM peptide (LRRASLG, American Peptide, Sunnyvale, CA) was added a DMSO solution of a compound of the present invention to a final concentration of 30 µM. The resulting mixture was incubated at 30 °C for 10 min. The reaction was initiated by the addition of 10 µL of Aurora-2 stock solution to give a final concentration of 70 nM in the assay The rates of reaction were obtained by monitoring absorbance at 340 nm over a 5 minute read time at 30 °C using a BioRad Ultramark plate reader (Hercules, CA). The K_i values were determined from the rate data as a function of inhibitor concentration. Examples of compounds that were found to inhibit Aurora-2 include III-a-116, III-a-117, III-a-136, III-a-138, III-a-139, III-a-140, and III-a-141

Example 35

CDK-2 INHIBITION ASSAY

Compounds were screened in the following manner for their ability to inhibit CDK-2 using a standard coupled enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249).

To an assay stock buffer solution containing 0 1M HEPES 7.5, 10 mM $MgCl_2$, 1 mM DTT, 25 mM NaCl, 2.5 mM

phosphoenolpyruvate, 300 mM NADH, 30 mg/ml pyruvate kinase, 10 mg/ml lactate dehydrogenase, 100 mM ATP, and 100 μM peptide (MAHHHRSPRKRAKKK, American Peptide, Sunnyvale, CA) was added a DMSO solution of a compound of the present invention to a final concentration of 30 μM The resulting mixture was incubated at 30 °C for 10 min

The reaction was initiated by the addition of 10 μL of CDK-2/Cyclin A stock solution to give a final concentration of 25 nM in the assay The rates of reaction were obtained by monitoring absorbance at 340 nm over a 5-minute read time at 30 °C using a BioRad Ultramark plate reader (Hercules, CA). The K_i values were determined from the rate data as a function of inhibitor concentration.

The following compounds were shown to have K_i values than 0 1 μM for CDK-2 III-a-116, III-a-142, III-a-149, and III-a-152.

The following compounds were shown to have K_i values between 0 1 μM and 1 μM for CDK-2 III-a-146, III-a-148, III-a-150, III-a-155, III-a-162, and III-a-174

The following compounds were shown to have K_i values between 1 0 and 20 0 μM for CDK-2 III-a-117, III-a-156, and III-a-159

Example 36

LCK INHIBITION ASSAY

The compounds were evaluated as inhibitors of human Lck kinase using either a radioactivity-based assay or spectrophotometric assay

Lck Inhibition Assay A Radioactivity-based Assay

The compounds were assayed as inhibitors of full length bovine thymus Lck kinase (from Upstate

Biotechnology, cat. no 14-106) expressed and purified from baculo viral cells Lck kinase activity was monitored by following the incorporation of ^{33}P from ATP into the tyrosine of a random poly Glu-Tyr polymer substrate of composition, Glu Tyr = 4:1 (Sigma, cat no P-0275) The following were the final concentrations of the assay components 0 025 M HEPES, pH 7.6, 10 mM $MgCl_2$, 2 mM DTT, 0.25 mg/ml BSA, 10 µM ATP (1-2 µCi ^{33}P-ATP per reaction), 5 mg/ml poly Glu-Tyr, and 1-2 units of recombinant human Src kinase. In a typical assay, all the reaction components with the exception of ATP were pre-mixed and aliquoted into assay plate wells Inhibitors dissolved in DMSO were added to the wells to give a final DMSO concentration of 2 5% The assay plate was incubated at 30 C for 10 min before initiating the reaction with ^{33}P-ATP After 20 min of reaction, the reactions were quenched with 150 µl of 10% trichloroacetic acid (TCA) containing 20 mM Na_3PO_4 The quenched samples were then transferred to a 96-well filter plate (Whatman, UNI-Filter GF/F Glass Fiber Filter, cat no 7700-3310) installed on a filter plate vacuum manifold Filter plates were washed four times with 10% TCA containing 20 mM Na_3PO_4 and then 4 times with methanol 200µl of scintillation fluid was then added to each well. The plates were sealed and the amount of radioactivity associated with the filters was quantified on a TopCount scintillation counter. The radioactivity incorporated was plotted as a function of the inhibitor concentration. The data was fitted to a competitive inhibition kinetics model to get the K_i for the compound

Lck Inhibition Assay B Spectrophotometric Assay

The ADP produced from ATP by the human recombinant Lck kinase-catalyzed phosphorylation of poly Glu-Tyr substrate was quanitified using a coupled enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249) In this assay one molecule of NADH is oxidised to NAD for every molecule of ADP produced in the kinase reaction The disappearance of NADH can be conveniently followed at 340 nm.

The following were the final concentrations of the assay components 0.025 M HEPES, pH 7 6, 10 mM $MgCl_2$, 2 mM DTT, 5 mg/ml poly Glu-Tyr, and 50 nM of recombinant human Lck kinase. Final concentrations of the components of the coupled enzyme system were 2 5 mM phosphoenolpyruvate, 200 µM NADH, 30 µg/ml pyruvate kinase and 10 µg/ml lactate dehydrogenase

In a typical assay, all the reaction components with the exception of ATP were pre-mixed and aliquoted into assay plate wells Inhibitors dissolved in DMSO were added to the wells to give a final DMSO concentration of 2 5% The assay plate was incubated at 30 °C for 10 min before initiating the reaction with 150 µM ATP The absorbance change at 340 nm with time, the rate of the reaction, was monitored on a molecular devices plate reader The data of rate as a function of the inhibitor concentration was fitted to competitive inhibition kinetics model to get the K_i for the compound

The following compounds were shown to have K_i values than 1 µM for Lck III-a-170, III-a-171, III-a-172, III-a-173, III-a-181, and III-a-203

The following compounds were shown to have K_i values between 1 0 and 20 0 µM for Lck III-a-204, III-a-205, III-a-206, and III-a-207.

Example 37

AKT3 INHIBITION ASSAY

Compounds were screened for their ability to inhibit AKT3 using a standard coupled enzyme assay (Fox et al , Protein Sci , (1998) 7, 2249) Assays were carried out in a mixture of 100 mM HEPES 7.5, 10 mM MgCl2, 25 mM NaCl , 1 mM DTT and 1 5% DMSO Final substrate concentrations in the assay were 170 µM ATP (Sigma Chemicals) and 200 µM peptide (RPRAATF, American Peptide, Sunnyvale, CA) Assays were carried out at 30 °C and 45 nM AKT3 Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 300 µM NADH, 30 µg/ML pyruvate kinase and 10 µg/ml lactate dehydrogenase.

An assay stock buffer solution was prepared containing all of the reagents listed above, with the exception of AKT3, DTT, and the test compound of interest 56 µl of the stock solution was placed in a 384 well plate followed by addition of 1 µl of 2 mM DMSO stock containing the test compound (final compound concentration 30 µM) The plate was preincubated for about 10 minutes at 30°C and the reaction initiated by addition of 10 µl of enzyme (final concentration 45 nM) and 1 mM DTT. Rates of reaction were obtained using a BioRad Ultramark plate reader (Hercules, CA) over a 5 minute read time at 30°C. Compounds showing greater than 50% inhibition versus standard wells containing the assay mixture and DMSO without test compound were titrated to determine IC_{50} values

Selected compounds of this invention that inhibit AKT3 include III-a-238

While we have presented a number of embodiments of this invention, it is apparent that our basic construction can be altered to provide other embodiments which utilize the compounds and methods of this invention Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments which have been represented by way of example

Appendix A Names of Table 1 Compound Numbers III-a-

1. 4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid dimethylamide,
2 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-pyrrolidin-1-yl-methanone,
3: {4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-pyrrolidin-1-yl-methanone,
4 4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide,
5: [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-morpholin-4-yl-methanone,
6· [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[1,4']bipiperidinyl-1'-yl-methanone,
7 {4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(3-hydroxy-piperidin-1-yl)-methanone,
8. {4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[1,4']bipiperidinyl-1'-yl-methanone,
9 [4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[1,4']bipiperidinyl-1'-yl-methanone;
10 {4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[1,4']bipiperidinyl-1'-yl-methanone,
11: [4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-hydroxy-piperidin-1-yl)-methanone;
12· [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone;
13 [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-phenyl-piperazin-1-yl)-methanone;
14: [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone,
15 [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone;
16· {4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-morpholin-4-yl-methanone;
17: 4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide,
18: [4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-morpholin-4-yl-methanone,
19. 4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide,

20 4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide,

21 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone,

22 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-phenyl-piperazin-1-yl)-methanone,

23 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone,

24 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone,

25 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-pyridin-2-yl-piperazin-1-yl)-methanone;

26 {4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-morpholin-4-yl-methanone,

27 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-hydroxy-piperidin-1-yl)-methanone;

28 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[1,4']bipiperidinyl-1'-yl-methanone,

29 4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide,

30 [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanone,

31 [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(2-hydroxymethyl-piperidin-1-yl)-methanone;

32 [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone,

33 4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide,

34 {4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone,

35 {4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone,

36 4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide,

37 [4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-phenyl-piperazin-1-yl)-methanone,

38 [4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-methyl-[1,4]diazepan-1-yl)-methanone,

39 [4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone,

40 4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide,

41: {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-methyl-[1,4]diazepan-1-yl)-methanone,

42 4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide;

43 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[2-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone;

44 {4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-phenyl-piperazin-1-yl)-methanone;

45 [4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone,

46: [4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(3-hydroxy-piperidin-1-yl)-methanone,

47 [4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanone,

48 [4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone,

49 {4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone,

50 {4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanone,

51· {4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-methyl-[1,4]diazepan-1-yl)-methanone,

52 1-(4-{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carbonyl}-piperazin-1-yl)-ethanone;

53 {4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone,

54 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(3-hydroxy-piperidin-1-yl)-methanone;

55 [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-methyl-[1,4]diazepan-1-yl)-methanone,

56 1-(4-{4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carbonyl}-piperazin-1-yl)-ethanone;

57. {4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-methyl-[1,4]diazepan-1-yl)-methanone,

58· [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(3-hydroxy-piperidin-1-yl)-methanone,

59 4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid methyl-(2-pyridin-2-yl-ethyl)-amide,

60 [4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[2-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone;

61 {4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[2-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone,

62 4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide,

63 {4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-pyridin-2-yl-piperazin-1-yl)-methanone,

64 [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-hydroxy-piperidin-1-yl)-methanone,

65 {4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-hydroxy-piperidin-1-yl)-methanone,

66 {4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-hydroxy-piperidin-1-yl)-methanone;

67 {4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-pyridin-2-yl-piperazin-1-yl)-methanone,

68 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone,

69 1-{4-[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrole-2-carbonyl]-piperazin-1-yl}-ethanone,

70 {4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone,

71 [4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-pyrrolidin-1-yl-methanone,

72 {4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-morpholin-4-yl-methanone,

73: 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid benzylamide,

74 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3,4-difluoro-benzylamide,

75 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

76 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 4-fluoro-benzylamide,

77 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-benzylamide,

78 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 4-methoxy-benzylamide,

79 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

80 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide;

81 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide,

82 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide,

83 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide,

84 4-(2,5-Diamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

85 4-(2-Amino-5-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide;

86 4-(5-Acetylamino-2-amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

87: 4-[2-Amino-5-(3-methyl-ureido)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

88. 4-(2-Amino-5-hydroxy-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

89 4-(2-Amino-5-methylaminomethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

90 4-(2-Amino-5-hydroxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide;

91 4-[2-Cyclohexylamino-5-(3-methyl-ureido)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

92: 4-[2-Acetylamino-5-(3-methyl-ureido)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

93: 4-(5-Hydroxy-2-methanesulfonylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide;

94 4-(2-Amino-5-methanesulfonyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

95. 4-(2-Amino-5-hydroxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3,4-difluoro-benzylamide,

96 4-(2-Cyclohexylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3,4-difluoro-benzylamide,

97 4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (pyridin-4-ylmethyl)-amide,

98 4-[5-(3,5-Dichloro-phenyl)-2-phenylamino-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 3-trifluoromethyl-benzylamide;

99 4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

100 4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide;

101 4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-dimethylamino-2-pyridin-3-yl-ethyl)-amide,

102 4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 4-methanesulfonyl-benzylamide;

103 4-[5-(3,5-Dichloro-phenyl)-2-phenylamino-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide,

104. 4-[5-(3,5-Dichloro-phenyl)-2-phenylamino-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-morpholin-4-yl-2-pyridin-3-yl-ethyl)-amide,

105 4-[2-Amino-5-(3-fluoro-5-trifluoromethyl-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

106 4-(2-Amino-5-propyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide;

107. 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide,

108 4-(5-Methyl-2-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide,

109 4-(2-Methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide,

110 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-dimethylamino-ethyl)-amide,

111 4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid propylamide,

112 4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-phenyl-propyl)-amide,

113 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (naphthalen-1-ylmethyl)-amide,

114 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid cyclopropylamide,

115 4-(2-Ethylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 2-trifluoromethyl-benzylamide,

116 4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

117 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

118 4-(2-Ethylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (4-methyl-cyclohexyl)-amide,

119: 4-(5-Ethyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid isopropylamide;

120 4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-amino-ethyl)-amide,

121: 4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide,

122: 4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide;

123: 1-{4-[4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carbonyl]-piperazin-1-yl}-ethanone,

124 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-phenyl-propyl)-amide;

125 4-(2-Amino-5-ethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-(6-methoxy-1H-indol-3-yl)-ethyl]-amide,

126 4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-phenoxy-ethyl)-amide,

127: 4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (1-methyl-3-phenyl-propyl)-amide;

128. 4-(5-Methyl-2-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (1H-benzoimidazol-2-ylmethyl)-amide,

129 4-(5-Methyl-2-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (1-hydroxymethyl-3-methyl-butyl)-amide,

130 4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-hydroxymethyl-2-(1H-imidazol-4-yl)-ethyl]-amide,

131 4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide,

132 4-[2-(2-Diethylamino-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 3,4-difluoro-benzylamide,

133. 4-[5-Methyl-2-(2-piperidin-1-yl-quinazolin-4-ylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid benzylamide,

134 4-(5-Methyl-2-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-4-fluoro-phenyl)-2-hydroxy-ethyl]-amide,

135 4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-4-fluoro-phenyl)-2-hydroxy-ethyl]-amide,

136 4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

137. 4-[2-(3-Methoxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

138 4-[2-(3-Hydroxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

139. 4-[2-(Benzo[1,3]dioxol-5-ylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

140: 4-[5-Methyl-2-(4-sulfamoyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

141 4-[2-(3-Benzyloxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

142. 4-[2-(4-Hydroxy-cyclohexylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

143 4-(5-Cyclohexyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

144 4-(5-Cyclopropyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

145 4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-4-methyl-phenyl)-2-hydroxy-ethyl]-amide,

146 4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

147 4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-4-methyl-phenyl)-2-hydroxy-ethyl]-amide,

148 4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

149 4-[5-Methyl-2-(3-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

150 4-(2-Benzylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

151 4-[2-(3,4-Dimethyl-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

152 4-[2-(4-Benzyloxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

153 4-(2-Isopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

154 4-[5-Methyl-2-(2,2,2-trifluoro-ethylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

155 4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

156 4-[2-(2-Methoxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

157 4-[5-Methyl-2-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

158 4-(2-Isobutylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

159 4-[2-(Cyclopropylmethyl-amino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

160 4-(5-Methoxymethyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

161 4-(2-Amino-5-methoxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

162 4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

163 4-(5-Methyl-2-propylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

164 4-(5-Methoxymethyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

165 4-(5-Hydroxymethyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

166 4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

167 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-amide,

168 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-amide,

169 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-2-phenyl-ethyl)-amide,

170 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-hydroxymethyl-2-phenyl-ethyl)-amide,

171 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-hydroxymethyl-2-phenyl-ethyl)-amide,

172 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide,

173 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide,

174 4-[2-(1-Hydroxymethyl-cyclopropylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

175 4-[2-(2-Hydroxy-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

176 4-[2-(2-Hydroxy-1-methyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

177 4-[2-(2-Hydroxy-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

178 4-[2-(2-Hydroxy-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

179 4-[2-(2-Hydroxy-cyclohexylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

121 4-[2-(2-Hydroxy-1-methyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

121 4-[2-(3-Dimethylamino-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

180 4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide,

181 4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide,

183 4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-2-phenyl-ethyl)-methyl-amide,

184 {[4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carbonyl]-amino}-phenyl-acetic acid methyl ester,

186 4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide,

187: 4-(2-Ethylamino-5-methoxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

188 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-pyridin-3-yl-ethyl)-amide,

189. 4-(2-Ethylamino-5-hydroxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

190 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-5-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-amide;

191 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-phenyl)-2-hydroxy-ethyl]-amide,

192· 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(2-fluoro-phenyl)-2-hydroxy-ethyl]-amide;

193 4-[2-(2-Cyclopropyl-1-hydroxymethyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

194 4-[2-(2,3-Dimethyl-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

195· 4-(2-Ethoxyamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

196. 4-[2-(1-Hydroxymethyl-2-methyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

197. 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-oxo-1-phenyl-propyl)-amide;

198 4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

199 4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

200 4-[2-(2-Chloro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

201 4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

200 4-[2-(3-Dimethylamino-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

202 4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

203 4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(2-methoxy-phenyl)-ethyl]-amide,

204 4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide,

205. 4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

206 4-(2-Methoxyamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

207 4-(2-Isopropoxyamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

208. 4-[2-(3-Dimethylamino-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

209. 4-[2-(2-Chloro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

210 4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

211 4-[2-(2,3-Dimethyl-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

212 4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

213 4-(2-Acetylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

214 4-(5-Methyl-2-o-tolylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

215 4-[5-Methyl-2-(pyridin-3-ylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

216 4-{5-Methyl-2-[(tetrahydro-furan-2-ylmethyl)-amino]-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

217. 4-{5-Methyl-2-[(tetrahydro-furan-2-ylmethyl)-amino]-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

218 N'-{4-[5-(2-Hydroxy-1-phenyl-ethylcarbamoyl)-1H-pyrrol-3-yl]-5-methyl-pyrimidin-2-yl}-hydrazinecarboxylic acid ethyl ester,

219 4-{5-Methyl-2-[(pyridin-3-ylmethyl)-amino]-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

220 4-(2-Cyclopropylmethoxyamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

221 4-[2-(Isoxazol-3-ylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

222 4-[2-(2-Hydroxy-1-methyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

223: 4-(5-Methyl-2-o-tolylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide;

224: 4-(5-Methyl-2-o-tolylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide,

225 4-[2-(2-Hydroxy-ethoxyamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

226 4-[2-(N',N'-Dimethyl-hydrazino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

227. 4-[5-Methyl-2-(2-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

228 4-[5-Methyl-2-(morpholin-4-ylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

229: 4-[5-Methyl-2-(5-methyl-isoxazol-3-ylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

230 4-{2-[1-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-5-methyl-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

231 4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-phenyl)-2-hydroxy-ethyl]-amide;

232 4-[2-(1-Hydroxymethyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide,

233: 4-[2-(2-Hydroxy-1-hydroxymethyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide,

234 4-[2-(1-Hydroxymethyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

235 4-[2-(2-Hydroxy-1-hydroxymethyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

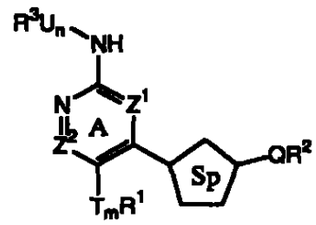
236 4-[2-(1-Hydroxymethyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

237 4-[5-Methyl-2-(2-methyl-cyclopropylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide, and

238 4-(2-Cyanoamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide

We claim

1 A method of inhibiting ERK-2 activity in a patient, which method comprises administering to said patient a compound of formula I



I

or a pharmaceutically acceptable derivative thereof, wherein:

Sp is a spacer group comprising a 5-membered heteroaromatic ring, wherein Ring A and QR^2 are attached to Sp at non-adjacent positions, and wherein Sp has up to two R^6 substituents, provided that two substitutable carbon ring atoms in Sp are not simultaneously substituted by R^6,

Z^1 and Z^2 are each independently selected from N or CH,

T and Q are each an independently selected linker group;

U is selected from $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, or $-SO_2-$,

m and n are each independently selected from zero or one,

R^1 is selected from hydrogen, CN, halogen, R, $N(R^7)_2$, OR, or OH,

R^2 is selected from $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, $-(CH_2)_yCH(R^8)CH(R^5)_2$, $-N(R^4)_2$, or $-NR^4(CH_2)_yN(R^4)_2$,

y is 0-6,

R^3 is selected from R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, or $-(CH_2)_yCH(R^8)N(R^4)_2$,

each R is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms,

each R^4 is independently selected from R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, or $-(CH_2)_yCH(R^5)_2$;

each R^5 is independently selected from R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

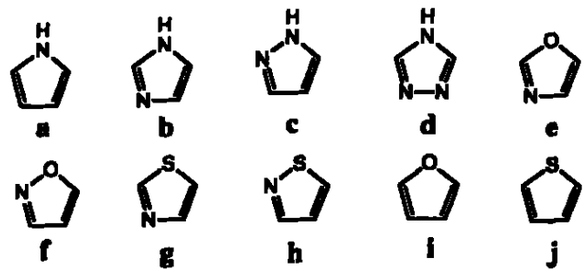
each R^6 is independently selected from R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring,

R^8 is selected from R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, or $(CH_2)_wSR^7$; and

each w is independently selected from 0-4

2. The method according to claim 1, wherein Sp is selected from one of the following



or a pharmaceutically acceptable derivative thereof

3 The method according to claim 2, wherein said compound has one or more features selected from the group consisting of.

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, amino, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring,

(c) Q is $-CO-$, $-CO_2-$, $-CONH-$, $-SO_2-$, $-SO_2NH-$, $-OC(O)NH-$, $-C(O)ONH-$, or $-CONHNH-$;

(d) R^2 is $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$,

(f) R^4 is R, R^7, or $-(CH_2)_yCH(R^5)_2$; and

(g) R^5 is an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5-6 membered heteroaryl, or 5-6 membered heterocyclyl.

4. The method according to claim 3, wherein.

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring;

(b) T_mR^1 is hydrogen, amino, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring,

(c) Q is $-CO-$, $-CO_2-$, $-CONH-$, $-SO_2-$, $-SO_2NH-$, $-OC(O)NH-$, $-C(O)ONH-$, or $-CONHNH-$,

(d) R^2 is $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$;

(f) R^4 is R, R^7, or $-(CH_2)_yCH(R^5)_2$, and

(g) R^5 is an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5-6 membered heteroaryl, or 5-6 membered heterocyclyl.

5 The method according to claim 3, wherein said compound has one or more features selected from the group consisting of

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, $-CH(CH_2OH)CH_2$cyclopropyl, or an optionally substituted phenyl, benzyl, or isoxazolyl group;

(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, or CH_2NHCH_3,

(c) Q is -CO-, -CONH-, $-SO_2-$, or $-SO_2NH-$,

(d) R^2 is $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$, wherein R^8 is OH or CH_2OH, and

(e) R^5 is $-CH_2OH$, $-(CH_2)_2OH$, isopropyl, or an optionally substituted group selected from pyrrolidin-1-yl, morpholin-4-yl, piperidin-1-yl, piperazin-1-yl, 4-methyl[1,4]diazepan-1-yl, 4-phenyl-piperazine-1-yl, pyridin-3-yl, pyridin-4-yl, imidazolyl, furan-2-yl, 1,2,3,4-tetrahydroisoquinoline, tetrahydrofuran-2-yl, cyclohexyl, phenyl, or benzyl

6 The method according to claim 5, wherein

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, $-CH(CH_2OH)CH_2$cyclopropyl, or an optionally substituted phenyl, benzyl, or isoxazolyl group;

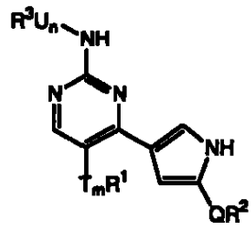
(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, or CH_2NHCH_3;

(c) Q is -CO-, -CONH-, $-SO_2-$, or $-SO_2NH-$,

(d) R^2 is $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$, wherein R^8 is OH or CH_2OH, and

(e) R^5 is $-CH_2OH$, $-(CH_2)_2OH$, isopropyl, or an optionally substituted group selected from pyrrolidin-1-yl, morpholin-4-yl, piperidin-1-yl, piperazin-1-yl, 4-methyl[1,4]diazepan-1-yl, 4-phenyl-piperazine-1-yl, pyridin-3-yl, pyridin-4-yl, imidazolyl, furan-2-yl, 1,2,3,4-tetrahydroisoquinoline, tetrahydrofuran-2-yl, cyclohexyl, phenyl, or benzyl

7. The method according to claim 2, wherein said compound is of formula III-a:



III-a

or a pharmaceutically acceptable derivative thereof.

8 The method according to claim 7, wherein said compound has one or more features selected from the group consisting of.

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring;

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring;

(c) Q is -CO-, $-CO_2-$, -CONH-, $-SO_2-$, $-SO_2NH-$, -OC(O)NH-, -C(O)ONH-, or -CONHNH-;

(d) R^2 is $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$,

(f) R^4 is R, R^7, or $-(CH_2)_yCH(R^5)_2$, and

(g) R^5 is an optionally substituted group selected from phenyl, 5-6 membered heteroaryl, or 5-6 membered heterocyclyl.

9 The method according to claim 8, wherein

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring,

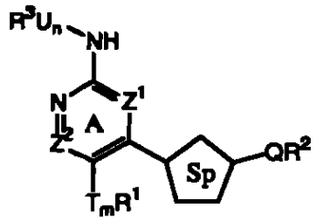
(c) Q is -CO-, -CO_2-, -CONH-, -SO_2-, -SO_2NH-, -OC(O)NH-, -C(O)ONH-, or -CONHNH-;

(d) R^2 is -$NR^6(CH_2)_yN(R^4)_2$, -$(CH_2)_yR^5$, -$(CH_2)_yCH(R^5)_2$, or -$(CH_2)_yCH(R^6)CH(R^5)_2$;

(f) R^4 is R, R^7, or -$(CH_2)_yCH(R^5)_2$, and

(g) R^5 is an optionally substituted group selected from phenyl, 5-6 membered heteroaryl, or 5-6 membered heterocyclyl

A method of inhibiting ERK-2 activity in a biological sample, which method comprises contacting said sample with a compound of formula I:



I

or a pharmaceutically acceptable derivative thereof, wherein

Sp is a spacer group comprising a 5-membered heteroaromatic ring, wherein Ring A and QR^2 are attached to Sp at non-adjacent positions, and wherein Sp has up to two R^6 substituents, provided that two substitutable carbon ring atoms in Sp are not simultaneously substituted by R^6,

Z^1 and Z^2 are each independently selected from N or CH,

T and Q are each an independently selected linker group;

U is selected from -NR^7-, -NR^7CO-, -NR^7CONR^7-, -NR^7CO_2-, -O-, -$CONR^7$-, -CO-, -CO_2-, -OC(O)-, -NR^7SO_2-, -SO_2NR^7-, -$NR^7SO_2NR^7$-, or -SO_2-,

m and n are each independently selected from zero or one,

R^1 is selected from hydrogen, CN, halogen, R, $N(R^7)_2$, OR, or OH;

R^2 is selected from $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, $-(CH_2)_yCH(R^8)CH(R^5)_2$, $-N(R^4)_2$, or $-NR^4(CH_2)_yN(R^4)_2$,

y is 0-6,

R^3 is selected from R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, or $-(CH_2)_yCH(R^8)N(R^4)_2$;

each R is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms;

each R^4 is independently selected from R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, or $-(CH_2)_yCH(R^5)_2$,

each R^5 is independently selected from R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$;

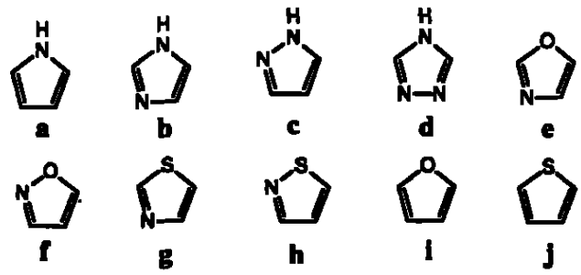
each R^6 is independently selected from R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$;

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring;

R^8 is selected from R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, or $(CH_2)_wSR^7$; and

each w is independently selected from 0-4.

11. The method according to claim 10, wherein Sp is selected from one of the following



or a pharmaceutically acceptable derivative thereof.

12. The method according to claim 11, wherein said compound has one or more features selected from the group consisting of:

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, amino, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring;

(c) Q is $-CO-$, $-CO_2-$, $-CONH-$, $-SO_2-$, $-SO_2NH-$, $-OC(O)NH-$, $-C(O)ONH-$, or $-CONHNH-$,

(d) R^2 is $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$;

(f) R^4 is R, R^7, or $-(CH_2)_yCH(R^5)_2$, and

(g) R^5 is an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5-6 membered heteroaryl, or 5-6 membered heterocyclyl

13 The method according to claim 12, wherein:

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4}

aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, amino, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring,

(c) Q is -CO-, $-CO_2-$, -CONH-, $-SO_2-$, $-SO_2NH-$, -OC(O)NH-, -C(O)ONH-, or -CONHNH-;

(d) R^2 is $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^6)CH(R^5)_2$,

(f) R^4 is R, R^7, or $-(CH_2)_yCH(R^5)_2$, and

(g) R^5 is an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5-6 membered heteroaryl, or 5-6 membered heterocyclyl

14. The method according to claim 12, wherein said compound has one or more features selected from the group consisting of

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, $-CH(CH_2OH)CH_2$cyclopropyl, or an optionally substituted phenyl, benzyl, or isoxazolyl group,

(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, or CH_2NHCH_3,

(c) Q is -CO-, -CONH-, $-SO_2-$, or $-SO_2NH-$,

(d) R^2 is $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^6)CH(R^5)_2$, wherein R^6 is OH or CH_2OH, and

(e) R^5 is $-CH_2OH$, $-(CH_2)_2OH$, isopropyl, or an optionally substituted group selected from pyrrolidin-1-yl, morpholin-4-yl, piperidin-1-yl, piperazin-1-yl, 4-methyl[1,4]diazepan-1-yl, 4-phenyl-piperazine-1-yl, pyridin-3-yl, pyridin-4-yl, imidazolyl, furan-2-yl, 1,2,3,4-tetrahydroisoquinoline, tetrahydrofuran-2-yl, cyclohexyl, phenyl, or benzyl

15 The method according to claim 14, wherein:

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, $-CH(CH_2OH)CH_2$cyclopropyl, or an optionally substituted phenyl, benzyl, or isoxazolyl group,

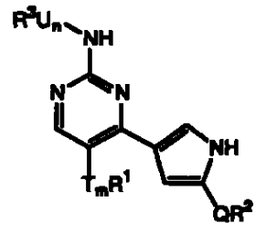
(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, or CH_2NHCH_3,

(c) Q is $-CO-$, $-CONH-$, $-SO_2-$, or $-SO_2NH-$,

(d) R^2 is $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$, wherein R^8 is OH or CH_2OH, and

(e) R^5 is $-CH_2OH$, $-(CH_2)_2OH$, isopropyl, or an optionally substituted group selected from pyrrolidin-1-yl, morpholin-4-yl, piperidin-1-yl, piperazin-1-yl, 4-methyl[1,4]diazepan-1-yl, 4-phenyl-piperazine-1-yl, pyridin-3-yl, pyridin-4-yl, imidazolyl, furan-2-yl, 1,2,3,4-tetrahydroisoquinoline, tetrahydrofuran-2-yl, cyclohexyl, phenyl, or benzyl.

16 The method according to claim 11, wherein said compound is of formula III-a.



III-a

or a pharmaceutically acceptable derivative thereof.

17 The method according to claim 16, wherein said compound has one or more features selected from the group consisting of:

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring;

(c) Q is $-CO-$, $-CO_2-$, $-CONH-$, $-SO_2-$, $-SO_2NH-$, $-OC(O)NH-$, $-C(O)ONH-$, or $-CONHNH-$,

(d) R^2 is $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$,

(f) R^4 is R, R^7, or $-(CH_2)_yCH(R^5)_2$, and

(g) R^5 is an optionally substituted group selected from phenyl, 5-6 membered heteroaryl, or 5-6 membered heterocyclyl

18 The method according to claim 17, wherein

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring,

(c) Q is $-CO-$, $-CO_2-$, $-CONH-$, $-SO_2-$, $-SO_2NH-$, $-OC(O)NH-$, $-C(O)ONH-$, or $-CONHNH-$,

(d) R^2 is $-NR^4(CH_2)_yN(R^4)_2$, $-(CH_2)_yR^5$, $-(CH_2)_yCH(R^5)_2$, or $-(CH_2)_yCH(R^8)CH(R^5)_2$;

(f) R^4 is R, R^7, or $-(CH_2)_yCH(R^5)_2$, and

(g) R^5 is an optionally substituted group selected from phenyl, 5-6 membered heteroaryl, or 5-6 membered heterocyclyl.

19 A method of inhibiting ERK-2 activity in a patient, which method comprises administering to said patient a compound selected from the group consisting of.

4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid dimethylamide;

{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-pyrrolidin-1-yl-methanone,

{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-pyrrolidin-1-yl-methanone,

4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide;

[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-morpholin-4-yl-methanone,

[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[1,4']bipiperidinyl-1'-yl-methanone,

{4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(3-hydroxy-piperidin-1-yl)-methanone,

{4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[1,4']bipiperidinyl-1'-yl-methanone,

[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[1,4']bipiperidinyl-1'-yl-methanone,

{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[1,4']bipiperidinyl-1'-yl-methanone,
[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-hydroxy-piperidin-1-yl)-methanone,
[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone,
[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-phenyl-piperazin-1-yl)-methanone;
[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone;
[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone;
{4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-morpholin-4-yl-methanone,
4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide;
[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-morpholin-4-yl-methanone,
4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide,
4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide;
{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone;
{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-phenyl-piperazin-1-yl)-methanone,
{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone,
{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone,
{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-pyridin-2-yl-piperazin-1-yl)-methanone,
{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-morpholin-4-yl-methanone,
{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-hydroxy-piperidin-1-yl)-methanone,
{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[1,4']bipiperidinyl-1'-yl-methanone;
4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide,
[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanone;
[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(2-hydroxymethyl-piperidin-1-yl)-methanone;
[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone;

4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide;

{4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone,

{4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone;

4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide,

[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-phenyl-piperazin-1-yl)-methanone,

[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-methyl-[1,4]diazepan-1-yl)-methanone,

[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone,

4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide;

{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-methyl-[1,4]diazepan-1-yl)-methanone;

4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide;

{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[2-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone;

{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-phenyl-piperazin-1-yl)-methanone,

[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone;

[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(3-hydroxy-piperidin-1-yl)-methanone;

[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanone,

[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone;

{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone,

{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanone,

{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-methyl-[1,4]diazepan-1-yl)-methanone,

1-(4-{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carbonyl}-piperazin-1-yl)-ethanone,

{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone,

{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(3-hydroxy-piperidin-1-yl)-methanone,

[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-methyl-[1,4]diazepan-1-yl)-methanone,

1-(4-{4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carbonyl}-piperazin-1-yl)-ethanone,

{4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-methyl-[1,4]diazepan-1-yl)-methanone,

[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(3-hydroxy-piperidin-1-yl)-methanone,

4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid methyl-(2-pyridin-2-yl-ethyl)-amide;

[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-[2-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone;

{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[2-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone,

4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide;

{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-pyridin-2-yl-piperazin-1-yl)-methanone;

[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-(4-hydroxy-piperidin-1-yl)-methanone,

{4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-hydroxy-piperidin-1-yl)-methanone;

{4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-hydroxy-piperidin-1-yl)-methanone;

{4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-(4-pyridin-2-yl-piperazin-1-yl)-methanone,

{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;

1-{4-[4-(2-Amino-5-m-tolyl-pyrimidin-4-yl)-1H-pyrrole-2-carbonyl]-piperazin-1-yl}-ethanone,

{4-[2-Amino-5-(3,4-dimethoxy-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone,

[4-(2-Amino-5-phenyl-pyrimidin-4-yl)-1H-pyrrol-2-yl]-pyrrolidin-1-yl-methanone;

{4-[2-Amino-5-(3-chloro-phenyl)-pyrimidin-4-yl]-1H-pyrrol-2-yl}-morpholin-4-yl-methanone,

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid benzylamide,

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3,4-difluoro-benzylamide;

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 4-fluoro-benzylamide,

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-benzylamide;

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 4-methoxy-benzylamide;

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide,

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide,

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide,

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide,

4-(2,5-Diamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide;

4-(2-Amino-5-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

4-(5-Acetylamino-2-amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

4-[2-Amino-5-(3-methyl-ureido)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

4-(2-Amino-5-hydroxy-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide;

4-(2-Amino-5-methylaminomethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

4-(2-Amino-5-hydroxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

4-[2-Cyclohexylamino-5-(3-methyl-ureido)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide;

4-[2-Acetylamino-5-(3-methyl-ureido)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

4--(5-Hydroxy-2-methanesulfonylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide,

4-(2-Amino-5-methanesulfonyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3-chloro-4-fluoro-benzylamide;

4-(2-Amino-5-hydroxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3,4-difluoro-benzylamide,

4-(2-Cyclohexylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 3,4-difluoro-benzylamide,

4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (pyridin-4-ylmethyl)-amide,

4-[5-(3,5-Dichloro-phenyl)-2-phenylamino-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 3-trifluoromethyl-benzylamide;

4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide;

4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-dimethylamino-2-pyridin-3-yl-ethyl)-amide,

4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 4-methanesulfonyl-benzylamide;

4-[5-(3,5-Dichloro-phenyl)-2-phenylamino-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide;

4-[5-(3,5-Dichloro-phenyl)-2-phenylamino-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-morpholin-4-yl-2-pyridin-3-yl-ethyl)-amide;

4-[2-Amino-5-(3-fluoro-5-trifluoromethyl-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(2-Amino-5-propyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide;

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide,

4-(5-Methyl-2-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide,

4-(2-Methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide;

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-dimethylamino-ethyl)-amide,

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid propylamide,

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-phenyl-propyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (naphthalen-1-ylmethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid cyclopropylamide,

4-(2-Ethylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid 2-trifluoromethyl-benzylamide,

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,
4-(2-Ethylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (4-methyl-cyclohexyl)-amide,
4-(5-Ethyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid isopropylamide,
4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-amino-ethyl)-amide,
4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid benzyl-methyl-amide;
4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide,
1-{4-[4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carbonyl]-piperazin-1-yl}-ethanone,
4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-phenyl-propyl)-amide,
4-(2-Amino-5-ethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-(6-methoxy-1H-indol-3-yl)-ethyl]-amide;
4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-phenoxy-ethyl)-amide,
4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (1-methyl-3-phenyl-propyl)-amide;
4-(5-Methyl-2-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (1H-benzoimidazol-2-ylmethyl)-amide;
4-(5-Methyl-2-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (1-hydroxymethyl-3-methyl-butyl)-amide,
4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-hydroxymethyl-2-(1H-imidazol-4-yl)-ethyl]-amide;
4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide,
4-[2-(2-Diethylamino-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid 3,4-difluoro-benzylamide,
4-[5-Methyl-2-(2-piperidin-1-yl-quinazolin-4-ylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid benzylamide,
4-(5-Methyl-2-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-4-fluoro-phenyl)-2-hydroxy-ethyl]-amide,
4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-4-fluoro-phenyl)-2-hydroxy-ethyl]-amide,
4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,
4-[2-(3-Methoxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(3-Hydroxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(Benzo[1,3]dioxol-5-ylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[5-Methyl-2-(4-sulfamoyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(3-Benzyloxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(4-Hydroxy-cyclohexylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(5-Cyclohexyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(5-Cyclopropyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-4-methyl-phenyl)-2-hydroxy-ethyl]-amide,

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-4-methyl-phenyl)-2-hydroxy-ethyl]-amide,

4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide;

4-[5-Methyl-2-(3-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Benzylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(3,4-Dimethyl-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(4-Benzyloxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(2-Isopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(2,2,2-trifluoro-ethylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Methoxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Isobutylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(Cyclopropylmethyl-amino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(5-Methoxymethyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Amino-5-methoxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(5-Methyl-2-propylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-amide;

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-amide,

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-2-phenyl-ethyl)-methyl-amide;

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-2-phenyl-ethyl)-amide,

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-hydroxymethyl-2-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-hydroxymethyl-2-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide,

4-[2-(1-Hydroxymethyl-cyclopropylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-1-methyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-cyclohexylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(5-Hydroxymethyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

{[4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carbonyl]-amino}-phenyl-acetic acid methyl ester;

4-[2-(2-Hydroxy-1-methyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(3-Dimethylamino-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide;

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide,

4-(2-Ethylamino-5-methoxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-pyridin-3-yl-ethyl)-amide;

4-(2-Ethylamino-5-hydroxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-5-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-phenyl)-2-hydroxy-ethyl]-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(2-fluoro-phenyl)-2-hydroxy-ethyl]-amide;

4-[2-(2-Cyclopropyl-1-hydroxymethyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(2,3-Dimethyl-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Ethoxyamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(1-Hydroxymethyl-2-methyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-oxo-1-phenyl-propyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide;

4-[2-(2-Chloro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

4-[2-(3-Dimethylamino-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide;

4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide;

4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(2-methoxy-phenyl)-ethyl]-amide,

4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide,

4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

4-(2-Methoxyamino-5-methyl-pyrimidın-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amıde;

4-(2-Isopropoxyamıno-5-methyl-pyrimidın-4-yl)-1H-pyrrole-2-carboxylıc acıd (2-hydroxy-1-phenyl-ethyl)-amıde,

4-[2-(3-Dımethylamıno-phenylamino)-5-methyl-pyrımıdın-4-yl]-1H-pyrrole-2-carboxylıc acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

4-[2-(2-Chloro-phenylamino)-5-methyl-pyrımıdın-4-yl]-1H-pyrrole-2-carboxylic acıd (2-hydroxy-1-m-tolyl-ethyl)-amıde,

4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrımıdın-4-yl]-1H-pyrrole-2-carboxylic acıd (2-hydroxy-1-m-tolyl-ethyl)-amide,

4-[2-(2,3-Dimethyl-phenylamino)-5-methyl-pyrimidın-4-yl]-1H-pyrrole-2-carboxylic acıd (2-hydroxy-1-m-tolyl-ethyl)-amide;

4-[2-(3-Fluoro-phenylamıno)-5-methyl-pyrımidın-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amıde,

4-(2-Acetylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(5-Methyl-2-o-tolylamıno-pyrimidın-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(pyridin-3-ylamino)-pyrimıdin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amıde;

4-{5-Methyl-2-[(tetrahydro-furan-2-ylmethyl)-amıno]-pyrimıdın-4-yl}-1H-pyrrole-2-carboxylıc acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-{5-Methyl-2-[(tetrahydro-furan-2-ylmethyl)-amino]-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

N'-{4-[5-(2-Hydroxy-1-phenyl-ethylcarbamoyl)-1H-pyrrol-3-yl]-5-methyl-pyrimidin-2-yl}-hydrazinecarboxylic acid ethyl ester,

4-{5-Methyl-2-[(pyrıdin-3-ylmethyl)-amıno]-pyrımidın-4-yl}-1H-pyrrole-2-carboxylıc acid (2-hydroxy-1-phenyl-ethyl)-amıde,

4-(2-Cyclopropylmethoxyamıno-5-methyl-pyrimidın-4-yl)-1H-pyrrole-2-carboxylic acıd (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(Isoxazol-3-ylamino)-5-methyl-pyrimidın-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amıde,

4-(2-Cyanoamıno-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-1-methyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

4-(5-Methyl-2-o-tolylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

4-(5-Methyl-2-o-tolylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide,

4-[2-(2-Hydroxy-ethoxyamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(N',N'-Dimethyl-hydrazino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(2-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(morpholin-4-ylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(5-methyl-isoxazol-3-ylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-{2-[1-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-5-methyl-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-phenyl)-2-hydroxy-ethyl]-amide,

4-[2-(1-Hydroxymethyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide;

4-[2-(2-Hydroxy-1-hydroxymethyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide,

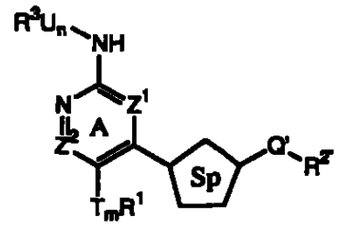
4-[2-(1-Hydroxymethyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

4-[2-(2-Hydroxy-1-hydroxymethyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(1-Hydroxymethyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide, and

4-[5-Methyl-2-(2-methyl-cyclopropylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide

20 A compound of formula I'



I'

or a pharmaceutically acceptable derivative thereof, wherein:

Sp is a spacer group comprising a 5-membered heteroaromatic ring, wherein Ring A and Q'$R^{2'}$ are attached to Sp at non-adjacent positions; and wherein Sp has up to two R^6 substituents, provided that two substitutable carbon ring atoms in Sp are not simultaneously substituted by R^6;

Z^1 and Z^2 are each independently selected from N or CH,

T is a linker group;

Q' is selected from $-CO_2-$, $-C(O)NR^7-$ or $-SO_2NR^7-$;

U is selected from $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, or $-SO_2-$;

m and n are each independently selected from zero or one;

R^1 is selected from hydrogen, CN, halogen, R, $N(R^7)_2$, OR, or OH;

$R^{2'}$ is selected from $-(CH_2)_yCH(R^5)_2$ or $-(CH_2)_yCH(R^8)CH(R^5)_2$;

y is 0-6;

R^3 is selected from R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, or $-(CH_2)_yCH(R^8)N(R^4)_2$,

each R is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10}

aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms,

each R^4 is independently selected from R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, or $-(CH_2)_yCH(R^5)_2$,

each R^5 is independently selected from R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$;

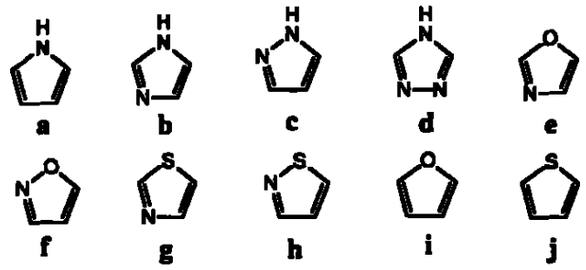
each R^6 is independently selected from R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$;

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring,

R^8 is selected from R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^6)_2$, or $(CH_2)_wSR^7$, and

each w is independently selected from 0-4

21 The compound according to claim 20, wherein Sp is selected from one of the following:



or a pharmaceutically acceptable derivative thereof

22 The compound according to claim 21, wherein said compound has one or more features selected from the group consisting of·

(a) R^3 is hydrogen, carbocyclyl, -CH(R^8)R, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_nR^1 is hydrogen, amino, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring; and

(c) R^5 is R or OR^7, wherein R is carbocyclic, or an optionally substituted 5 or 6-membered aryl or heteroaryl ring

23. The compound according to claim 22, wherein.

(a) R^3 is hydrogen, carbocyclyl, -CH(R^8)R, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring;

(b) T_nR^1 is hydrogen, amino, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring, and

(c) R^5 is R or OR^7, wherein R is carbocyclic, or an optionally substituted 5 or 6-membered aryl or heteroaryl ring

24 The compound according to claim 22, wherein said compound has one or more features selected from the group consisting of:

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl,

-CH(CH$_2$OH)phenyl, -CH(CH$_2$OH)ethyl, -CH(CH$_2$OH)$_2$, -CH(CH$_2$OH)isopropyl, -CH(CH$_2$OH)CH$_2$cyclopropyl, or an optionally substituted phenyl, benzyl, or isoxazolyl group,

(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, NHC(O)$NHCH_3$, or CH_2NHCH_3, and

(c) R^5 is OH, CH_2OH, carbocyclic, or an optionally substituted phenyl or pyridyl ring, and Q' is -C(O)NH-

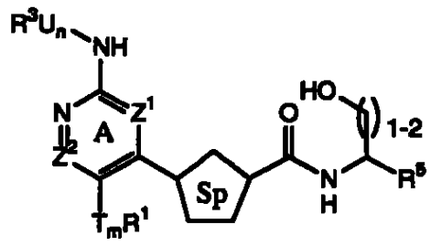
25 The compound according to claim 24, wherein

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, -CH(CH$_2$OH)phenyl, -CH(CH$_2$OH)ethyl, -CH(CH$_2$OH)$_2$, -CH(CH$_2$OH)isopropyl, -CH(CH$_2$OH)CH$_2$cyclopropyl, or an optionally substituted phenyl, benzyl, or isoxazolyl group;

(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, NHC(O)$NHCH_3$, or CH_2NHCH_3, and

(c) R^5 is OH, CH_2OH, carbocyclic, or an optionally substituted phenyl or pyridyl ring, and Q' is -C(O)NH-

26 The compound according to claim 21, wherein said compound is of formula I=



I"

or a pharmaceutically acceptable derivative thereof

27. The compound according to claim 26, wherein said compound has one or more features selected from the group consisting of·

(a) R^3 is hydrogen, carbocyclyl, -CH(R^8)R, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring; and

(c) R^5 is an optionally substituted 6-membered aryl, heteroaryl, or carbocyclic ring

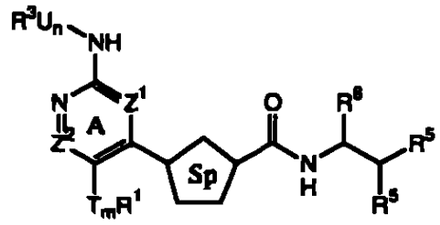
28. The compound according to claim 27, wherein:

(a) R^3 is hydrogen, carbocyclyl, -CH(R^8)R, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring; and

(c) R^5 is an optionally substituted 6-membered aryl, heteroaryl, or carbocyclic ring

29 The compound according to claim 21, wherein said compound is of formula I°



I°

or a pharmaceutically acceptable derivative thereof.

30 The compound according to claim 29, wherein said compound has one or more features selected from the group consisting of·

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^6)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring;

(b) T_mR^1 is hydrogen, amino, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring, and

(c) R^5 is R or OR^7, wherein R is carbocyclic, or an optionally substituted 5 or 6-membered aryl or heteroaryl ring

31 The compound according to claim 30, wherein.

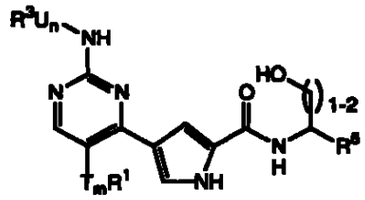
(a) R^3 is hydrogen, carbocyclyl, $-CH(R^6)R$, or an optionally substituted group selected from C_{1-4}

aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, amino, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring, and

(c) R^5 is R or OR^7, wherein R is carbocyclic, or an optionally substituted 5 or 6-membered aryl or heteroaryl ring

32 A compound of formula III-a':



III-a'

or a pharmaceutically acceptable derivative thereof, wherein:

T is a linker group,

U is selected from $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, or $-SO_2-$;

m and n are each independently selected from zero or one,

R^1 is selected from hydrogen, CN, halogen, R, $N(R^7)_2$, OR, or OH,

R^3 is selected from R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, or $-(CH_2)_yCH(R^8)N(R^4)_2$,

each R is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10}

aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms,

each R^4 is independently selected from R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, or $-(CH_2)_yCH(R^5)_2$,

each R^5 is independently selected from R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

each R^6 is independently selected from R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring,

R^8 is selected from R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, or $(CH_2)_wSR^7$, and

each w is independently selected from 0-4

33 The compound according to claim 32, wherein said compound has one or more features selected from the group consisting of

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring, and

(c) R^5 is an optionally substituted 6-membered aryl, heteroaryl, or carbocyclic ring

34. The compound according to claim 33, wherein:

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^6)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring;

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring, and

(c) R^5 is an optionally substituted 6-membered aryl, heteroaryl, or carbocyclic ring

35 The compound according to claim 33, wherein said compound has one or more features selected from the group consisting of:

(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, $-CH(CH_2OH)CH_2$cyclopropyl, or an optionally substituted phenyl or benzyl group,

(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, or CH_2NHCH_3, and

(c) R^5 is cyclohexyl or an optionally substituted phenyl or pyridylring

36. The compound according to claim 35, wherein:

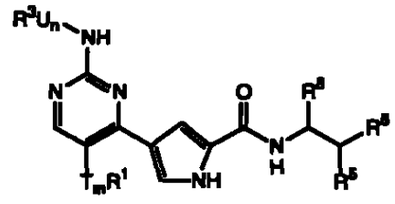
(a) R^3 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, isopropyl, $-CH(CH_2OH)$phenyl, $-CH(CH_2OH)$ethyl, $-CH(CH_2OH)_2$, $-CH(CH_2OH)$isopropyl, $-CH(CH_2OH)CH_2$cyclopropyl, or

an optionally substituted phenyl or benzyl group,

(b) T_mR^1 is selected from optionally substituted phenyl, methyl, ethyl, propyl, cyclopropyl, cyclohexyl, CH_2OCH_3, CH_2OH, OH, NH_2, $NHCH_3$, NHAc, $NHC(O)NHCH_3$, or CH_2NHCH_3; and

(c) R^5 is cyclohexyl or an optionally substituted phenyl or pyridylring

37 A compound of formula III-a°



III-a°

or a pharmaceutically acceptable derivative thereof, wherein

T is a linker group,

U is selected from $-NR^7-$, $-NR^7CO-$, $-NR^7CONR^7-$, $-NR^7CO_2-$, $-O-$, $-CONR^7-$, $-CO-$, $-CO_2-$, $-OC(O)-$, $-NR^7SO_2-$, $-SO_2NR^7-$, $-NR^7SO_2NR^7-$, or $-SO_2-$,

m and n are each independently selected from zero or one,

R^1 is selected from hydrogen, CN, halogen, R, $N(R^7)_2$, OR, or OH;

y is 0-6;

R^3 is selected from R^7, R, $-(CH_2)_yCH(R^8)R$, CN, $-(CH_2)_yCH(R^8)CH(R^5)_2$, or $-(CH_2)_yCH(R^8)N(R^4)_2$,

each R is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10}

aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms,

each R^4 is independently selected from R, R^7, $-COR^7$, $-CO_2R$, $-CON(R^7)_2$, $-SO_2R^7$, $-(CH_2)_yR^5$, or $-(CH_2)_yCH(R^5)_2$;

each R^5 is independently selected from R, OR, CO_2R, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$,

each R^6 is independently selected from R^7, F, Cl, $(CH_2)_yN(R^7)_2$, $N(R^7)_2$, OR^7, SR^7, NR^7COR^7, $NR^7CON(R^7)_2$, $CON(R^7)_2$, SO_2R^7, $NR^7SO_2R^7$, COR^7, CN, or $SO_2N(R^7)_2$;

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring;

R^8 is selected from R, $(CH_2)_wOR^7$, $(CH_2)_wN(R^4)_2$, or $(CH_2)_wSR^7$; and

each w is independently selected from 0-4.

38. The compound according to claim 37, wherein said compound has one or more features selected from the group consisting of:

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_mR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-4} aliphatic or a 5-6 membered aryl or heteroaryl ring, and

(c) R^5 is R or OR^7, and R^8 is R^7 or OR^7

39 The compound according to claim 38, wherein

(a) R^3 is hydrogen, carbocyclyl, $-CH(R^8)R$, or an optionally substituted group selected from C_{1-4} aliphatic, 3-6 membered heterocyclic, or a 5-6 membered aryl or heteroaryl ring,

(b) T_nR^1 is hydrogen, $N(R^4)_2$, OH, 3-6 membered carbocyclyl, or an optionally substituted group selected from C_{1-6} aliphatic or a 5-6 membered aryl or heteroaryl ring; and

(c) R^5 is R or OR^7, and R^8 is R^7 or OR^7

40 A compound selected from the group consisting of:

4-[2-Amino-5-(3-chloro-2-fluoro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide;

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide;

4-(2-Amino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide,

4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-Amino-5-(3,5-dichloro-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-dimethylamino-2-pyridin-3-yl-ethyl)-amide;

4-[5-(3,5-Dichloro-phenyl)-2-phenylamino-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-morpholin-4-yl-2-pyridin-3-yl-ethyl)-amide,

4-[2-Amino-5-(3-fluoro-5-trifluoromethyl-phenyl)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide,

4-(5-Methyl-2-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (1-hydroxymethyl-3-methyl-butyl)-amide,

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-hydroxymethyl-2-(1H-imidazol-4-yl)-ethyl]-amide,

4-(5-Methyl-2-methylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-4-fluoro-phenyl)-2-hydroxy-ethyl]-amide,

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-4-fluoro-phenyl)-2-hydroxy-ethyl]-amide,

4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(3-Methoxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(3-Hydroxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(Benzo[1,3]dioxol-5-ylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(4-sulfamoyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(3-Benzyloxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(4-Hydroxy-cyclohexylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(5-Cyclohexyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(5-Cyclopropyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-4-methyl-phenyl)-2-hydroxy-ethyl]-amide;

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide;

4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-4-methyl-phenyl)-2-hydroxy-ethyl]-amide,

4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

4-[5-Methyl-2-(3-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Benzylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(3,4-Dimethyl-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(4-Benzyloxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Isopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(2,2,2-trifluoro-ethylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Methoxy-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(4-trifluoromethoxy-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Isobutylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(Cyclopropylmethyl-amino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(5-Methoxymethyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(2-Amino-5-methoxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(5-Methyl-2-propylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-amide,

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-amide;

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-2-phenyl-ethyl)-methyl-amide;

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-2-phenyl-ethyl)-amide,

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide;

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-hydroxymethyl-2-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-hydroxymethyl-2-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (3-hydroxy-1-phenyl-propyl)-amide,

4-[2-(1-Hydroxymethyl-cyclopropylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[2-(2-Hydroxy-1-methyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-cyclohexylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(5-Hydroxymethyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

{[4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carbonyl]-amino}-phenyl-acetic acid methyl ester,

4-[2-(2-Hydroxy-1-methyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(3-Dimethylamino-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide;

4-(2-Amino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide,

4-(2-Ethylamino-5-methoxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-pyridin-3-yl-ethyl)-amide;

4-(2-Ethylamino-5-hydroxymethyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-5-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-amide;

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-phenyl)-2-hydroxy-ethyl]-amide;

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(2-fluoro-phenyl)-2-hydroxy-ethyl]-amide,

4-[2-(2-Cyclopropyl-1-hydroxymethyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2,3-Dimethyl-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-(2-Ethoxyamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(1-Hydroxymethyl-2-methyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-oxo-1-phenyl-propyl)-amide,

4-(2-Ethylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

4-[2-(2-Chloro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

4-[2-(3-Dimethylamino-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide,

4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethyl]-amide;

4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [2-hydroxy-1-(2-methoxy-phenyl)-ethyl]-amide,

4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide,

4-(2-Cyclopropylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide;

4-(2-Methoxyamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Isopropoxyamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(3-Dimethylamino-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide;

4-[2-(2-Chloro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

4-[2-(2-Hydroxy-1-phenyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide;

4-[2-(2,3-Dimethyl-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

4-[2-(3-Fluoro-phenylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide;

4-(2-Acetylamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(5-Methyl-2-o-tolylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(pyridin-3-ylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-{5-Methyl-2-[(tetrahydro-furan-2-ylmethyl)-amino]-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-{5-Methyl-2-[(tetrahydro-furan-2-ylmethyl)-amino]-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

N'-{4-[5-(2-Hydroxy-1-phenyl-ethylcarbamoyl)-1H-pyrrol-3-yl]-5-methyl-pyrimidin-2-yl}-hydrazinecarboxylic acid ethyl ester,

4-{5-Methyl-2-[(pyridin-3-ylmethyl)-amino]-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Cyclopropylmethoxyamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(Isoxazol-3-ylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(2-Cyanoamino-5-methyl-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(2-Hydroxy-1-methyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide;

4-(5-Methyl-2-o-tolylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

4-(5-Methyl-2-o-tolylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide;

4-[2-(2-Hydroxy-ethoxyamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(N',N'-Dimethyl-hydrazino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(2-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[5-Methyl-2-(morpholin-4-ylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide;

4-[5-Methyl-2-(5-methyl-isoxazol-3-ylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-{2-[1-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-5-methyl-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-(5-Methyl-2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-2-carboxylic acid [1-(3-fluoro-phenyl)-2-hydroxy-ethyl]-amide;

4-[2-(1-Hydroxymethyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide,

4-[2-(2-Hydroxy-1-hydroxymethyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid [1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide,

4-[2-(1-Hydroxymethyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-m-tolyl-ethyl)-amide,

4-[2-(2-Hydroxy-1-hydroxymethyl-ethylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide,

4-[2-(1-Hydroxymethyl-propylamino)-5-methyl-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide; and

4-[5-Methyl-2-(2-methyl-cyclopropylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide.

41 A composition comprising a compound according to any of claims 20-40 and a pharmaceutically acceptable carrier

42 The composition according to claim 41, further comprising an additional therapeutic agent

43. A method of inhibiting ERK2, GSK-3, Aurora, CDK2, or Lck activity in a patient comprising the step of administering to said patient a therapeutically effective amount of the composition according to claim 41.

44. The method according to claim 43, wherein said method inhibits ERK2 activity in a patient.

45. A method of treating an ERK2-mediated disease in a patient in need thereof, said method comprising the step of administering to said patient a therapeutically effective amount of the composition according to claim 41

46 The method according to claim 45, further comprising the step of administering to said patient an additional therapeutic agent.

47. The method according to claim 45, wherein said disease is selected from cancer, stroke, diabetes, hepatomegaly, cardiovascular disease, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders, inflammation, neurological disorders, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukemia (CML), liver disease, pathologic immune conditions involving T cell activation, or CNS disorders

48. The method according to claim 47, wherein the disease is cancer

49. The method according to claim 48, wherein the disease is a cancer selected from breast; ovary, cervix, prostate, testis, genitourinary tract; esophagus; larynx, glioblastoma, neuroblastoma; stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma; bone, colon, adenoma; pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma; seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma; myeloid disorders; lymphoid disorders, Hodgkin's, hairy cells; buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine; colon-

rectum, large intestine, rectum, brain and central nervous system, or leukemia

50. The method according to claim 45, wherein the disease is cardiovascular disease

51 The method according to claim 50, wherein the disease is a cardiovascular disease selected from restenosis, cardiomegaly, artherosclerosis, myocardial infarction, or congestive heart failure.

52 A method of treating a GSK-3-mediated disease in a patient in need thereof, said method comprising the step of administering to said patient a therapeutically effective amount of the composition according to claim 41

53 The method according to claim 52, further comprising the step of administering to said patient an additional therapeutic agent

54 The method according to claim 52, wherein said disease is diabetes

55 The method according to claim 52, wherein said disease is Alzheimer's disease.

56. The method according to claim 52, wherein said disease is schizophrenia

57 A method of enhancing glycogen synthesis in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically

effective amount of the composition according to claim 41

58 A method of lowering blood levels of glucose in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically effective amount of the composition according to claim 41

59 A method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically effective amount of the composition according to claim 41

60. A method of inhibiting the phosphorylation of β-catenin in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically effective amount of the composition according to claim 41.

61 A method of treating an Aurora-2-mediated disease in a patient in need thereof, said method comprising the step of administering to said patient a therapeutically effective amount of the composition according to claim 41

62. The method according to claim 61, further comprising the step of administering to said patient an additional therapeutic agent

63 The method according to claim 61, wherein said disease is selected from colon, breast, stomach, or ovarian cancer

64 A method of treating CDK-2-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a composition according to claim 41

65 The method according to claim 64, wherein said disease is selected from cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, or an autoimmune disease

66. A method of treating a Lck-mediated disease, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a composition according to claim 41

67 The method according to claim 66, wherein said disease is selected from an autoimmune disease or transplant rejection

68 A method of inhibiting ERK2, Aurora-2, GSK-3, CDK-2, or Lck activity in a biological sample comprising the step of contacting said biological sample with a compound according to any one of claims 20-40.

69 A composition for coating an implantable device comprising a compound according to claim 20 and a carrier suitable for coating said implantable device

70 An implantable device coated with a composition according to claim 69

"DOCKETED FOR: 12/18/02"

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44 1)

To:
VERTEX PHARMACEUTICALS INC
Attn. Robidoux, Andrea
130 Waverly Street
Cambridge, MA 02139-4242
UNITED STATES OF AMERICA

Date of mailing *(day/month/year)* 18/10/2002	
Applicant's or agent's file reference VPI01-103	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 02/ 03791	International filing date *(day/month/year)* 08/02/2002
Applicant VERTEX PHARMACEUTICALS INCORPORATED	

1 [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46)

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.. (41-22) 740 14.35

For more detailed instructions, see the notes on the accompanying sheet.

2 [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made

4 Further action(s) The applicant is reminded of the following.

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later)

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marthe Oldendorf

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

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

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

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

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

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

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

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English, if the language of the international application is French, the letter must be in French.

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The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new,

(iv) the claim replaces one or more claims as filed,

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1 [Where originally there were 48 claims and after amendment of some claims there are 51]
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers, claims 30, 33 and 36 unchanged, new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]
"Claims 1 to 15 replaced by amended claims 1 to 11 "

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled, new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled, claims 14, 15 and 16 replaced by amended claim 14, claim 17 subdivided into amended claims 15, 16 and 17, new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published

It must be brief, not exceeding 500 words if in English or if translated into English

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim

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

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

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

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below
VPI01-103		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 02/ 03791	08/02/2002	09/02/2001

Applicant

VERTEX PHARMACEUTICALS INCORPORATED

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau

This International Search Report consists of a total of 5 sheets.

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

1 **Basis of the report**

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

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

b With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing

[ ] contained in the international application in written form

[ ] filed together with the international application in computer readable form

[ ] furnished subsequently to this Authority in written form

[ ] furnished subsequently to this Authority in computer readble form

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2 [X] Certain claims were found unsearchable (See Box I)

3. [ ] Unity of invention is lacking (see Box II)

4 With regard to the title,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows.

5 With regard to the abstract,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6 The figure of the drawings to be published with the abstract is Figure No

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure

[ ] because this figure better characterizes the invention.

[X] None of the figures

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/04 C07D401/14 C07D413/14 C07D405/14 C07D403/14
A61K31/506 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 792 778 A (S DE LASZLO ET AL.) 11 August 1998 (1998-08-11) column 1 -column 60	1,2,10, 11
A	column 65 -column 82	20,41-44
Y	WO 97 05878 A (MERCK) 20 February 1997 (1997-02-20) cited in the application the whole document	1,2,10, 11
A	claims; example 122, table VI	20
Y	WO 99 58523 A (SEARLE) 18 November 1999 (1999-11-18) cited in the application claims 1,51	1,2,10, 11
A	claim 1	20

-/—

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2002	18/10/2002

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, Tx. 31 651 epo nl Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 16442 A (MERCK) 9 May 1997 (1997-05-09) the whole document	1,2,10, 11
A	claims	20,41-44
Y	WO 95 13067 A (SMITHKLINE BEECHAM) 18 May 1995 (1995-05-18) the whole document	1,2,10, 11
A	claims	20
Y	WO 00 26209 A (NOVARTIS) 11 May 2000 (2000-05-11) claims	1,2,10, 11
Y	WO 99 32121 A (SMITHKLINE BEECHAM) 1 July 1999 (1999-07-01) page 0, claims	1,2,10, 11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1 [X] Claims Nos.
because they relate to subject matter not required to be searched by this Authority, namely

Although claims 1 to 19, 43 to 67 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition

2 [ ] Claims Nos.
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically

3. [ ] Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1 [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2 [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee

3 [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.

4 [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5792778 A	11-08-1998	AU 705082 B2	13-05-1999
		AU 6768996 A	05-03-1997
		CA 2228136 A1	20-02-1997
		EP 0863757 A1	16-09-1998
		JP 11510510 T	14-09-1999
		JP 3294616 B2	24-06-2002
		WO 9705877 A1	20-02-1997
WO 9705878 A	20-02-1997	AU 699148 B2	26-11-1998
		AU 6769196 A	05-03-1997
		CA 2228050 A1	20-02-1997
		EP 0871444 A1	21-10-1998
		JP 11510511 T	14-09-1999
		WO 9705878 A1	20-02-1997
		US 5837719 A	17-11-1998
WO 9958523 A	18-11-1999	AU 3859999 A	29-11-1999
		EP 1077971 A1	28-02-2001
		JP 2002514640 T	21-05-2002
		WO 9958523 A1	18-11-1999
WO 9716442 A	09-05-1997	AU 702887 B2	11-03-1999
		AU 1120897 A	22-05-1997
		EP 0859771 A1	26-08-1998
		JP 11514651 T	14-12-1999
		WO 9716442 A1	09-05-1997
WO 9513067 A	18-05-1995	EP 0727998 A1	28-08-1996
		JP 9505055 T	20-05-1997
		WO 9513067 A1	18-05-1995
		US 6288062 B1	11-09-2001
WO 0026209 A	11-05-2000	AU 6476599 A	22-05-2000
		WO 0026209 A1	11-05-2000
WO 9932121 A	01-07-1999	AU 1924699 A	12-07-1999
		CA 2314980 A1	01-07-1999
		EP 1037639 A1	27-09-2000
		JP 2001526230 T	18-12-2001
		WO 9932121 A1	01-07-1999
		US 6335340 B1	01-01-2002
		ZA 9811631 A	21-06-1999

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 August 2002 (22.08.2002)

PCT

(10) International Publication Number
WO 02/064586 A2

(51) International Patent Classification[7] C07D 403/04, 401/14, 413/14, 405/14, 403/14, A61K 31/506, A61P 35/00

(21) International Application Number PCT/US02/03791

(22) International Filing Date 8 February 2002 (08.02.2002)

(25) Filing Language English

(26) Publication Language English

(30) Priority Data
60/267,818 9 February 2001 (09.02.2001) US
60/328,768 12 October 2001 (12.10.2001) US

(71) Applicant *(for all designated States except US)* VERTEX PHARMACEUTICALS INCORPORATED [US/US], Patent Department, 130 Waverly Street, Cambridge MA 02139-4242 (US).

(72) Inventors, and

(75) Inventors/Applicants *(for US only)* CAO, Jingrong [CN/US] 15 Madison Avenue, Newton, MA 02460 (US). GREEN, Jeremy [GB/US], 21 Greystone Court, Burlington, MA 01803 (US). HALE, Michael [US/US], 42 Sunset Road, Bedford, MA 01730 (US). MALTAIS, Francois [CA/US], 24 Randolph Drive, Tewksbury, MA 10876 (US) STRAUB, Judy [US/US] 70 Kinnaird Street, Cambridge, MA 01235 (US) TANG, Qing [CN/US], 2377 Massachusetts Avenue Cambridge, MA 02140 (US) ARONOV, Alex [RU/US], 13 Circuit Lane Watertown, MA 02472 (US).

(74) Agents ROBIDOUX, Andrea et al., Vertex Pharmaceuticals Inc , 130 Waverly Street, Cambridge MA 02139-4242 (US)

(81) Designated States *(national)* AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI GB GD, GE, GH GM HR HU, ID IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK LR, LS LT LU, LV MA, MD, MG MK MN, MW, MX MZ NO, NZ, OM PH, PL, PT RO, RU SD SE, SG SI SK, SL, TJ, TM TN TR, TT TZ, UA UG, US, UZ VN YU, ZA ZM ZW

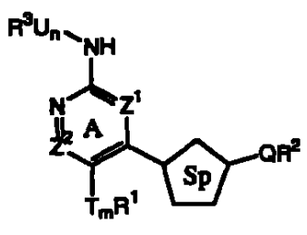
(84) Designated States *(regional)* ARIPO patent (GH, GM, KE, LS, MW, MZ, SD SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM AZ, BY, KG, KZ, MD, RU TJ, TM), European patent (AT BE, CH, CY, DE, DK ES FI, FR, GB, GR, IE, IT LU, MC, NL, PT SE, TR), OAPI patent (BF BJ CF CG, CI CM GA GN, GQ GW ML, MR, NE, SN TD TG).

Published
without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/064586 A2

(54) Title: HETEROCYCLIC INHIBITORS OF ERK2 AND USES THEREOF



(I)

(57) Abstract: Described herein are compounds that are useful as protein kinase inhibitors having the formula (I) wherein Z^1 and Z^2 are each independently nitrogen or CH and Ring A T_mR^1 QR^2 U_nR^3 and Sp are as described in the specification The compounds are especially useful as inhibitors of ERK2 and for treating diseases in mammals that are alleviated by a protein kinase inhibitor, particularly diseases such as cancer, inflammatory disorders, restenosis, diabetes, and cardiovascular disease

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

VOSSIUS & PARTNER
Siebertstrasse 4
D-81675 Munchen
ALLEMAGNE

EINGEGANGEN
Vossius & Partner
24. April 2003
Frist
beachb.

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	23/04/2003
Applicant's or agent's file reference: G2529 PCT	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 02/ 03791	08/02/2002	09/02/2001

Applicant

VERTEX PHARMACEUTICALS INCORPORATED et al

1 The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3 Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx. 523656 epmu d Fax. (+49-89) 2399-4465	LODOLO F Tel. (+49-89) 2399 2828

Form PCT/IPEA/416 (August 2002) P20473

PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
G2529 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 02/ 03791	08/02/2002	09/02/2001
International Patent Classification (IPC) or national classification and IPC		
C07D403/04		
Applicant		
VERTEX PHARMACEUTICALS INCORPORATED et al		

1 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36

2 This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3 This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/09/2002	16/04/2003
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx. 523656 epmu d Fax. (+49-89) 2399-4465	VERHULST W Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)

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I. Basis of the report

The basis of this international preliminary examination is the application as originally filed

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66 1(e) PCT), see also international search report)

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i e does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references)

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

VOSSIUS & PARTNER
Siebertstrasse 4
D-81675 München
ALLEMAGNE

EINGANGEN
27 Nov 2002

WRITTEN OPINION

(PCT Rule 66)

Date of mailing (day/month/year)	26/11/2002
Applicant's or agent's file reference: G2529 PCT	REPLY DUE: within 1 / 00 months/days from the above date of mailing

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US 02/ 03791	08/02/2002	09/02/2001

International Patent Classification (IPC) or both national classification and IPC

C07D403/04

Applicant

VERTEX PHARMACEUTICALS INCORPORATED et al.

1 This written opinion is the first drawn up by this International Preliminary Examining Authority

2 This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [X] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

3 The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3
For the form and the language of the amendments, see Rules 66.8 and 66.9

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4 The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 09/06/2003

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx 523656 epmu d Fax (+49-89) 2399-4465	Examiner Formalities officer (incl. extension of time limits) Tel. (+49-89) 2399 2828

Form PCT/IPEA/408 (cover sheet) (march 2002)

3500
397

I. Basis of the opinion

The basis of this written opinion is the application as originally filed

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66 1(e) PCT, see also international search report)

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

1 To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out

2 In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i e does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

3 If amendments are filed, the applicant should comply with the requirements of Rule 66 8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out

NB Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested

SUPERINDUSTRIA Y COMERCIO
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Dependencia: 0020 DIVISION DE NUEVAS CREACIONES

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379

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 55,204
FECHA : AGOSTO 6 DE 2003

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
PARRA RODRIGUEZ & CAVELIE	CONSIGNACION	BANCO POPULAR	050-00110-6	6992870	06/08/2003	400.000.00
PARRA RODRIGUEZ & CAVELIE	CONSIGNACION	BANCO POPULAR	050-00110-6	10427056	06/08/2003	36,000.00

***** 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	400,000.00
		TOTAL : $	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

385
389

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud	( )	( )
Representacion gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA INCOMPLETA	( )	( )

Firma Responsable

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03067863 00000000 Folios: 381

Fecha Fecha (AMD): 2003-06-06 15:29:34
Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Industria y Comercio
SUPERINTENDENCIA

394
400

2020
Bogotá, D.C.,

Doctor: **Oficio N°** 09945
ERNESTO CAVELIER FRANCO
Apoderado
VERTEX PHARMACEUTICALS INCORPORATED

ASUNTO:	Radicación N°	03-67869
	Solicitud internacional	PCT/US2002/03791
	Fecha inicio fase nacional	09/09/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 14 NOV 2003.

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