Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

21. **EXPEDIENTE No.** 04-129793

54. **TITULO** COMPUESTOS DE AMIDA DE ACIDO 3-AMINO-TIENO/2,3-b/PIRIDINO-2-CARBOXILICO SUSTITUIDO Y PROCEDIMIENTOS PARA PREPARARLOS Y SUS USOS

51. **CLASIFICACION INTERNACIONAL** A61K31/38 ; A61K31/435 A61P29/00.

71. **SOLICITANTE** BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

DOMICILIO Ridgefield, Connecticut, Estados Unidos de América.

74. **APODERADO** EMILIO FERRERO

C.C. 438.019 de Usaquén.

22. **BOGOTA, D.C.,** 29/12/2004.

(FORMA P-10)

SS

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

1

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04129793 00000000 Folios: 342
Fecha (AMD): 2004-12-29 18:05:56 5n
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

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

2 SOLICITANTE (71)

Nombre: **BOEHRINGER INGELHEIM PHARMACEUTICALS, INC** sociedad constituida y existente bajo las leyes de Delaware, Estados Unidos de América

Dirección: 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América
Domicilio: Ridgefield, Connecticut, Estados Unidos de América

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

3 REPRESENTANTE APODERADO

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

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

4 INVENTOR (ES) (72)

1. **Charles L. CYWIN**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

2. **Zhidong CHEN**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

3. **Jonathan EMEIGH**
6 Kenmere Blvd., Dambury, Connecticut 06810, Estados Unidos de América

4. **Roman Wolfgang FLECK**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

5. **Ming-Hong HAO**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

6. **Eugene HICKEY**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

7. **Weimin LIU**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

8. **Daniel Richard MARSHALL**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

4 INVENTOR (ES) (72)

9. **Tina WICK**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

10. **Peter NEMOTO**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

11. **Ronald John SORCEK**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

12. **Sanxing SUN**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

13. **Jiang-Ping WU**
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

5 PCT (86)

Solicitud Internacional No. PCT/US03/17343 Fecha: 3 de Junio de 2003

Publicación Internacional No. WO 03/103661 A1 Fecha: 18 de Diciembre de 2003

6 Título (54)

COMPUESTOS DE AMIDA DE ÁCIDO 3-AMINO-TIENO[2,3-B]PIRIDIN -2-CARBOXÍLICO SUSTITUIDO Y PROCEDIMIENTOS PARA PREPARARLOS Y SUS USOS

7 Clasificación Internacional (51) A61K 31/38 // A61K31/435, A61P29/00

8 Prioridad SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	6 de Junio de 2002	60/386.312
US	26 de Marzo de 2003	60/457.867

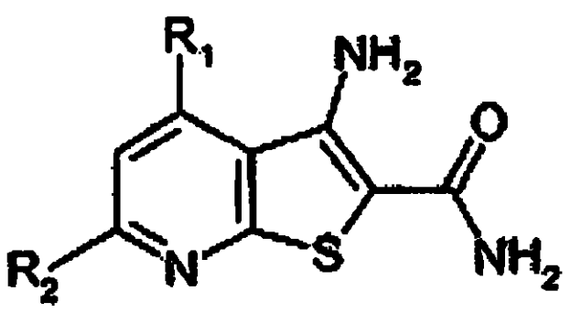
9 Comprobante de pago No.: 04 – 99.407 **Fecha:** 27 de Diciembre de 2004

10 Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 422.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☒ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11

FIGURA CARACTERÍSTICA



(I)

12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

PRP

CAVELIER
ABOGADOS
CARRERA 4ª Nº 72-35
BOGOTA, D.E. - COLOMBIA

0569

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

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

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

I (we), the undersigned/Yo (nosotros), abajo firmado (a)
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

of/domiciliado (a) en 900 Ridgebury Road,
Ridgefield, Connecticut 06877, United
States of America,

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

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

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

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

Given and signed this/Dado y firmado hoy 29th
day of August, 1996
In/en Ridgefield, Connecticut USA

Signature / Firma

Dr. Robert P. Raymond
Chief Patent Counsel
Boehringer Ingelheim Pharmaceuticals, Inc.

96912
ANA MARIA SALVETTI
TRADUCTORA PUBLICA
INGLES - ITALIANO - ESPAÑOL
RES. No. 158 - MINJUSTICIA

CAVELIER ABOGADOS
WPPODERE-3 (MINUTA Nº 12.1.1.2.6 USA)

9/087

CERTIFICADO NOTARIAL (INDIVIDUO)

A los 29 días del mes de AGOSTO de 19 96

ante mí, Notario Público de Connecticut, EE.UU.

compareció(eron) personalmente Dr. Robert P. Raymond

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

MARY-ELLEN M. DEVLIN
NOTARY PUBLIC
MY COMMISSION EXPIRES OCT. 31, 2000

Notario Público

Mary-Ellen M. Devlin
My Commission Expires 10/31/2000

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 29 day of August 19 96

before me, a Notary Public of Connecticut, USA

personally appeared Dr. Robert P. Raymond

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

Notary Public

Mary-Ellen M. Devlin
My Commission Expires 10/31/2000

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy, 29 de Agosto de 19 96

compareció(eron) ante mí
Dr. Robert P. Raymond

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

denominada BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Certifico:

1. Que he visto los siguientes documentos:*

ESCRITURA DE LA SOCIEDAD, ESTATUTOS Y VARIOS RESOLUCIONES DE LA JUNTA DIRECTIVA BIL-071 de fecha 29 de noviembre de 1984.

28 DIC 2004

2. Que dichos documentos prueban lo siguiente:

2.1. Que BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
es una Sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes de l Estado de Delaware, Estados Unidos de América

2.2. Que el domicilio de dicha Sociedad/Compañía es
900 Ridgebury Road, Ridgefield, Connecticut 06877, Estados Unidos de América

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

2.4. Que el(los) Sr.(Sres.) DR. ROBERT P. RAYMOND

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

Ciudad Ridgefield
Estado Connecticut, EE.UU.
Hoy 29 Agosto de 19 96

Notario Público

*Los documentos deben identificarse con fecha y origen.

NOTARIAL CERTIFICATE (CORPORATION)

On this 29 day of August 19 96

appeared before me

Dr. Robert P. Raymond

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

named BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

I Certify:

1. That I have seen the following documents:*

Corporate Charter, By-Laws and various, board resolutions, BIL-071 dated November 29, 1984.

2. That the above documents duly prove the following:

2.1. That BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
is a Corporation/Company legally constituted and in existence in accordance with the laws of the State of Delaware, United States of America

2.2. That the domicile of said Corporation/Company is
900 Ridgebury Road, Ridgefield, Connecticut 06877, United States of America

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

2.4. That Mr.(Messrs.) Dr. Robert P. Raymond

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

City Ridgefield
State Connecticut, USA
This 29th day of August 19 96

MARY-ELLEN M. DEVLIN
NOTARY PUBLIC
MY COMMISSION EXPIRES OCT. 31, 2000

Notary Public

*Documents must be identified with date and origin.

5

STATE OF CONNECTICUT
COUNTY OF FAIRFIELD } ss. RIDGEFIELD

I, Barbara Serfilippi, Clerk of the Town of Ridgefield

in said County, do hereby certify that Mary Ellen M. Devlin by and before whom the foregoing (or annexed) acknowledgment was taken, was at the time of taking the same a notary public (or other officer) residing (or authorized to act) in said County, and was authorized by the laws of said State to take and certify acknowledgments in said State, and, further, that I believe that the signature to the certificate of acknowledgment is genuine.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed the seal of the State and Town this

29th day of August 19 96.

96912
ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES - ITALIANO - ESPAÑOL
REG. No. 158 M.INJUSTICIA

Barbara Serfilippi
Town Clerk

AD[illegible]16 FORM 223

(0404/07/T/Rev. 11-92)

STATE OF CONNECTICUT
OFFICE OF THE SECRETARY OF THE STATE

I, MILES S. RAPOPORT, Secretary of the State of Connecticut, and keeper of the seal thereof,

DO HEREBY CERTIFY: that BARBARA SERFILIPPI was duly elected or appointed to the office of TOWN CLERK for the town of RIDGEFIELD in the County of FAIRFIELD in said State, for the term of JANUARY 1996 to JANUARY 5, 1998;

and that to his/her acts and attestations as such, full faith and credit are and ought to be given, in and out of Court.

In Testimony Whereof, I have hereunto set my hand and affixed the Great Seal of the State of Connecticut, at Hartford, on August 30, 1996.

Miles S. Rapoport
Secretary of the State

COPIA QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA
08 DIC 2004
PABLO MENDEZ BARAJAS
NOTARIO (E)

96912
ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES - ITALIANO - ESPAÑOL
REG. No 158 M.INJUSTICIA

6

CONSULADO DE COLOMBIA

535 Boylston Street 11th Floor Boston, MA 02116 Tel: (617)536-6222 Fax (617)536-9372

No 1156

El suscrito Cónsul de Colombia en Boston, MA, Estados Unidos vistos los documentos presentados

CERTIFICA:

Que el señor(a) **MILES S RAPOPORT**, quien autenticó la firma de **BARBARA SERFILIPPI**, secretario de la ciudad de Ridgefield, Connecticut, en el documento adjunto ejercía en la fecha allí indicada las funciones de **SECRETARIO DE ESTADO DEL ESTADO DE CONNECTICUT, USA** y su firma y sello son los que acostumbra a usar en sus actos oficiales. Que la compañía **BOEHRINGER INGELHEIM FARMACEUTICALS INC.**, con domicilio principal en la ciudad de **RIDGEFIELD, CONNECTICUT**, es sociedad constituida bajo las leyes del estado de **DELAWARE**, Estados Unidos y tienen y ejerce su objeto social conforme a las leyes de ese país. Que el señor **ROBERT P RAYMOND** en su calidad de **CONSEJERO JEFE DE PATENTES** de dicha compania esta debidamente autorizado para otorgar este poder a nombre de estas companias y, para los fines y propositos alli expresados.

La presente certificación se expide en cumplimiento del artículo 480 del Código de Comercio.

El Cónsul no asume responsabilidad por el contenido del documento.

Esta certificación se expide en Boston a los 13 días del mes de Septiembrede 1996

Pagado Impuesto de Timbre US$56.oo

LUIS FERNANDO LEMAITRE
CÓNSUL

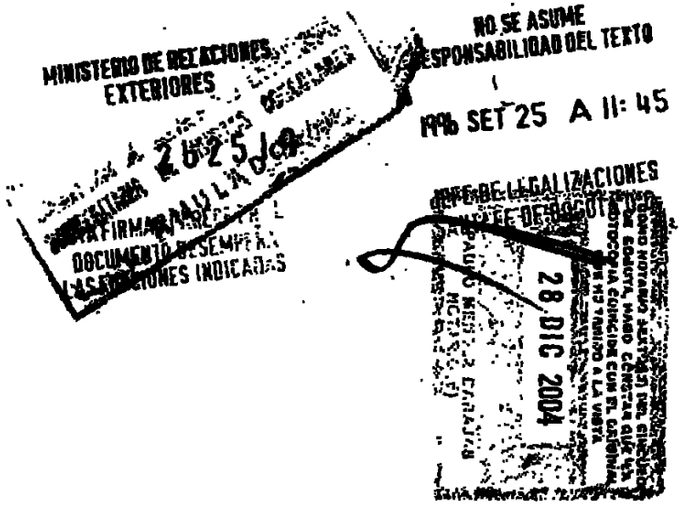
COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON LA COPIA QUE HA TENIDO A LA VISTA

28 DIC 2004

PABLO MEJIA
NOTARIO

96912

ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES-ITALIANO - ESPAÑOL
RES. NO. 158 M. JUSTICIA


MINISTERIO DE RELACIONES EXTERIORES
NO SE ASUME RESPONSABILIDAD DEL TEXTO
1996 SET 25 A 11:45
DIRECCION DE LEGALIZACIONES
28 DIC 2004

CERTIFICACION NOTARIAL Y AUTENTICACION CONSULAR

1. Es necesaria la legalización con certificado notarial. El Notario Público debe certificar:

1.1. Que la compañía está legalmente constituída y actualmente existente.

1.2. Su domicilio.

1.3. Que el propósito del poder está incluído en el objeto social de la compañía.

1.4. Que el poderdante está autorizado para dar el poder en nombre de la compañía.

Los documentos que hay que mostrarle al Notario Público para probar los puntos anteriores, deben estar expresados en el Certificado Notarial con fecha y origen:

2.1. Respecto a los puntos 1.1, 1.2 y 1.3 sugerimos referirse a los artículos de constitución con fecha y lugar de otorgamiento; y

2.2. Para el punto 1.4 sugerimos mencionar la resolución de la Junta Directiva o los estatutos, según los cuales la persona que otorga el poder está autorizada para ello.

3. Enseguida el Señor Cónsul de Colombia debe autenticar la firma del Notario Público.

NOTARIAL CERTIFICATION AND CONSULAR AUTENTIFICATION

1. Notarial legalization is necessary. The Notary Public must certify:

1.1. That the company is legally constituted and presently existent.

1.2. Its place of business.

1.3. That the purpose of the Power-of-Attorney is included in the activities of the company.

1.4. That the grantor is empowered to give the Power of Attorney in the name of the company he represents.

2. The documents which the Notary Public had before him to prove the above points must be listed by him in the Notarial Certificate with dated and origin:

2.1. In connection with points 1.1., 1.2. and 1.3 we suggest referring to the articles of incorporation with date and place of execution.

2.2. For point 1.4 we suggest to mention the resolution of the Board of Directors and/or the by-laws whereby the person who grants the Power of Attorney has been authorized to give it.

3. Then the Colombian Consul must legalize the signature of the Notary Public.

NOTA PARA EL SEÑOR CONSUL COLOMBIANO: Según el artículo 259 del C. de P.C. el Señor Cónsul debe autenticar la última precedente autenticación.

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

28 DIC 2004

PABLO [illegible]
NOTARIO

TRADUCCION OFICIAL No.96912 de un documento escrito en inglés, el cual para su identificación se sella con el sello del Traductor al mismo tiempo que la presente. Esta Traducción ha sido preparada por Ana María Salvetti, Traductora Oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y aprobada por el Ministerio de Justicia colombiano mediante Resolución No.158 de 1991.

(Se traducen sellos y legalizaciones que aparecen a continuación de un poder escrito en inglés y español, otorgado por la sociedad **BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.**, a favor de Germán CAVELIER, Gonzalo PERDOMO, Emilio FERRERO, y Luz Clemencia de PAEZ.)

Dado y firmado el 29 de agosto de 1996 en Ridgefield, Connecticut EE.UU. (Firmado), ilegible, Robert P. Raymond, Principal Asesor de Patentes. Boehringer Ingelheim Pharmaceuticals, Inc.

(en inglés y español): CERTIFICACION NOTARIAL (INDIVIDUO) referente a la firma que antecede. (Firmado), Mary-Ellen M. Devlin, Notario Público. Mi comisión expira el [illegible] del 2000. Sello seco del Notario.

CERTIFICACION NOTARIAL (SOCIEDAD) referente a la existencia y representación de la sociedad mencionada. (Firmado), Mary-Ellen M. Devlin, Notario Público. Mi comisión expira el 31 de octubre del 2000. Sello seco del Notario.

COMO NOTARIO DEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOGRAFIA QUE ANTECEDE CORRESPONDE A LA PERSONA QUE SE VINO A LA VISTA

28 DIC 2004

PABLO MENDEZ BAT
NOTARIO

ESTADO DE CONNECTICUT

CONDADO DE FAIRFIELD, ss. RIDGEFIELD

Yo, Barbara Serfilippi, Escribano de la Población de

Ridgefield, en dicho Condado, por medio del presente certifico que Mary Ellen M. Devlin, por y ante quien el anterior reconocimiento (o adjunto) fue tomado, era al momento de tomarlo, un Notario Público (u otro funcionario) domiciliado (o autorizado para actuar) en dicho Condado, y que estaba autorizado por las leyes de dicho Estado para tomar y certificar reconocimientos en dicho Estado, y además, que creo que la firma que aparece en el certificado de reconocimiento es auténtica.

En Testimonio de lo Cual, he firmado y estampado del sello del Esado y Población hoy, 29 de agosto de 1996. (Firmado), Barbara Serfilippi, Escribano.

(0404/07/T/Rev.11-92)

ESTADO DE CONNECTICUT

OFICINA DEL SECRETARIO DEL ESTADO

Yo, Miles S. Rapoport, Secretario del Estado de Connecticut, y guardián de su Sello, POR MEDIO DEL PRESENTE CERTIFICO que BARBARA SERFILIPPI fue debidamente elegida [illegible] para el cargo de ESCRIBANO DEL CONDADO para la población de RIDGEFIELD en el Condado de FAIRFIELD en dicho Estado, para el período que va del 1o. de enero de 1996 al 5 de enero de 1998 y que sus actos oficiales en calidad de tal merecen completa fe y crédito dentro y fuera de la Corte. En testimonio de lo cual, he firmado y estampado el Gran Sello del Estado de Connecticut, en Hartford, el 30 de agosto de 1996. (Firma facsimilar), Miles S. Rapoport, Secretario del Estado. Adherido se encuentra sello de oblea del Estado de Connecticut. Sello seco del Consulado de Colombia en Boston,

EE.UU.

(en español): **Certificación No.1156** del 13 de septiembre de 1996, de la firma que antecede por el Consulado de Colombia en Boston. Pagados impuesto de timbre y derechos de fondo rotatorio. (Firmado), Luis Fernando Lemaitre, Cónsul. Sello consular en tinta. **Certificación No.213241** del 24 de septiembre de 1996 de la firma que antecede por el Ministerio de Relaciones Exteriores. (Firmado), Jefe Legalizaciones.

Es traducción fiel y completa de la cual se [illegible] archivos de esta oficina para su confrontación y a las cuales me remito.

Santa fe de Bogotá, 30 de septiembre de 1996.

COLO-7612-801-005-5

ams/~~59~~-60

ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES - ITALIANO - ESPAÑOL
RES. NO. 188 MINJUSTICIA

DESPACHO DEL NOTARIO SEXTO ENCARGADO DE BOGOTA. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
28 DIC 2004
PABLO MENDEZ BARAJAS
NOTARIO (E)

MINISTERIO DE RELACIONES EXTERIORES
DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS
CUYA FIRMA APARECE EN
2 6 3 9 8 1

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA HAGO CONSTAR QUE LA FIRMA DE
C.C.
COINCIDE CON LA REGISTRADA POR EL (LA) EN ESTA NOTARIA.
30 SET. 1996
SANTAFE D BOGOTA, D.C.

NOTARIA SEXTA
Encargado

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C
30 SET 12:07

NO SE ASUME RESPONSABILIDAD DEL TEXTO

CAVELIER
ABOGADOS

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11

Señor Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Poderdante: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Poder conferido el: 29-08-96

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

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

28 DIC 2004

PABLO MENDEZ BARAJAS
NOTARIO (E)

Señor Jefe,

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

Acepto:

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

2e-780-2

NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

Santafé de Bogotá D. C. 06 SET 1996

Ante MI JUAN MANUEL BOTERO MEDINA

NOTARIO SEXTO DEL CIRCULO DE BOGOTA

Compareció(eron) personalmente

quien(es) exhibió(eron) la(s) C. C.

y la(s) Libreta(s) Militar(es).

domiciliado(s) en [illegible], y dijo(eron) que la(s) firma(s) que aparece(n) en el presente escrito es(son) la(s) suya(s), y que el contenido del mismo es cierto.
En constancia se firma esta diligencia.

28 DIC 2004

PABLO MENDEZ BARAJAS
NOTARIO (E)

REPUBLICA DE COLOMBIA
Notaría Sexta
SANTAFE DE BOGOTA D. C.

12

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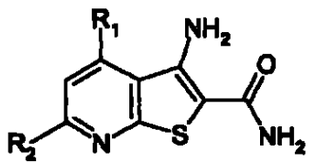
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(54) Title: SUBSTITUTED 3-AMINO-THIENO[2,3-*b*]PYRIDINE-2-CARBOXYLIC ACID AMIDE COMPOUNDS AND PROCESSES FOR PREPARING AND THEIR USES



(I)

(57) Abstract: Disclosed are compounds of formula (I), wherein R_1 and R_2 are defined herein, which are useful as inhibitors of the kinase activity of the IκB kinase (IKK) complex. The compounds are therefore useful in the treatment of IKK mediated diseases including autoimmune diseases inflammatory diseases and cancer. Also disclosed are pharmaceutical compositions comprising these compounds and processes for preparing these compounds.

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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.

SUBSTITUTED 3-AMINO-THIENO[2,3-*b*]PYRIDINE-2-CARBOXYLIC ACID AMIDE COMPOUNDS AND PROCESSES FOR PREPARING AND THEIR USES

APPLICATION DATA

This application claims benefit to US provisional application No. 60/386,312 filed June 6, 2002 and US provisional application No. 60/457,867, filed March 26, 2003 and are hereby claimed and said applications are herein incorporated by reference.

TECHNICAL FIELD OF THE INVENTION

This invention relates to substituted 3-amino-thieno[2,3-*b*]pyridine-2-carboxylic acid amide compounds useful as inhibitors of the kinase activity of the IκB kinase (IKK) complex. The compounds are therefore useful in the treatment of IKK-mediated diseases including autoimmune diseases, inflammatory diseases and cancer. The invention also relates to processes for preparing such compounds and pharmaceutical compositions comprising them.

BACKGROUND OF THE INVENTION

NF-κB or nuclear factor κB is a transcription factor that induces the expression of a large number of pro-inflammatory and anti-apoptotic genes. These include cytokines such as IL-1, IL-2, TNF-α and IL-6, chemokines including IL-8 and RANTES, as well as other pro-inflammatory molecules including COX-2 and cell adhesion molecules such as ICAM-1, VCAM-1, and E-selectin. The NF-κB family includes homo- and heterodimeric transcription factors composed of members of the Rel family (see for example P.A. Baeurle and D. Baltimore, *Cell*, 1996, *87*, 13). Under resting conditions, NF-κB is present in the cytosol of cells as a complex with IκB. The IκB family of proteins serve as inhibitors of NF-κB, interfering with the function of its nuclear localization signal (see for example U. Siebenlist et al., *Ann. Rev. Cell Biol.*, 1994, *10*, 405). Upon disruption of the IκB- NF-κB complex following cell activation, NF-κB translocates to the nucleus and activates gene transcription. Disruption of the IκB- NF-κB complex and subsequent activation of NF-κB is initiated by degradation of IκB.

Upon cellular activation by a variety of pro-inflammatory stimuli including IL-1, TNF-α and LPS (bacterial lipopolysaccharide), two specific serine residues of IκB are phosphorylated. Upon phosphorylation, IκB undergoes polyubiquination and subsequent degradation by the 26S proteasome (see for example V.J. Palombella et al., *Cell*, 1994, *78*, 773), freeing NF-κB to translocate to the nucleus. The phosphorylation of IκB is carried out by the IκB kinases (see for example a review by M. Karin and M. Delhase, *Seminars in Immunology*, 2000, *12*, 85). The traditional IKK complex includes at least three subunits, IKKα (also called IKK-1), IKKβ (or IKK-2) and IKKγ (or NEMO), although other relevant complexes involving IKKα and IKKβ may exist. IKKα and IKKβ are both catalytic subunits while IKKγ is believed to be a regulatory subunit. Both IKKα and IKKβ can phosphorylate IκB. For the purposes of this document, the terms IKK or IKK complex refers to any complex that has kinase activity derived from IKKα and/or IKKβ subunits.

In vivo, activation of IKK occurs upon phosphorylation of its catalytic subunit. Both IKKα and IKKβ can be phosphorylated on serine residues, S177 and S181 of the activation loop in the case of IKKβ, and S176 and S180 of the activation loop for IKKα. An IKKβ mutant having alanines in place of serines at 177 and 181 prevented IKKβ phosphorylation and subsequent activation of the IKK complex by TNFα, IL-1 and other upstream activators. These results support a key role for IKKβ in phosphorylation of IκB following proinflammatory stimulation.

Studies in which the NF-κB pathway has been inhibited in cells and animals support the concept that inhibition of the phosphorylation of IκB is a viable approach to treatment of inflammatory, autoimmune and other diseases. In these studies, NF-κB activation was prevented by expression of a non-degradable version of the IκB protein. Expression of this inhibitor in synovial cells derived from rheumatoid arthritis patients reduced the expression of TNF-α, IL-6, IL-1β and IL-8 while the anti-inflammatory molecules IL-10, IL-1rα and IL-11 were not affected. Matrix metalloproteinases (MMP1 and MMP3) were also down-regulated (J. Bondersen et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1999, *96*, 5668). Transgenic expression of the IκB inhibitor in T cells caused a significant reduction in the severity and onset of collagen–induced arthritis in mice (R. Seetharaman et al., *J. Immunol.*

1999, *163*, 1577). These experiments indicate that suppression of NF-κB in the diseased joint could reduce both the severity and progression of RA. In primary intestinal epithelial cells, the NF-κB inhibitor blocked the expression of IL-1, IL-8, iNOS and COX-2, mediators that are up-regulated during the course of inflammatory bowel disease (C. Jubin et al., *J. Immunol.*, 1998, *160*, 410). Expression of this inhibitor in certain tumor cells enhances killing of these cells by chemotherapeutic reagents (A.A. Beg and D. Baltimore, *Science*, 1996, *274*, 782).

Analysis of biopsies from lungs of patients with chronic obstructive pulmonary disease (COPD) found an increased expression of NF-κB that correlated with disease severity (A. Di Stefano *et al.*, *Eur. Resp. J.*, 2002, *1*, 437). Inhibition of NF-κB activation with inhibitors of IKK-β was among the anti-inflammatory approaches reported to be potentially useful in the treatment of COPD (P.J. Barnes, *Nature Rev. Drug Disc.*, 2002, *1*, 437). Likewise, inhibition of NF-κB activity has been mentioned as a therapeutic approach for asthma (A. Pahl and L. Szelenyi, *Infl. Res.*, 2002, *51*, 273).

A recent review describes the essential role of inflammatory mediators in the development cardiovascular disease. The inflammatory mediators and the cells that they recruit are reported to play a key role in the development of fatty streaks and plaques that lead to atherosclerosis. In addition they are reported to play a key role in subsequent degradation of the fibrous cap that forms over the plaque, leading to rupture and clot formation. If the clot grows large enough it can lead to myocardial infarction or stroke. Thus, anti-inflammatory drugs that can inhibit the production of these mediators and subsequent recruitment and activation of these cells may be beneficial in treatment of these diseases (P. Libby, *Scientific American*, 2002, 46).

A number of studies indicate that activation of NF-κB also plays a key role in the pathogenesis and development of cancer (see for example reviews by B. Haefner, *Drug Disc. Today*, 2002, *7*, 653 and M. Karin *et al.*, *Nat. Rev.* Cancer, 2002, *2*, 301). Studies have shown that cells in which NF-κB is constitutively active are resistant to apoptosis. This can contribute to carcinogenesis by preventing cell death in cells that have undergone chromosomal changes or damage. In addition tumor cells with constitutively active NF-

κB are resistant to anti-cancer therapies including chemotherapy and radiation. Further studies have linked activated NF-κB to a variety of lymphoid-, myeloid- and epithelial-derived malignancies including leukemia, lymphomas and breast, gastric, colorectal, lung, and pancreatic cancers. Thus it is suggested that inhibitors of NF-κB, including inhibitors of IKKα and IKKβ, may be useful either alone or in combination with other anti-cancer therapies in treating cancer.

Collectively, the studies described above provide support that inhibition of NF-κB function through inhibition of IKK may be a useful therapeutic approach to treatment of autoimmune and inflammatory disease, cardiovascular disease and cancer.

Studies have also been done in mice with targeted disruption of the IKKβ gene. Knockout of the IKKβ gene resulted in embryonic lethality due to apoptosis of hepatocytes. However, fibroblasts from the IKKβ knockouts did not undergo IKK and NF-κB activation upon stimulation with IL-1 or TNFα (Q. Li et al., *Science*, 1999, *284*, 321), supporting a key role for IKKβ in and NF-κB activation following inflammatory stimuli.

A conditional knockout was generated by expressing a liver-specific inducible dominant negative IκBα transagene (I. Lavon et al., *Nature Medicine*, 2000, *6*, 573). These mice were viable with no signs of liver dysfunction even after one year but they did have impaired immune function. This study supports the idea that inhibition of IKKβ can result in immune suppression without damage to the liver.

IKKα knock-out mice died shortly after birth and displayed a variety of skeletal defects and skin abnormalities. Fibroblast and thymocytes from these mice showed normal IKK activation and IκB degradation in response to TNFα, IL-1 or LPS (Y. Hu et al., *Science*, 1999, *284*, 316; K. Takeda et al., *Science*, 1999, *284*, 313). Recent studies with knock-out and knock-in mice have revealed distinct roles for IKKα in development and cell signaling. In contrast to the studies with IKKα knock-out mice, mice having a kinase inactive version of IKKα knocked in are viable and fertile, indicating that the perinatal lethality and abnormalities seen in the IKKα knock-out mice are not due to the lack of

kinase activity. However, these mice do have defects in B cell maturation and development of secondary lymphoid organs (U. Senftleben et al., *Science*, 2001, *293*, 1495). This phenotype appears to be due to a defect in processing of the NF-κB2/p100 protein to p52, the DNA binding form of this member of the Rel family of transcription factors. In turn, this leads to a defect in the activation of a subset of NF-κB target genes in B cells. In addition, other studies with these same mice have shown that IKKα kinase activity is required for NF-κB activation in the mammary epithelium during pregnancy (Cao, Y., et. al., *Cell*, 2001, *107*,763). This pathway is specifically activated through the TNF receptor family member RANK, requires phosphorylation of the canonical IKK substrate IκBα, and culminates in induction of the cell cycle regulatory gene Cyclin D1.

These studies indicate that an inhibitor of IKKα kinase activity may be useful in treating diseases associated with inappropriate B cell activation such as lupus (O.T. Chan et al., *Immunological Rev.*, 1999, *169*, 107) and rheumatoid arthritis (A. Gause and C. Borek, *Biodrugs*, 2001, *15*, 73). In addition, an inhibitor of IKKα may be useful in the treatment of breast cancer since NF-κB is constitutively active in a number of breast tumors and many of these tumors depend on Cyclin D1 for proliferation.

Some inhibitors of IKKβ have been reported. WO 01/58890 and WO 03/037886 describes heteroaromatic carboxamide derivatives as inhibitors of IKKβ. WO 01/68648 describes substituted β-carbolines having IKKβ inhibiting activity. Substituted indoles having IKKβ inhibitory activity are reported in WO 01/30774. WO 01/00610 describes substituted benzimidazoles having NF-κB inhibitory activity. Aspirin and salicylate have been reported to bind to and inhibit IKKβ (M. Yin et al., *Nature*, 1998, *396*, 77).

Substituted thienopyridines having cell adhesion inhibiting activity are reported in US 2001/0020030 A1 and A.O. Stewart et al., *J. Med. Chem.*, 2001, *44*, 988. Thienopyridines exhibiting gonadotropin releasing hormone antagonizing activity are reported in US 6,313,301. Substituted thienopyridines described as telomerase inhibitors are disclosed in U.S. 5,656,638.

A number of 4,6-disubstituted thieno[2,3-b]pyridine-2-carboxylic acid amides have been described in the chemical literature. Examples include 3-amino-4,6-dimethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-6-methyl-thieno[2,3-b]pyridine-2,4-dicarboxylic acid diamide, 3-amino-4-methyl-6-phenyl-thieno[2,3-b]-pyridine-2-carboxamide, 3-amino-6-methyl-4-phenyl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-6-(4-bromo-phenyl)-4-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-4-(4-bromo-phenyl)-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-6-methyl-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-butylamide, 3-amino-6-furan-2-yl-4-phenyl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-6-furan-2-yl-4-pyridin-3-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-4-(4-chloro-phenyl)-6-phenyl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-4-(4-fluoro-phenyl)-6-furan-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-4-(4-chloro-phenyl)-6-furan-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-4-(4-bromo-phenyl)-6-furan-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-4,6-bis-(4-chloro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-6-naphth-2-yl-4-pyridin-3-yl- thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-6-methyl-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-(2-hydroxyethyl)amide, 3-amino-6-methyl-4-piperidin-1-yl-thieno[2,3-b]-pyridine-2-carboxamide and 3-amino-4-methyl-6-hydroxy-thieno[2,3-b]-pyridine-2-carboxamide reported as intermediates for synthesis of tricyclic heterocycles and evaluated for anti-allergic activity (G. Wagner et al., *Pharmazie*, 1990, *45*, 102).

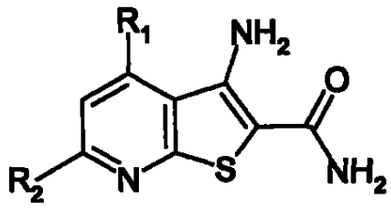
Other examples includes 3-amino-4,6-diphenyl-thieno[2,3-b]pyridine-2-carboxylic acid amide (A.M. Shestopalov et al., *J. Org. Chem. USSR*, (Engl. Transl.) 1984, *20*, 1382), 3-amino-6-methyl-4-pyridin-4-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide and 3-amino-6-methyl-4-pyridin-3-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (G. Wagner et al., *Pharmazie*, 1993, *48*, 514), 3-amino-4-methoxymethyl-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide (E.I. Kaigorodova et al., *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1996, *32*, 1234), 3-amino-6-phenyl-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-4-furan-2-yl-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide, 3-amino-4-(4-chloro-phenyl)-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide and 3-amino-4-furan-2-yl-6-phenyl-thieno[2,3-b]pyridine-2-

carboxylic acid amide (F.A. Attaby, *Phosphorus, Sulfur, Silicon Relat. Elem.*,1998, 139, 1), 3-amino-6-(4-chloro-phenyl)-4-thiophen-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (Y. Sharanin et al., *J. Org. Chem. USSR*, (Engl. Transl.) 1996, *32*, 1207), 3-amino-6-phenyl-4-pyridin-3-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide (A. Krauze, *Eur. J. Med. Chem. Chim. Ther.*, 1999, *34*, 301) and 3-amino-6-thiophen-2-yl-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide (M.I. Abdel-Monem et al., *Pharmazie*, 2001, *56*, 41).

In no case are these compounds described as having the ability to inhibit IKKα or IKKβ.

SUMMARY OF THE INVENTION

It is therefore an object of this invention to provide novel compounds according to the following formula (I):

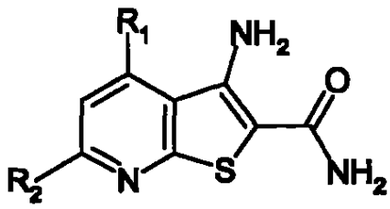


(I)

wherein the variables R_1 and R_2 are described herein which inhibit IKK. It is a further object of the invention to provide methods for treating diseases and pathological conditions exacerbated by IKK such as, but not limited to autoimmune diseases, inflammatory diseases and cancer. It is yet a further object of the invention to provide novel processes for preparation of the above-mentioned novel compounds.

DETAILED DESCRIPTION OF THE INVENTION

A first aspect of the invention comprises a method of treating an inflammatory or autoimmune condition by administration of certain novel and known molecules of the formula (I):



(I)

wherein:

R_1 is

(a) phenyl or heteroaryl selected from furanyl, thienyl, pyridyl, pyrrolyl, imidazolyl and benzofuranyl, optionally substituted with one to two R_3,

(b) heterocyclyl selected from 1-piperidinyl, 1-piperazinyl, 1-pyrrolidinyl and 4-morpholinyl, optionally substituted with one to two groups selected from C_{1-6}alkyl, $-CO_2C_{1-5}$alkyl, phenyl, benzyl, -OH and -C(O)heteroaryl, wherein the heteroaryl is selected from furanyl, thienyl, pyridyl and pyrrolyl,

(c) $R_6(CH_2)_mO-$,

(d) R_6OCH_2-,

(e) $R_6(CH_2)_mNH-$,

(f) $R_6(CH_2)_p(CH=CH)_n-$,

(g) C_{1-6}alkyl, optionally partially of fully halogenated and optionally substituted with one to two R_9,

(h) C_{1-6}alkoxy, optionally partially of fully halogenated and optionally substituted with one to two R_9,

(i) C_{1-6}alkyl$S(O)_n-$, optionally partially of fully halogenated and optionally substituted with one to two R_9,

(j) $-N(R_4)(R_5)$, or

(k) $-C(O)NHR'$, wherein R' is R_6, pyridyl or $-CH_3$;

R_2 is

(a) C_{1-6}alkyl, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(b) C_{1-6}alkoxy, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(c) C_{1-6}alkylamino, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(d) C_{1-6}alkylthio, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(e) heterocyclyl$(CH_2)_m$- wherein said heterocycle is selected from piperidinyl, piperazinyl, morpholinyl, azepanyl, pyrrolidinyl, 1,4-diazacycloheptanyl, azepanyl, 2,5-diazabicyclo[2.2.1]heptanyl, oxazepanyl and thiomorpholino and is optionally substituted with one or three R_7,

(f) heterocyclylCH_2O- wherein the heterocyclyl is selected from 1-piperidinyl, 1-piperazinyl, 4-morpholinyl and 1-pyrrolidinyl, optionally substituted with C_{1-6}alkyl,

(g) phenyl, optionally substituted with one or three R_3,

(h) $-N(R_4)(R_5)$,

(i) heteroaryl selected from furanyl, thienyl, imidazolyl, pyridyl and pyrrolyl, or

(j) –H;

R_3 is chosen from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, halogen, -CN, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-S(O)_nC_{1-6}$alkyl, $-NO_2$, -OH, $-CF_3$, $-N(R_4)(R_5)$, $-NHC(O)NHC_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$ and phenyl optionally substituted with halogen, C_{1-6}alkyl, -CN or C_{1-6}alkoxy;

R_4 and R_5 are independently selected from H, C_{1-6}alkyl, $-C(O)C_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, phenyl, pyridyl, benzyl, piperidinyl, phenylethyl and $(CH_3)_3COC(O)$-;

R_6 is a phenyl group optionally substituted with one or two groups selected from halogen, C_{1-6}alkyl, -CN, $-CO_2C_{1-6}$alkyl, $-C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ and C_{1-6}alkoxy, or R_6 is C_{3-6}cycloalkyl, $-CH_2OH$, naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

R_7 is selected from –OH, -CN, oxo, -CO_2C_{1-6}alkyl, -CO_2H, -$C(O)N(R_4)(R_5)$, -$N(R_4)(R_5)$, -$CH_2N(R_4)(R_5)$, -CH_2OH, C_{1-6}alkyl, -CO_2benzyl, hydroxyC_{1-6}alkyl, -$C(O)C_{1-6}$alkyl$N(R_4)(R_5)$, -$NHCO_2C_{1-6}$alkyl, -$NHC(O)N(R_4)(R_5)$, -$S(O)_nC_{1-6}$alkyl, $(CH_3)_3COC(O)$-, phenyl, pyridyl, $H_2NCH(R_8)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- and -C(O)heterocyclyl, wherein said heterocyclyl is selected from piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl, hydroxyimino, hydrozinocarbonyl, sulfamoyl, methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, 2-hydroxy-1-methylethylamino, carbamoylmethylamino, N'-phenylhydrazinocarbonyl or toluene-4-sulfonylamino;

R_8 is selected from C_{1-6}alkyl, -$(CH_2)_{1-4}NH_2$, phenyl or benzyl;

R_9 is selected from oxo, -OH, -NR_4R_5, -CO_2H and C_{1-6}alkoxy;

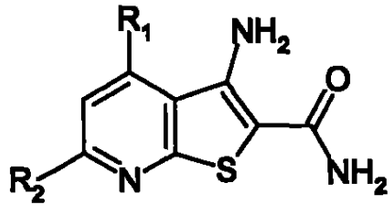
R_{10} is selected from oxo, -OH, -$N(R_4)(R_5)$, C_{1-6}alkoxy, -$C(O)C_{1-6}$alkyl, -$C(O)N(R_4)(R_5)$, R_6, and heteroaryl selected from furanyl, thienyl, imidazolyl, pyridyl, indolyl and pyrrolyl;

m is 0 or 1;

n is 0, 1 or 2; and

p is 0, 1, 2 or 3.

In its second aspect, the invention provides novel compounds of formula (I):



(I)

wherein:

R_1 is

(a) phenyl or heteroaryl selected from furanyl, thienyl, pyridyl, pyrrolyl, imidazolyl and benzofuranyl, optionally substituted with one to two R_3,

(b) heterocyclyl selected from 1-piperidinyl, 1-piperazinyl, 1-pyrrolidinyl and 4-morpholinyl, optionally substituted with one to two groups selected from C_{1-6}alkyl, -CO_2C_{1-5}alkyl, phenyl, benzyl, -OH and -C(O)heteroaryl, wherein the heteroaryl is selected from furanyl, thienyl, pyridyl and pyrrolyl,

(c) $R_6(CH_2)_mO$-,

(d) R_6OCH_2-,

(e) $R_6(CH_2)_mNH$-,

(f) $R_6(CH_2)_p(CH{=}CH)_n$-,

(g) C_{1-6}alkyl, optionally partially of fully halogenated and optionally substituted with one to two R_9,

(h) C_{1-6}alkoxy, optionally partially of fully halogenated and optionally substituted with one to two R_9,

(i) C_{1-6}alkyl$S(O)_n$-, optionally partially of fully halogenated and optionally substituted with one to two R_9,

(j) $-N(R_4)(R_5)$, or

(k) $-C(O)NHR'$, wherein R' is R_6, pyridyl or $-CH_3$;

R_2 is

(a) C_{1-6}alkyl, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(b) C_{1-6}alkoxy, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(c) C_{1-6}alkylamino, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(d) C_{1-6}alkylthio, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(e) heterocyclyl$(CH_2)_m$- wherein said heterocycle is selected from piperidinyl, piperazinyl, morpholinyl, azepanyl, pyrrolidinyl, 1,4-diazacycloheptanyl, azepanyl,

2,5-diazabicyclo[2.2.1]heptanyl, oxazepanyl and thiomorpholino and is optionally substituted with one to three R_7,

(f) heterocyclylCH_2O- wherein the heterocyclyl is selected from 1-piperidinyl, 1-piperazinyl, 4-morpholinyl and 1-pyrrolidinyl, optionally substituted with C_{1-6}alkyl,

(g) phenyl, optionally substituted with one to three R_3,

(h) $-N(R_4)(R_5)$,

(i) heteroaryl selected from furanyl, thienyl, imidazolyl, pyridyl and pyrrolyl, or

(j) –H;

R_3 is chosen from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, halogen, -CN, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-S(O)_2C_{1-6}$alkyl, $-NO_2$, -OH, $-CF_3$, $-N(R_4)(R_5)$, $-NHC(O)NHC_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$ and phenyl optionally substituted with halogen, C_{1-6}alkyl, -CN or C_{1-6}alkoxy;

R_4 and R_5 are independently selected from H, C_{1-6}alkyl, $-C(O)C_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, phenyl, pyridyl, benzyl, piperidinyl, phenylethyl and $(CH_3)_3COC(O)$-;

R_6 is a phenyl group optionally substituted with one or two groups selected from halogen, C_{1-6}alkyl, -CN, $-CO_2C_{1-6}$alkyl, $-C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ and C_{1-6}alkoxy, or R_6 is C_{3-6}cycloalkyl, $-CH_2OH$, naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

R_7 is selected from –OH, -CN, oxo, $-CO_2C_{1-6}$alkyl, $-CO_2H$, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, $-CH_2OH$, C_{1-6}alkyl, $-CO_2$benzyl, hydroxyC_{1-6}alkyl, $-C(O)C_{1-6}$alkyl$N(R_4)(R_5)$, $-NHCO_2C_{1-6}$alkyl, $-NHC(O)N(R_4)(R_5)$, $-S(O)_nC_{1-6}$alkyl, $(CH_3)_3COC(O)$-, phenyl, pyridyl, $H_2NCH(R_6)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- and -C(O)heterocyclyl, wherein said heterocyclyl is selected from piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl, hydroxyimino, hydrozinocarbonyl, sulfamoyl, methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, 2-hydroxy-1-methylethylamino, carbamoylmethylamino, N'-phenylhydrazinocarbonyl or toluene-4-sulfonylamino;

R_8 is selected from C_{1-6}alkyl, $-(CH_2)_{1-4}NH_2$, phenyl or benzyl;

R_9 is selected from oxo, -OH, $-NR_4R_5$, $-CO_2H$ and C_{1-6}alkoxy;

R_{10} is selected from oxo, -OH, $-N(R_4)(R_5)$, C_{1-6}alkoxy, $-C(O)C_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$, R_6, and heteroaryl selected from furanyl, thienyl, imidazolyl, pyridyl, indolyl and pyrrolyl;

m is 0 or 1;

n is 0, 1 or 2;

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof.

In another embodiment, there are provided novel compounds of the formula (I) as described above and wherein:

R_1 is

(a) phenyl or heteroaryl selected from furanyl, thienyl, pyridyl, pyrrolyl, imidazolyl and benzofuranyl optionally substituted with one to two R_3,
(b) $R_6(CH_2)_mO-$,
(c) R_6OCH_2-,
(d) $R_6(CH_2)_mNH-$,
(e) $R_6(CH_2)_p(CH=CH)_m-$,
(f) C_{1-6}alkyl, optionally partially of fully halogenated and optionally substituted with one to two R_9,
(g) C_{1-6}alkoxy, optionally partially of fully halogenated and optionally substituted with one to two R_9,
(h) C_{1-6}alkylthio,
(i) $-N(R_4)(R_5)$, or
(j) $-C(O)NHR'$, wherein R' is R_6, pyridyl or $-CH_3$.

R_2 is

(a) C_{1-6}alkyl, optionally substituted with R_{10},

(b) C_{1-6}alkoxy, optionally substituted with R_{10},

(c) C_{1-6}alkylamino, optionally substituted with R_{10},

(d) heterocyclyl selected from from 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, 1-azepanyl, 1-pyrrolidinyl, 1,4-diazacycloheptan-1-yl, 1-azepanyl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, oxazepan-4-yl and 4-thiomorpholino and is optionally substituted with one to three R_7,

(e) heterocyclylCH_2O- wherein the heterocyclyl is selected from 1-piperidinyl, 1-piperazinyl, 4-morpholinyl and 1-pyrrolidinyl, optionally substituted with C_{1-6}alkyl, or

(f) $-N(R_4)(R_5)$;

R_3 is chosen from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, halogen, -CN, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-S(O)_nC_{1-6}$alkyl, $-NO_2$, -OH, $-CF_3$, $-N(R_4)(R_5)$, $-NHC(O)NHC_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$ and phenyl optionally substituted with halogen, C_{1-6}alkyl, -CN or C_{1-6}alkoxy;

R_4 and R_5 are independently selected from H, C_{1-6}alkyl, $-C(O)C_{1-6}$alkyl, pyridyl, benzyl, piperidinyl and phenylethyl ;

R_6 is a phenyl group optionally substituted with one or two groups selected from Cl, F, C_{1-6}alkyl, -CN, $-CO_2C_{1-6}$alkyl, $-C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ and C_{1-6}alkoxy or R_6 is C_{3-6}cycloalkyl, $-CH_2OH$, naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

R_7 is selected from –OH, -CN, oxo, $-CO_2C_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, $-CH_2OH$, C_{1-6}alkyl, $-C(O)C_{1-6}$alkyl$N(R_4)(R_5)$, $-NHC(O)N(R_4)(R_5)$, $-S(O)_nC_{1-6}$alkyl, $H_2NCH(R_6)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$- and -C(O)heterocyclyl, wherein said heterocyclyl is selected from piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl, hydroxyimino, hydrozinocarbonyl, sulfamoyl, methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, 2-hydroxy-

1-methylethylamino, carbamoylmethylamino, N'-phenylhydrazinocarbonyl or toluene-4-sulfonylamino;

R_8 is selected from C_{1-6}alkyl, $-(CH_2)_{1-4}NH_2$, phenyl or benzyl;

R_9 is –OH;

R_{10} is selected from –OH, $-N(R_4)(R_5)$, C_{1-6}alkoxy and heteroaryl selected from furanyl, thienyl and pyridyl;

m is 0 or 1;

n is 0, 1 or 2;

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof.

In yet another embodiment of the invention there are provided novel compounds of the formula (I) as described above and wherein:

R_1 is

(a) phenyl or heteroaryl selected from furanyl, thienyl and pyridyl, optionally substituted with one to two R_3,

(b) $R_6(CH_2)_mO-$,

(c) R_6OCH_2-,

(d) $R_6(CH_2)_mNH-$,

(e) $R_6(CH_2)_p(CH=CH)_m-$,

(f) C_{1-6}alkyl,

(g) C_{1-6}alkylOH,

(h) $-CF_3$,

(i) C_{1-6}alkoxy,

(j) $-OC_{1-6}$alkylOH,

(k) C_{1-6}alkylthio,

(l) $-N(R_4)(R_5)$, or

(m)–C(O)NHR', wherein R' is R_6, pyridyl or $-CH_3$;

R_2 is heterocyclyl wherein said heterocycle is selected from 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, 1-azepanyl, 1-pyrrolidinyl, 1,4-diazacycloheptan-1-yl, 1-azepanyl 2,5-diazabicyclo[2.2.1]heptan-2-yl, oxazepan-4-yl and 4-thiomorpholino and is optionally substituted with one to three R_7,

R_3 is chosen from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, halogen, -CN, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-S(O)_nC_{1-6}$alkyl, $-NO_2$, -OH, $-CF_3$, $-N(R_4)(R_5)$, $-NHC(O)NHC_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$ and phenyl optionally substituted with halogen, C_{1-6}alkyl, -CN or C_{1-6}alkoxy;

R_4 and R_5 are independently selected from H, C_{1-6}alkyl, $-C(O)C_{1-6}$alkyl, pyridyl, benzyl, piperidinyl and phenylethyl;

R_6 is a phenyl group optionally substituted with one or two groups selected from Cl, F, C_{1-6}alkyl, -CN, $-CO_2C_{1-6}$alkyl, $-C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ and C_{1-6}alkoxy, or R_6 is C_{3-6}cycloalkyl, $-CH_2OH$, naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

R_7 is selected from –OH, -CN, oxo, $-CO_2C_{1-6}$alkyl, $-CO_2H$, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, $-CH_2OH$, C_{1-6}alkyl, $-C(O)C_{1-6}$alkylN$(R_4)(R_5)$, $-NHC(O)N(R_4)(R_5)$, $-S(O)_nC_{1-6}$alkyl, phenyl, pyridyl, $H_2NCH(R_8)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- and -C(O)heterocyclyl, wherein said heterocyclyl is selected from piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl, hydroxyimino, hydrozinocarbonyl, sulfamoyl, methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, 2-hydroxy-1-methylethylamino, carbamoylmethylamino, N'-phenylhydrazinocarbonyl or toluene-4-sulfonylamino;

R_8 is selected from C_{1-6}alkyl, $-(CH_2)_{1-4}NH_2$, phenyl or benzyl;

m is 0 or 1;

n is 0, 1 or 2;

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof.

In still another embodiment of the invention there are provided novel compounds of the formula (I) as described above and wherein:

R_1 is

(a) phenyl, optionally substituted with one to two R_3,

(b) R_6CH=CH-

(c) C_{1-6}alkyl,

(d) $-C_{2-3}$alkylOH,

(e) $-CF_3$,

(f) $-C_{1-6}$alkoxy,

(g) $-OC_{2-3}$alkylOH,

(h) $-C_{1-6}$alkylthio, or

(i) –C(O)NHR', wherein R' is R_6, pyridyl or $-CH_3$;

R_2 is

heterocyclyl wherein said heterocycle is selected from 1-piperidinyl, 1-piperazinyl, 1-azepanyl, 1,4-diazacycloheptan-1-yl and 1-azepanyl and is optionally substituted with one to three R_7;

R_3 is chosen from $-CH_3$, $-OCH_3$, F, Cl, $-CO_2CH_3$, $-SO_2CH_3$ and $-NO_2$;

R_4 and R_5 are independently selected from H, $-CH_3$ and benzyl;

R_6 is a phenyl group optionally substituted with one or two groups selected from Cl, F, C_{1-6}alkyl, -CN, CO_2C_{1-6}alkyl, $C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ and C_{1-6}alkoxy or R_6 is C_{3-6}cycloalkyl, $-CH_2OH$, naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

R_7 is selected from –OH, -CN, oxo, $-CO_2C_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, CH_2OH, C_{1-6}alkyl, $-C(O)C_{1-6}$alkylN$(R_4)(R_5)$, $-NHC(O)N(R_4)(R_5)$, $-S(O)_nC_{1-6}$alkyl, $H_2NCH(R_8)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- and -C(O)heterocyclyl, wherein said heterocyclyl is selected from piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl, hydroxyimino, hydrozinocarbonyl, sulfamoyl, methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, 2-hydroxy-1-methylethylamino, carbamoylmethylamino, N'-phenylhydrazinocarbonyl or toluene-4-sulfonylamino;

R_8 is selected from C_{1-6}alkyl, $-(CH_2)_{1-4}NH_2$, phenyl or benzyl;

and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof.

In a further embodiment of the invention there are provided novel compounds of the formula (I) as described above and wherein:

R_1 is

(a) $–CH_2CH_2CH_3$,

(b) $–OCH_2CH_3$,

(c) $–SCH_3$,

(d) –C(O)NHR', where R' is 3-pyridyl, or phenyl substituted in the 4-position with -OH, $-C(O)NH_2$, or $–SO_2NH_2$;

R_2 is heterocyclyl wherein said heterocycle is selected from 1-piperidinyl and 1-piperazinyl and is optionally substituted with one to three R_7;

R_4 and R_5 are independently selected from H, $-CH_3$ and benzyl;

R_6 is a phenyl group optionally substituted with one or two groups selected from Cl, F, $-CH_3$, -CN, $-CO_2CH_3$, $-C(O)NR_4R_5$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ and $-CH_3$, or R_6 is naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

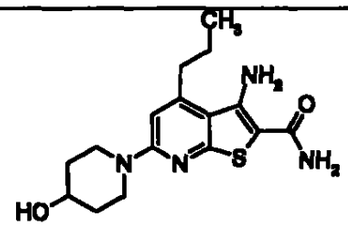
R_7 is selected from –OH, -CN, oxo, $-C(O)NH_2$, $-NH_2$, $-CH_2NH_2$, $-CH_3$, $-NHC(O)NH_2$, $H_2NCH(R_8)C(O)$-, $HOCH(R_6)CH_2NH$- , $R_6CH_2CH(OH)CH_2NH$- and $R_6OCH_2CH(OH)CH_2NH$-, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl, methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, carbamoylmethylamino or N'-phenylhydrazinocarbonyl;

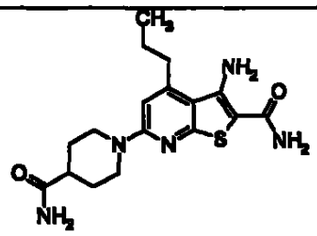
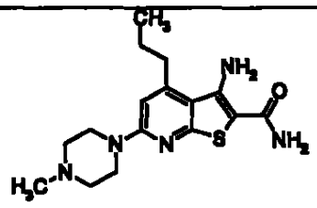
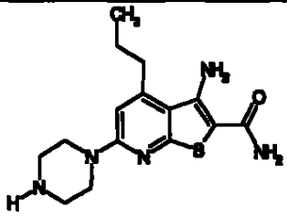
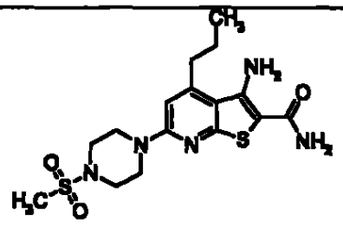
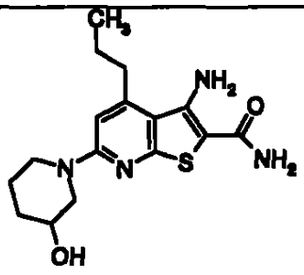
R_8 is $-(CH_2)_{1-4}NH_2$;

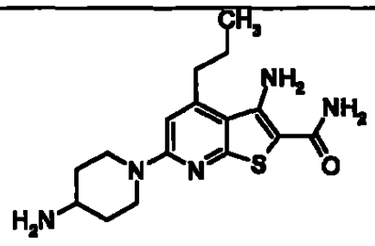
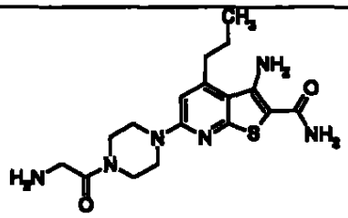
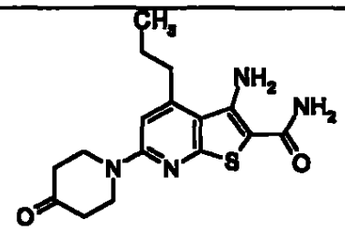
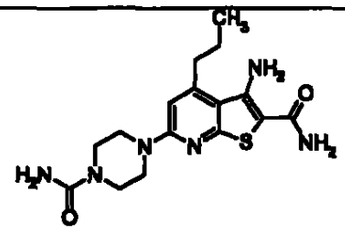
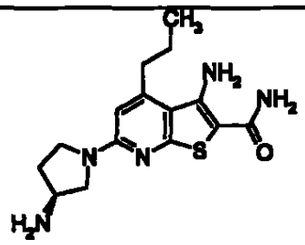
and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof;

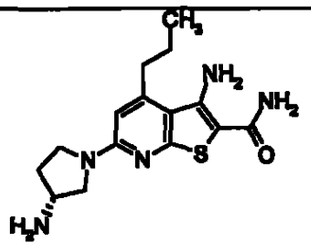
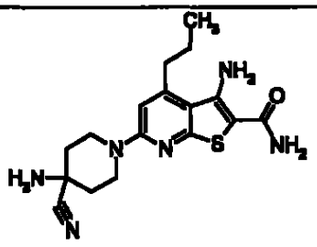
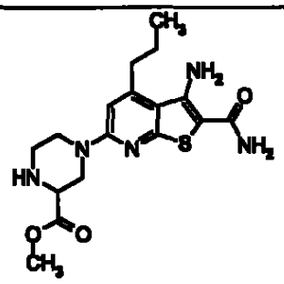
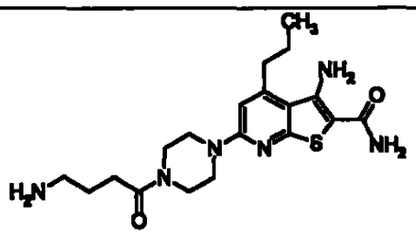
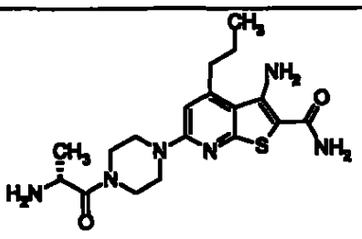
with the proviso that in each of the above embodiments of novel compounds, if R_1 is phenyl or heteroaryl, C_{1-6}alkyl, $-CF_3$, $-C(O)NR_4R_5$ or heterocyclyl, then R_2 is not C_{1-6}alkyl, phenyl, heteroaryl, $-CF_3$, or H. In the first aspect of the invention related to a method of treating an inflammatory or autoimmune condition with compounds of formula (I), this proviso does not apply.

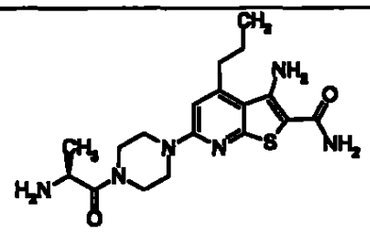
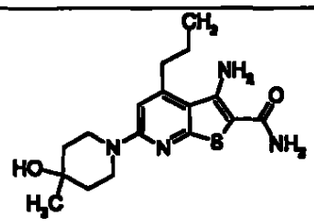
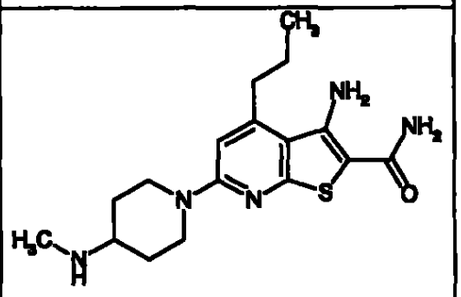
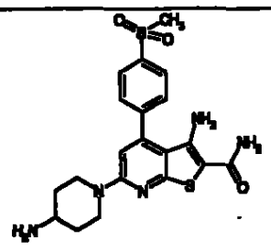
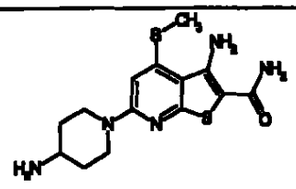
In a further embodiment of the invention, there are provided the following compounds:

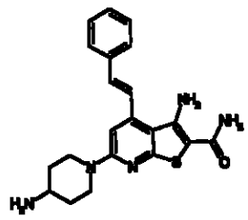
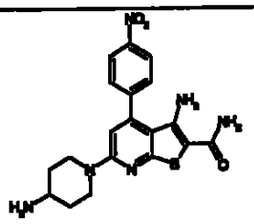
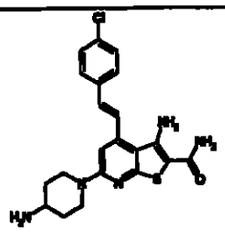
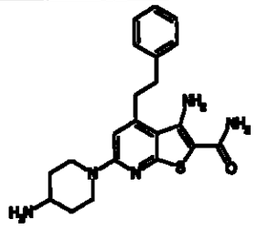
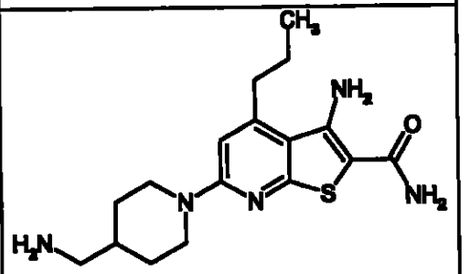
	Name	Structure
	3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

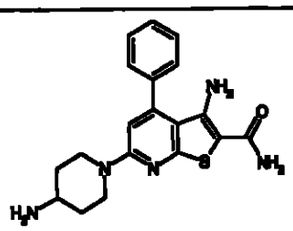
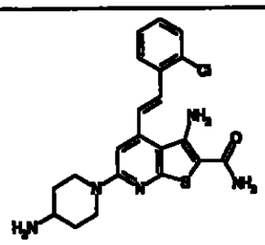
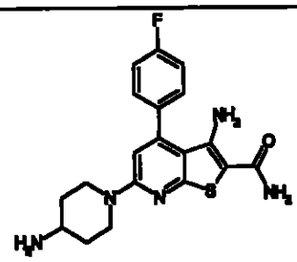
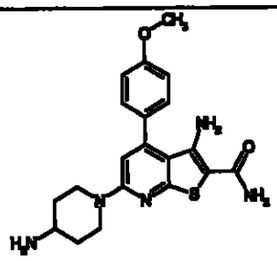
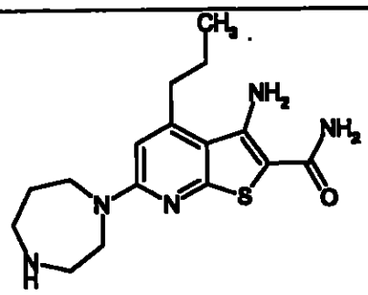
	3-Amino-6-(4-carbamoyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-methyl-piperazin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-piperazin-1-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-methanesulfonyl-piperazin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(3-hydroxy-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

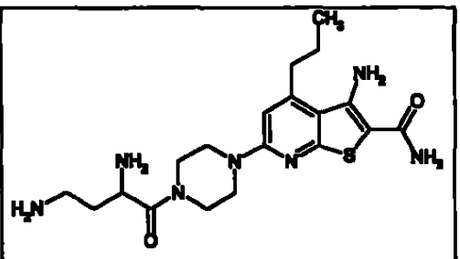
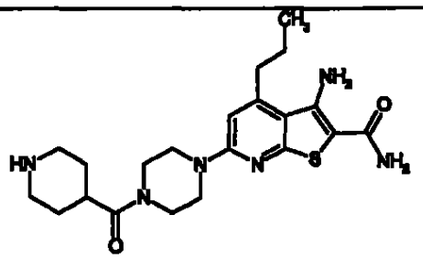
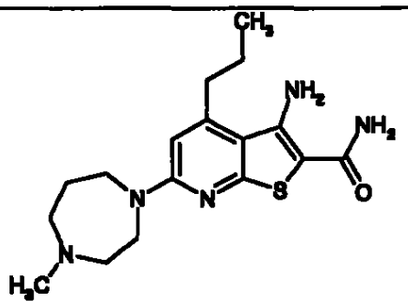
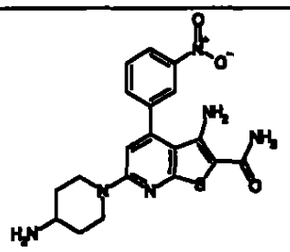
	3-Amino-6-(4-amino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[4-(2-amino-ethanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-oxo-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-carbamoyl-piperazin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-((S)-3-amino-pyrrolidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

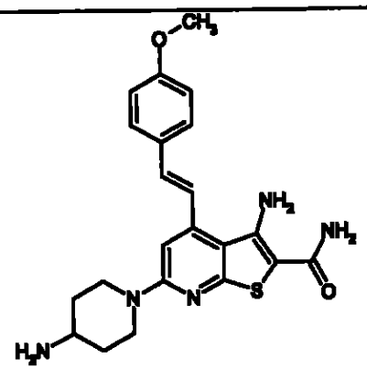
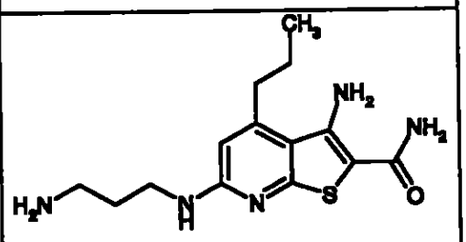
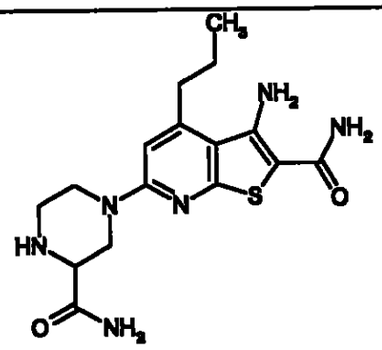
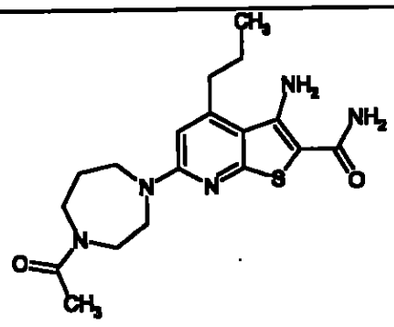
	3-Amino-6-((R)-3-amino-pyrrolidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-4-cyano-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	4-(3-Amino-2-carbamoyl-4-propyl-thieno[2,3-b]pyridin-6-yl)-piperazine-2-carboxylic acid *methyl* ester	
	3-Amino-6-[4-(4-amino-butanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[4-((R)-2-amino-propanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

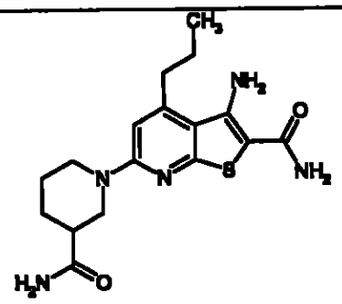
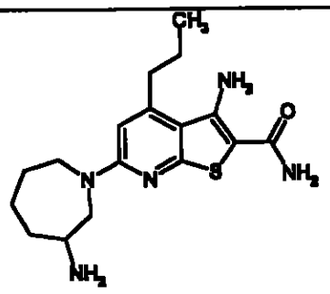
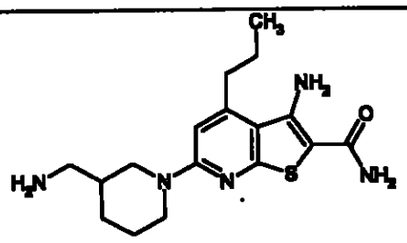
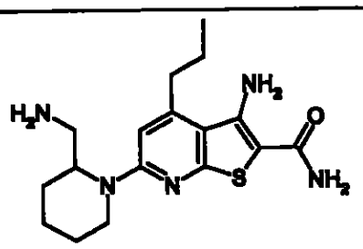
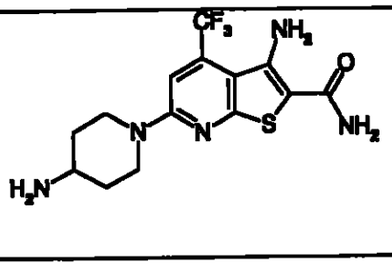
	3-Amino-6-[4-((S)-2-amino-propanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-hydroxy-4-methyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-methylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-methylsulfinyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

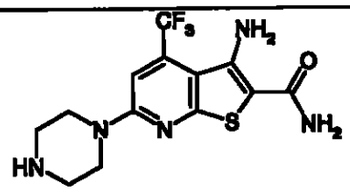
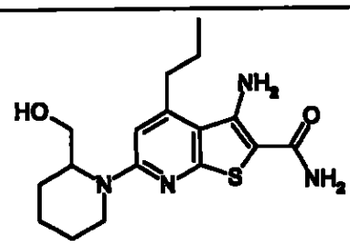
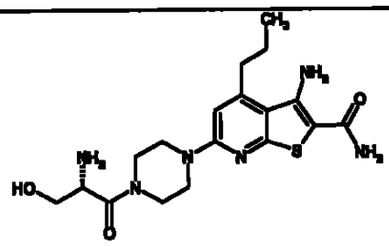
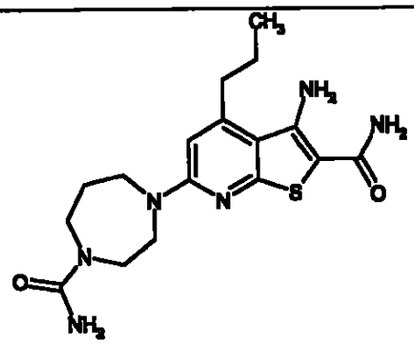
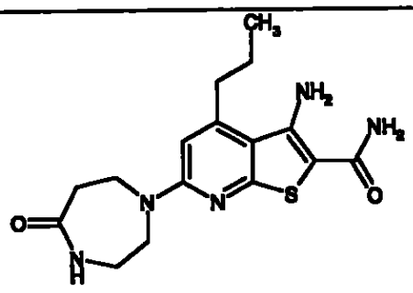
	3-Amino-6-(4-amino-piperidin-1-yl)-4-((E)-styryl)-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-nitro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-[(E)-2-(4-chloro-phenyl)-vinyl]-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-phenethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-aminomethyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

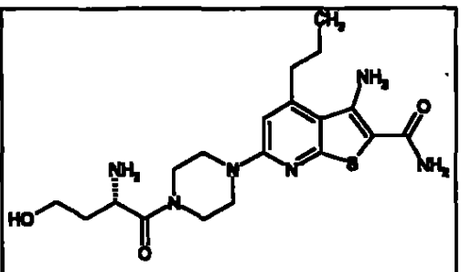
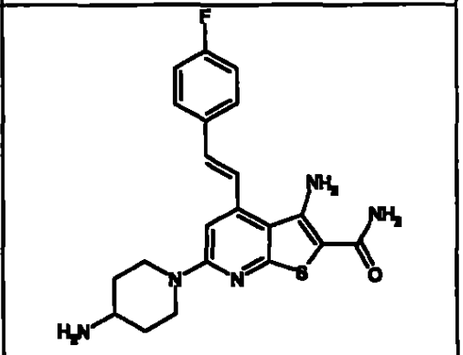
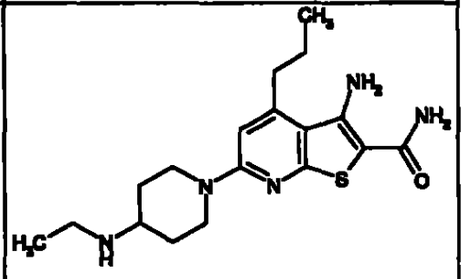
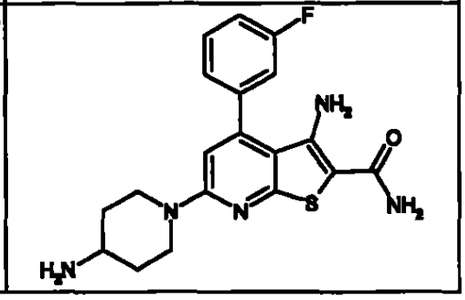
	3-Amino-6-(4-amino-piperidin-1-yl)-4-phenyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-[(E)-2-(2-chloro-phenyl)-vinyl]-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-fluoro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-methoxy-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[1,4]diazepan-1-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

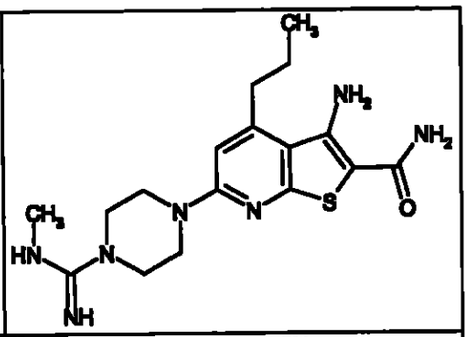
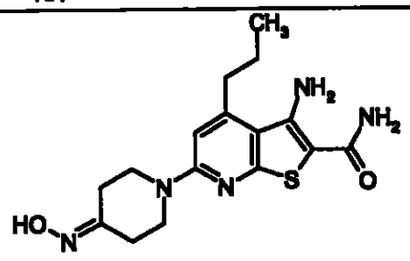
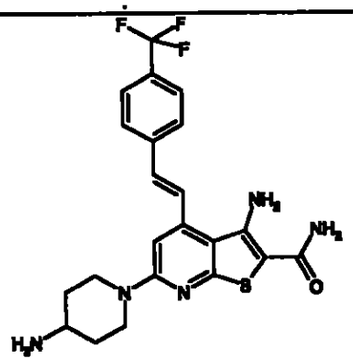
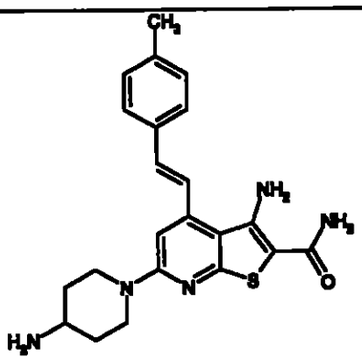
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	3-Amino-6-[4-(1-piperidin-4-yl-methanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-methyl-[1,4]diazepan-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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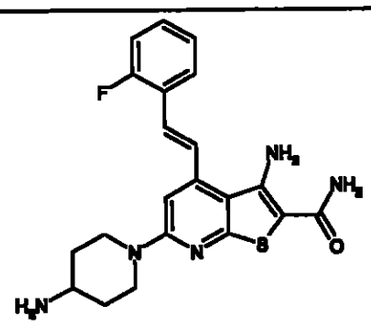
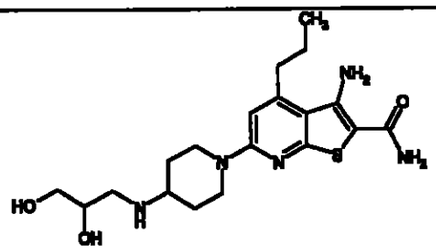
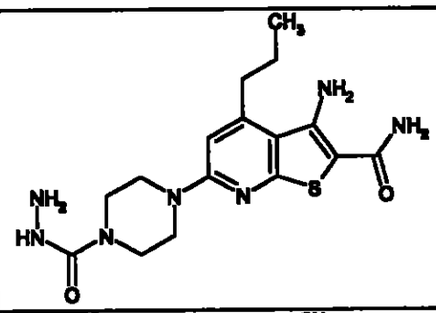
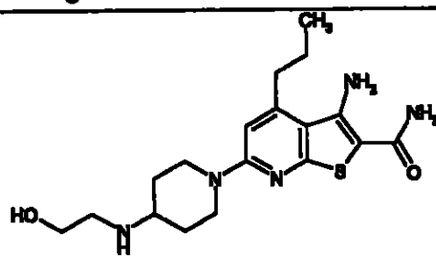
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	3-Amino-6-(3-amino-propylamino)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(3-carbamoyl-piperazin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	6-(4-Acetyl-[1,4]diazepan-1-yl)-3-amino-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

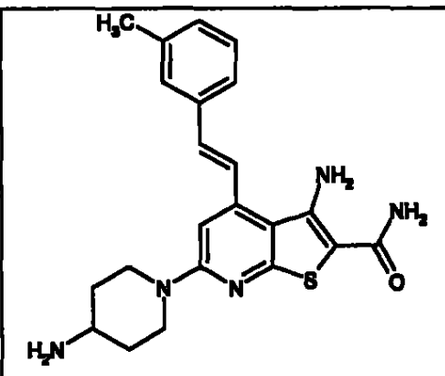
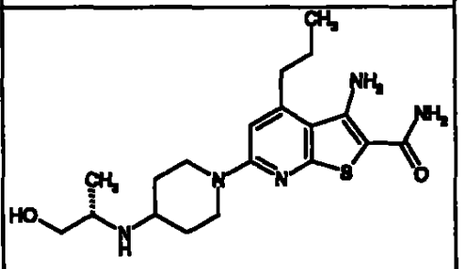
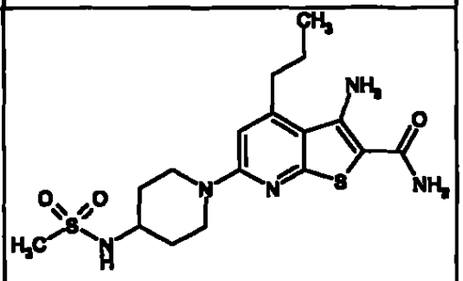
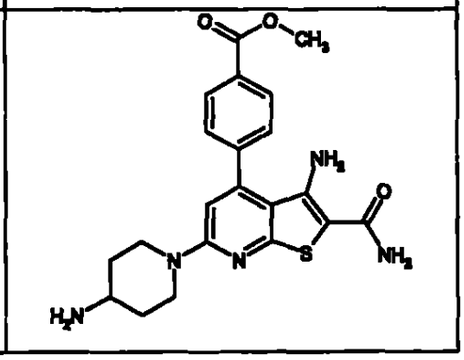
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	3-Amino-6-(3-amino-perhydro-azepin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(3-aminomethyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(2-aminomethyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

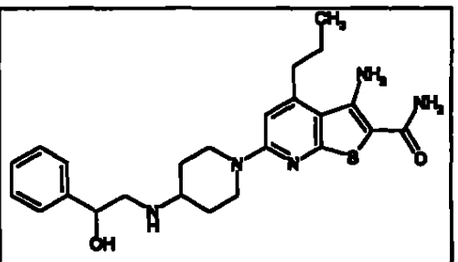
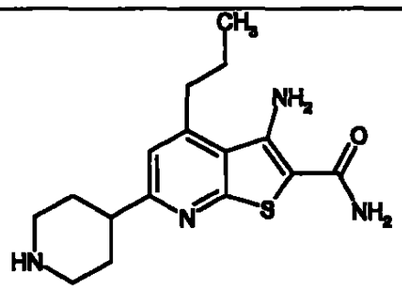
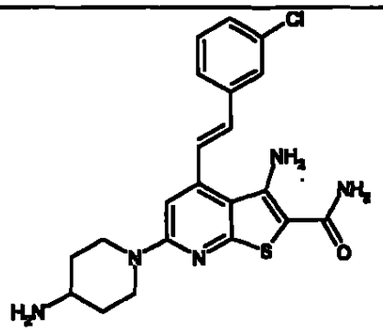
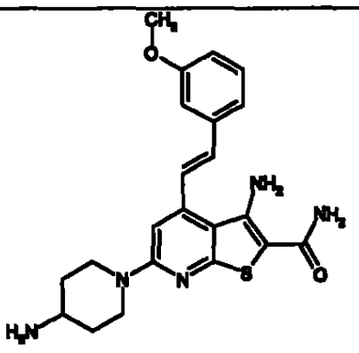
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	3-Amino-6-[4-((S)-2-amino-3-hydroxy-propionyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-carbamoyl-[1,4]diazepan-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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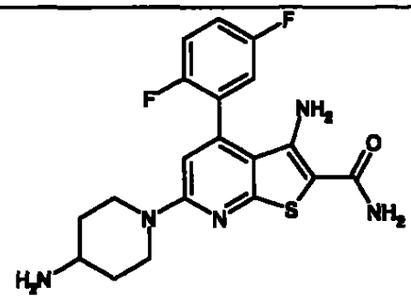
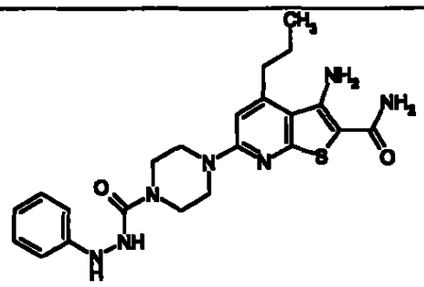
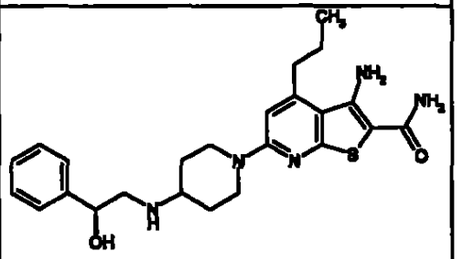
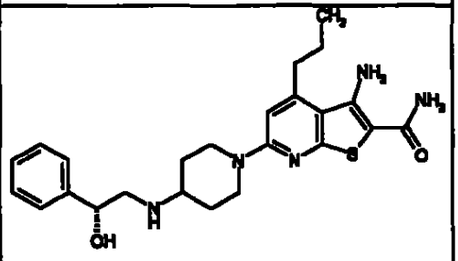
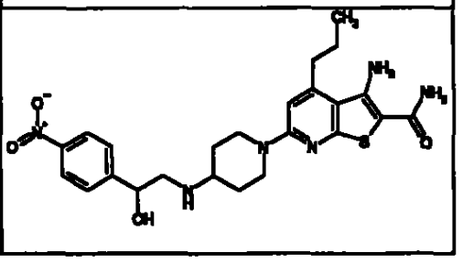
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	3-Amino-6-(4-amino-piperidin-1-yl)-4-[(E)-2-(4-fluoro-phenyl)-vinyl]-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-ethylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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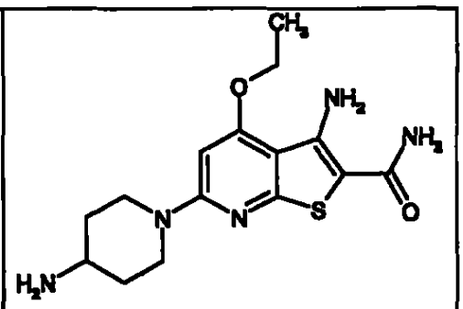
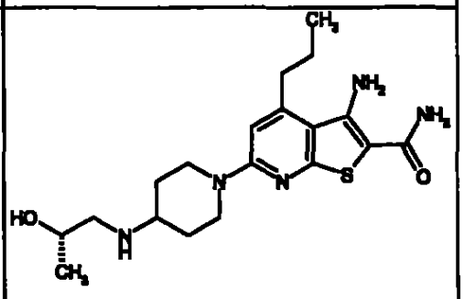
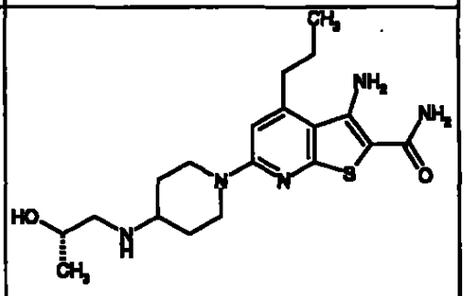
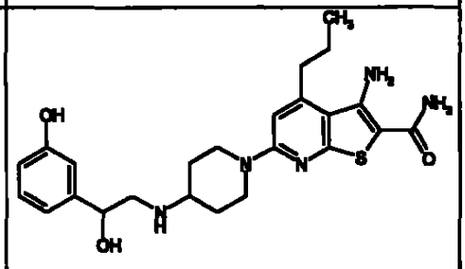
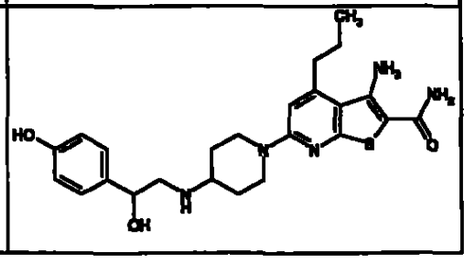
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	3-Amino-6-(4-hydroxyimino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-[(E)-2-(4-trifluoromethyl-phenyl)-vinyl]-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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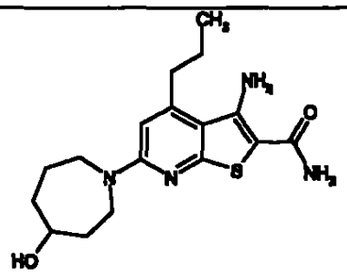
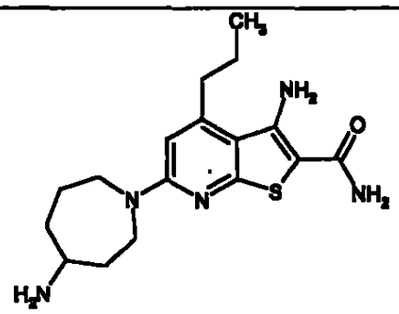
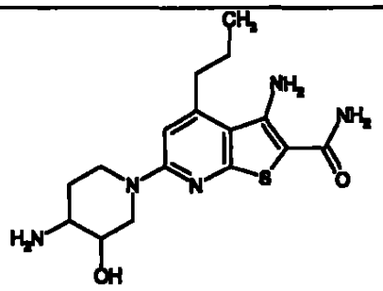
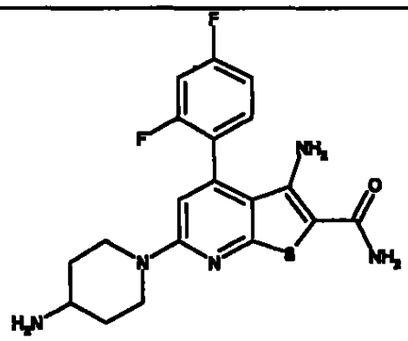
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	3-Amino-6-(4-hydrazinocarbonyl-piperazin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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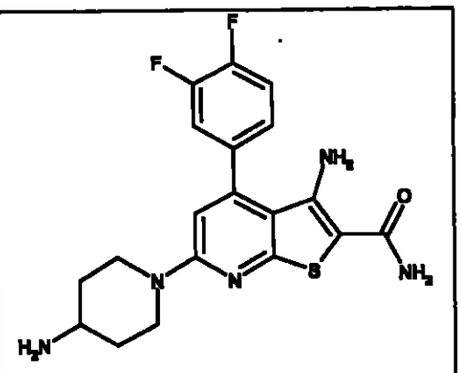
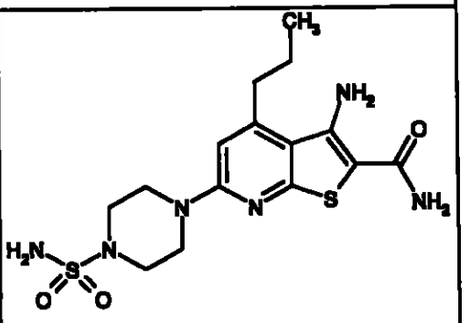
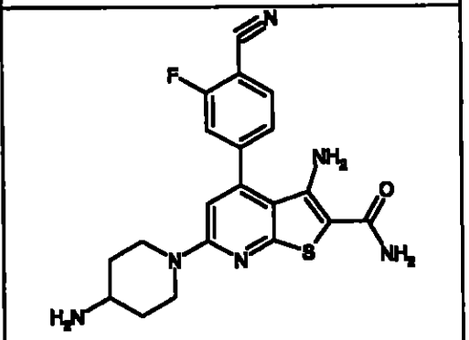
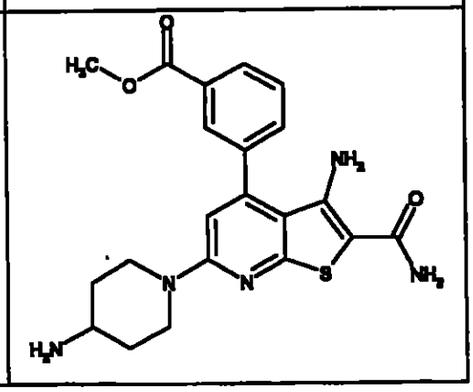
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	3-Amino-6-(4-methanesulfonylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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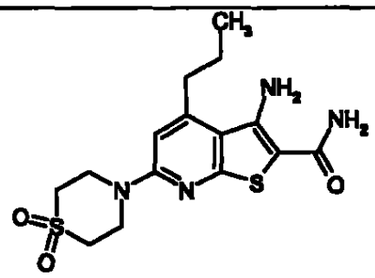
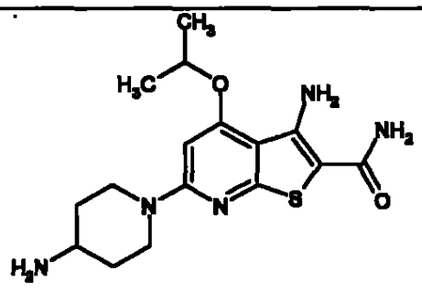
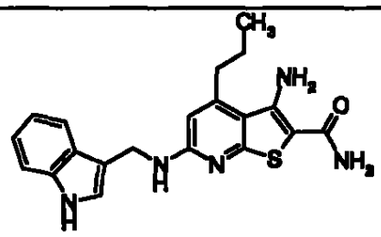
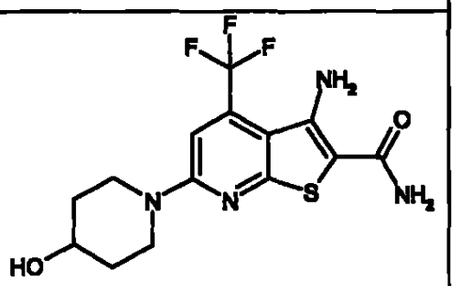
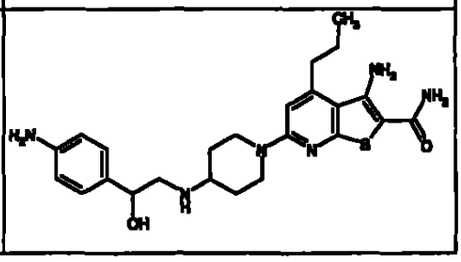
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	3-Amino-6-piperidin-4-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-[(E)-2-(3-chloro-phenyl)-vinyl]-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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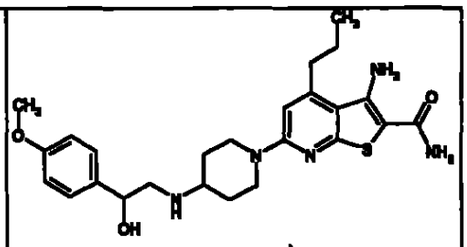
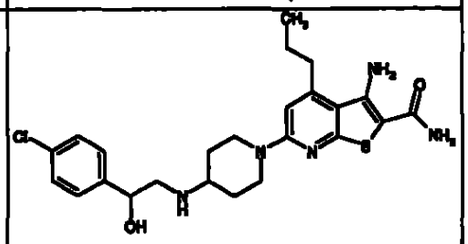
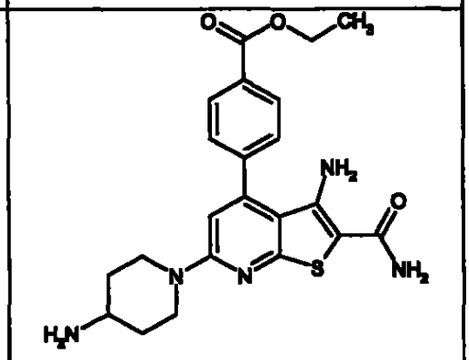
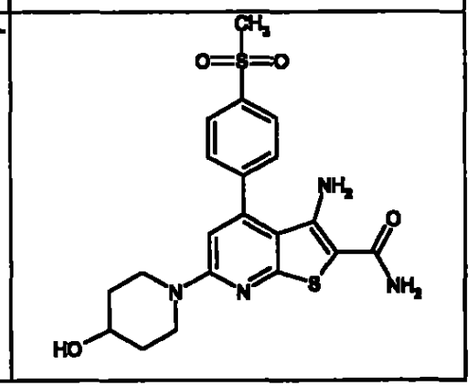
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	3-Amino-6-[4-((S)-2-hydroxy-2-phenyl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[4-((R)-2-hydroxy-2-phenyl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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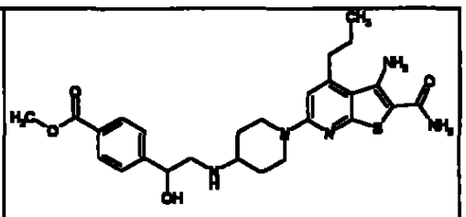
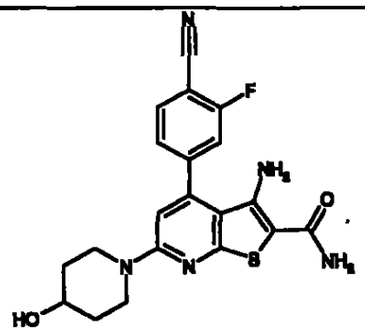
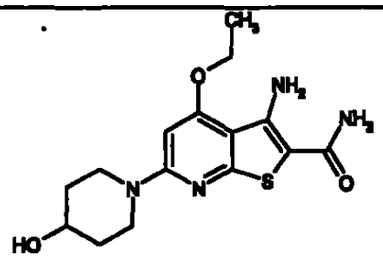
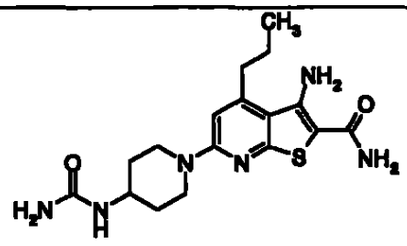
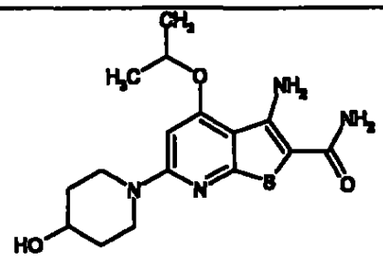
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	3-Amino-6-[4-((R)-2-hydroxy-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[4-((S)-2-hydroxy-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-{4-[2-hydroxy-2-(3-hydroxy-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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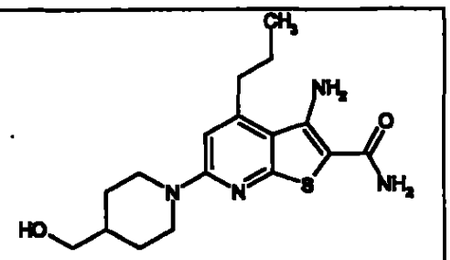
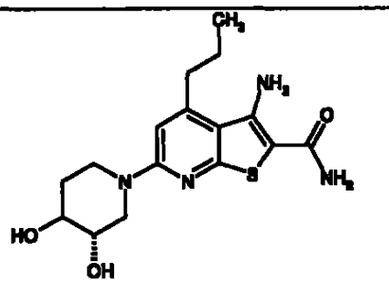
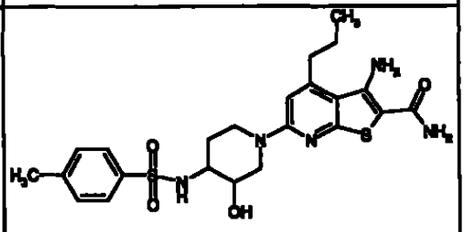
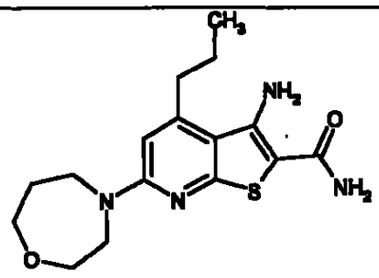
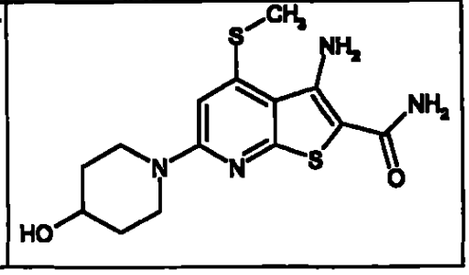
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	3-Amino-6-(4-amino-azepan-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-3-hydroxy-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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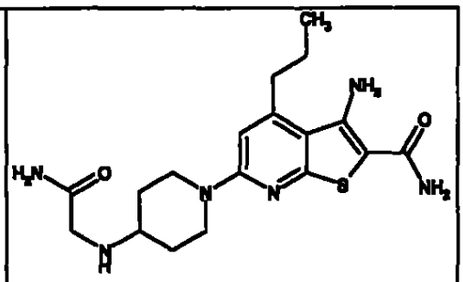
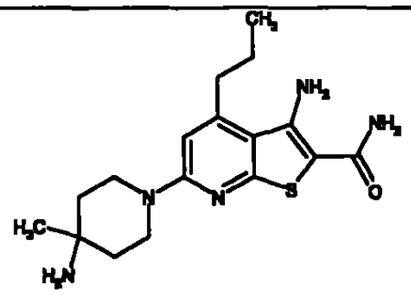
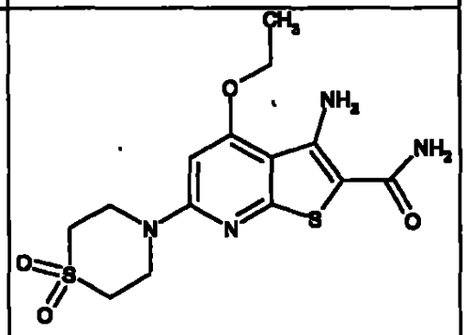
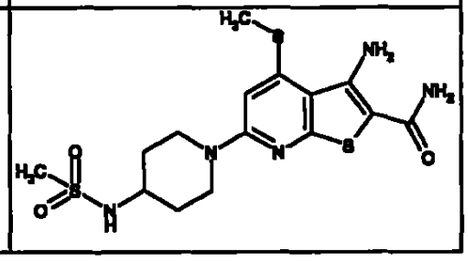
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	3-Amino-4-propyl-6-(4-sulfamoyl-piperazin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-cyano-3-fluoro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-[3-Amino-6-(4-amino-piperidin-1-yl)-2-carbamoyl-thieno[2,3-b]pyridin-4-yl]-benzoic acid methyl ester	

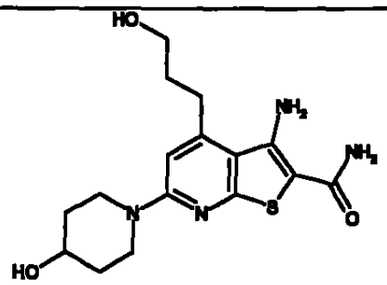
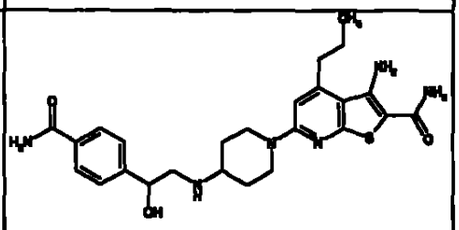
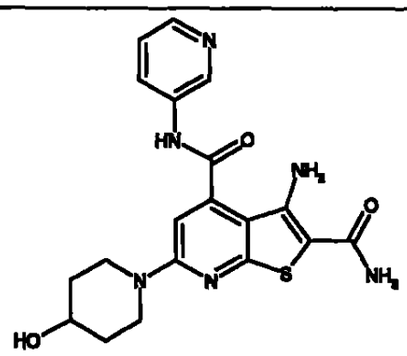
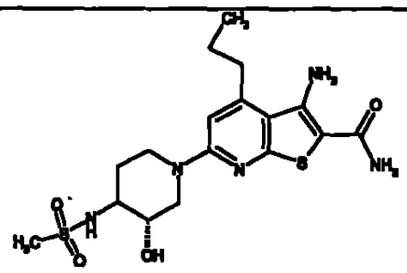
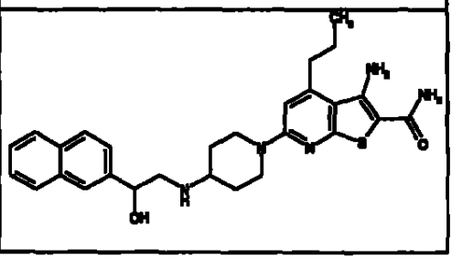
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	3-Amino-6-(4-amino-piperidin-1-yl)-4-isopropoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[(1H-indol-3-ylmethyl)-amino]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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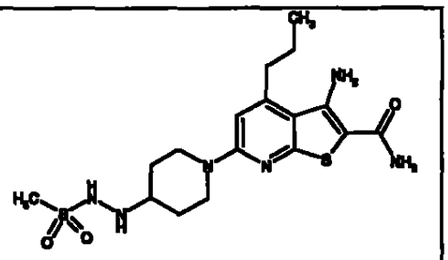
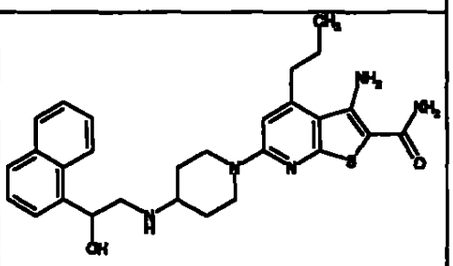
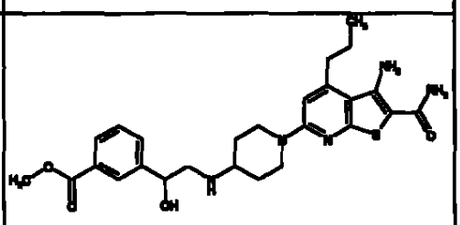
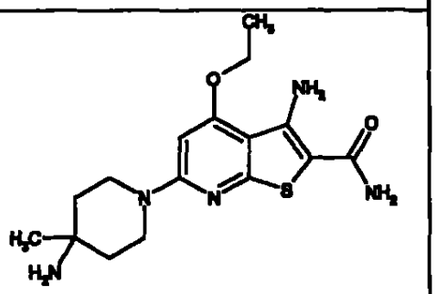
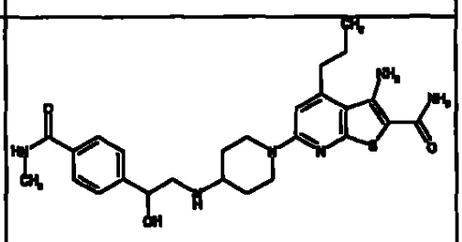
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	3-Amino-6-{4-[2-(4-chloro-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	4-[3-Amino-6-(4-amino-piperidin-1-yl)-2-carbamoyl-thieno[2,3-b]pyridin-4-yl]-benzoic acid ethyl ester	
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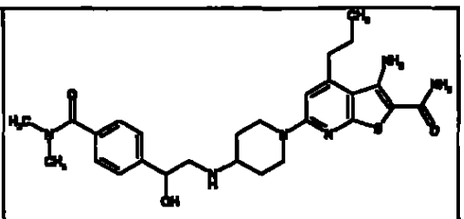
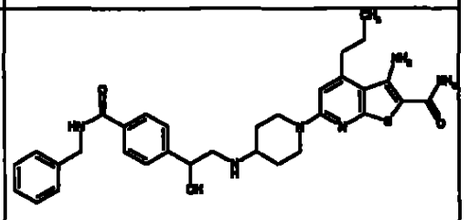
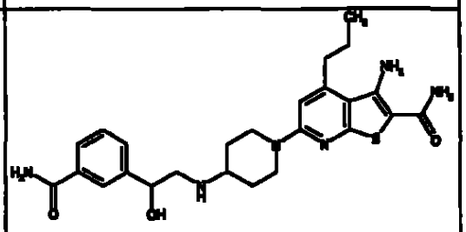
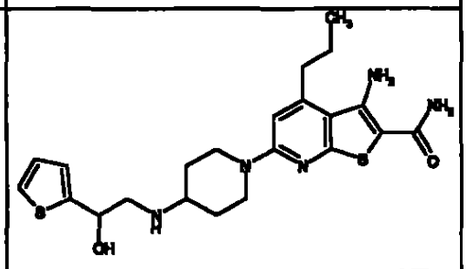
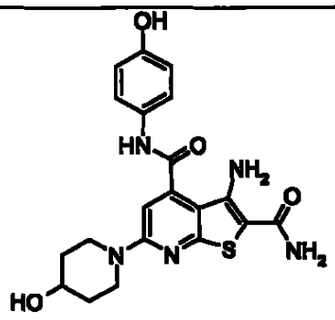
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	3-Amino-4-(4-cyano-3-fluoro-phenyl)-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-4-ethoxy-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-4-propyl-6-(4-ureido-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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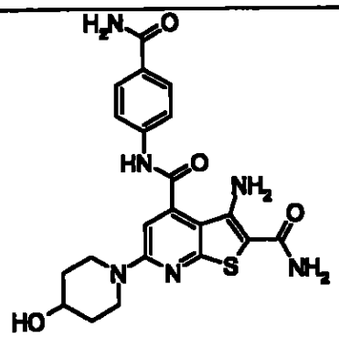
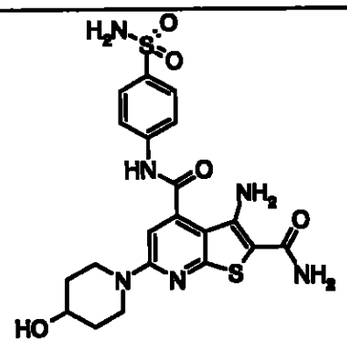
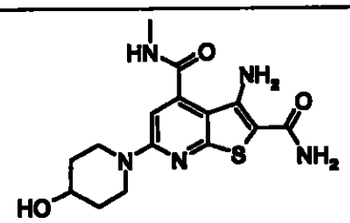
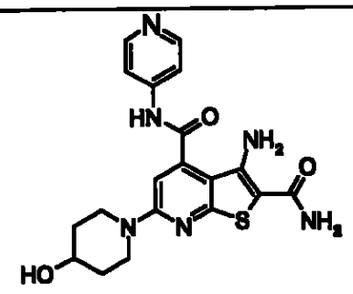
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	3-Amino-6-((S)-3,4-dihydroxy-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[3-hydroxy-4-(toluene-4-sulfonylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[1,4]oxazepan-4-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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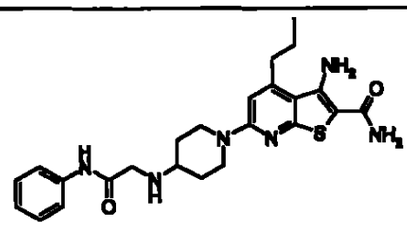
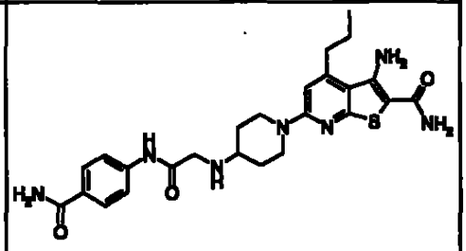
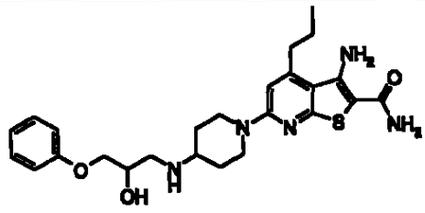
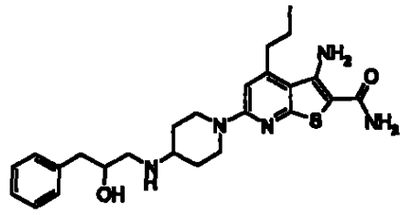
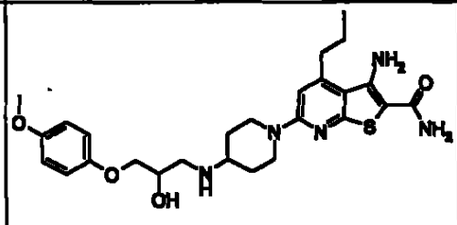
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	3-Amino-6-(1,1-dioxo-thiomorpholin-4-yl)-4-ethoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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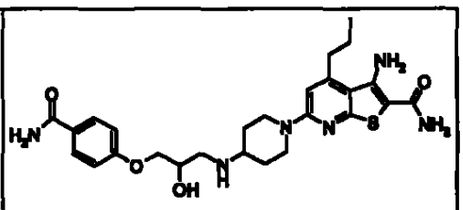
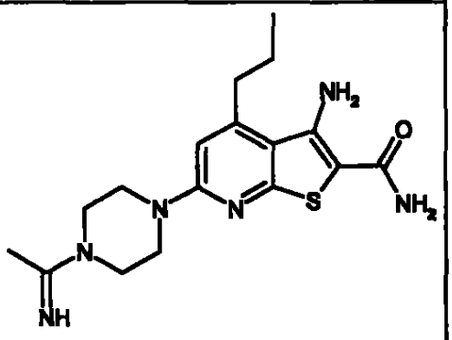
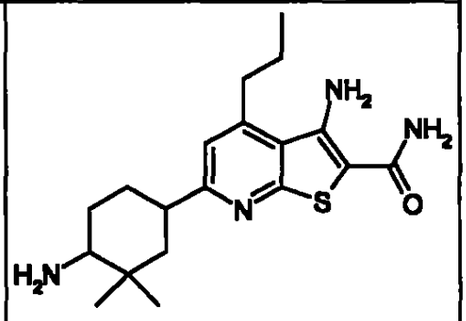
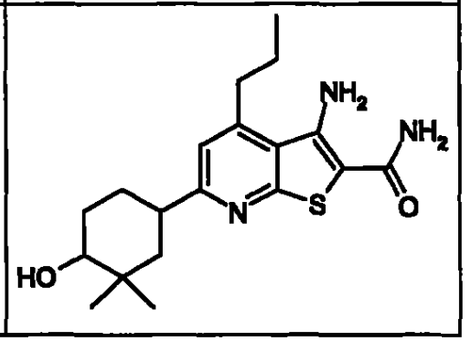
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	3-Amino-6-{4-[2-(4-carbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
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	3-Amino-6-((S)-3-hydroxy-4-methanesulfonylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[4-(2-hydroxy-2-naphthalen-2-yl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

	3-Amino-6-[4-(N'-methylsulfonyl-hydrazino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[4-(2-hydroxy-2-naphthalen-1-yl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-{2-[1-(3-Amino-2-carbamoyl-4-propyl-thieno[2,3-b]pyridin-6-yl)-piperidin-4-ylamino]-1-hydroxy-ethyl}-benzoic acid methyl ester	
	3-Amino-6-(4-amino-4-methyl-piperidin-1-yl)-4-ethoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-{4-[2-hydroxy-2-(4-methylcarbamoyl-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

	3-Amino-6-{4-[2-(4-dimethylcarbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-{4-[2-(4-benzylcarbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-{4-[2-(3-carbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[4-(2-hydroxy-2-thiophen-2-yl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-[(4-hydroxy-phenyl)-amide]	

	3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-[(4-carbamoyl-phenyl)-amide]	
	3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-[(4-sulfamoyl-phenyl)-amide]	
	3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-methylamide	
	3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-pyridin-4-ylamide	

	3-Amino-6-[4-(phenylcarbamoylmethyl-amino)-piperidin-1-yl]-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-{[(4-carbamoyl-phenylcarbamoyl)-methyl]-amino}-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-[4-(2-hydroxy-3-phenoxy-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide	
	3-Amino-6-[4-(2-hydroxy-3-phenyl-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide	
	3-Amino-6-{4-[2-hydroxy-3-(4-methoxy-phenoxy)-propylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide	

	3-Amino-6-{4-[3-(4-carbamoyl-phenoxy)-2-hydroxy-propylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide	
	3-Amino-6-[4-(1-imino-ethyl)-piperazin-1-yl]-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-amino-3,3-dimethyl-cyclohexyl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	
	3-Amino-6-(4-hydroxy-3,3-dimethyl-cyclohexyl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide	

and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof.

For all the compounds disclosed in this application, in the event the nomenclature is in conflict with the structure, it shall be understood that the compound is defined by the structure.

In another embodiment of the invention, there are provided the following compounds:

3-Amino-6-(4-oxo-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-4-cyano-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-methylsulfanyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-((E)-styryl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-nitro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[1,4]diazepan-1-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(2,4-diamino-butanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-[(E)-2-(4-methoxy-phenyl)-vinyl]-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(2-aminomethyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-piperazin-1-yl-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-((E)-2-p-tolyl-vinyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(2,3-dihydroxy-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(2-hydroxy-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-((E)-2-m-tolyl-vinyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-methanesulfonylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

4-[3-Amino-6-(4-amino-piperidin-1-yl)-2-carbamoyl-thieno[2,3-b]pyridin-4-yl]-benzoic acid methyl ester;

3-Amino-6-[4-(2-hydroxy-2-phenyl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-piperidin-4-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-(2,5-difluoro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(N'-phenyl-hydrazinocarbonyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-((S)-2-hydroxy-2-phenyl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-((R)-2-hydroxy-2-phenyl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-hydroxy-2-(4-nitro-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-ethoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-((S)-2-hydroxy-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-((S)-2-hydroxy-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-hydroxy-2-(3-hydroxy-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-hydroxy-2-(4-hydroxy-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-azepan-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-3-hydroxy-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-(2,4-difluoro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-cyano-3-fluoro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-isopropoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[(1H-indol-3-ylmethyl)-amino]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(4-amino-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-hydroxy-2-(4-methoxy-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(4-chloro-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

4-{2-[1-(3-Amino-2-carbamoyl-4-propyl-thieno[2,3-b]pyridin-6-yl)-piperidin-4-ylamino]-1-hydroxy-ethyl}-benzoic acid methyl ester;

3-Amino-4-(4-cyano-3-fluoro-phenyl)-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-4-ethoxy-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-4-propyl-6-(4-ureido-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-((S)-3,4-dihydroxy-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-methylsulfanyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-(3-hydroxy-propyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(4-carbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-pyridin-3-ylamide;

3-Amino-6-((S)-3-hydroxy-4-methanesulfonylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(2-hydroxy-2-naphthalen-2-yl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(N'-methylsulfonyl-hydrazino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(2-hydroxy-2-naphthalen-1-yl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-{2-[1-(3-Amino-2-carbamoyl-4-propyl-thieno[2,3-b]pyridin-6-yl)-piperidin-4-ylamino]-1-hydroxy-ethyl}-benzoic acid methyl ester;

3-Amino-6-(4-amino-4-methyl-piperidin-1-yl)-4-ethoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-hydroxy-2-(4-methylcarbamoyl-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(4-dimethylcarbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(4-benzylcarbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(3-carbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-[(4-hydroxy-phenyl)-amide];

3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-[(4-carbamoyl-phenyl)-amide];

3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-[(4-sulfamoyl-phenyl)-amide];

3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-pyridin-4-ylamide;

3-Amino-6-[4-(2-hydroxy-3-phenoxy-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(2-hydroxy-3-phenyl-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-hydroxy-3-(4-methoxy-phenoxy)-propylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[3-(4-carbamoyl-phenoxy)-2-hydroxy-propylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-3,3-dimethyl-cyclohexyl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof.

The invention includes pharmaceutically acceptable derivatives of compounds of formula (I). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable

acid, salt or ester of a compound of this invention, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound of this invention, a pharmacologically active metabolite or pharmacologically active residue thereof.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of this invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and *N*-$(C_1\text{-}C_4$ alkyl$)_4^+$ salts.

In addition, the compounds of this invention include prodrugs of compounds of the formula (I). Prodrugs include those compounds that, upon simple transformation, are modified to produce the compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction which occur enzymatically, metabolically or otherwise. Specifically, when a prodrug of this invention is administered to a patient, the prodrug may be transformed into a compound of formula (I), thereby imparting the desired pharmacological effect.

Any compounds of this invention containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration, or a combination of configurations.

Some of the compounds of the invention can exist in more than one tautomeric form. The invention includes all such tautomers.

The compounds of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated by the invention.

As used herein, the following abbreviations are used:

DMF is dimethylformamide;
DMSO is dimethyl sulfoxide
EtOAc is ethyl acetate;
EtOH is ethanol;
HPLC is high-performance liquid chromatography
MeOH is methanol;
THF is tetrahydrofuran;
TLC is thin layer chromatography

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. For example, "C_{1-6}alkoxy" is a C_{1-6}alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, pentoxy and hexoxy. All alkyl, alkylene or alkynyl groups shall be understood as being branched, unbranched unless otherwise specified. Other more specific definitions are as follows:

The term "alkyl" refers to a saturated aliphatic radical containing from one to ten carbon atoms or a mono- or polyunsaturated aliphatic hydrocarbon radical containing from two to twelve carbon atoms unless otherwise stated. The mono- or polyunsaturated aliphatic hydrocarbon radical contains at least one double or triple bond, respectively. "Alkyl" refers to both branched and unbranched alkyl groups. Examples of "alkyl" include alkyl groups which are straight chain alkyl groups containing from one to eight carbon atoms and branched alkyl groups containing from three to ten carbon atoms. Other examples include

lower alkyl groups which are straight chain alkyl groups containing from one to six carbon atoms and branched alkyl groups containing from three to six carbon atoms. It should be understood that any combination term using an "alk" or "alkyl" prefix refers to analogs according to the above definition of "alkyl". For example, terms such as "alkoxy", "alkythio" refer to alkyl groups linked to a second group via an oxygen or sulfur atom. "Alkanoyl" refers to an alkyl group linked to a carbonyl group (C=O). Each alkyl or alkyl analog described herein shall be understood to be optionally partially or fully halogenated.

The term "cycloalkyl" refers to the cyclic analog of an alkyl group, as defined above. Examples of cycloalkyl groups are saturated or unsaturated nonaromatic cycloalkyl groups containing from three to eight carbon atoms, and other examples include cycloalkyl groups having three to six carbon atoms.

The term "heterocycloalkyl" refers to a stable 4-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated, and is non-aromatic. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Examples of "heterocycloalkyl" include radicals such as pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, azetidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, hexahydropyrimidinyl, hexahydropyridazinyl, dihydro-oxazolyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide and imidazolidinyl-2,4-dione.

The term "halogen" refers to bromine, chlorine, fluorine or iodine.

The term "aryl" shall be understood to mean a 6-12 membered aromatic carbocycle, which can be a single ring or can be multiple rings fused together or linked covalently. The term "aryl" includes, for example, phenyl and naphthyl; other terms comprising "aryl" will have the same definition for the aryl component, examples of these moieties include: arylalkyl, aryloxy or arylthio.

The term "heteroaryl" refers to a stable 5-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic aromatic heterocycle radical. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heteroaryl group may be attached by any atom of the ring which results in the creation of a stable structure. Examples of "heteroaryl" include radicals such as furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl and phenoxazinyl.

The terms "optional" or "optionally" mean that the subsequently described event or circumstances may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

The term "substituted" means that any one or more hydrogens on an atom of a group or moiety, whether specifically designated or not, is replaced with a selection from the indicated group of substituents, provided that the atom's normal valency is not exceeded and that the substitution results in a stable compound. If a bond to a substituent is shown to cross the bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound, then such substituent may be bonded via any atom in such substituent. For example, when the substituent is piperazinyl, piperidinyl, or tetrazolyl, unless specified otherwise, such piperazinyl, piperidinyl, or tetrazolyl group may be bonded to the rest of the compound of the invention via any atom in such piperazinyl, piperidinyl, or tetrazolyl group. Generally, when any substituent or group occurs more than one time in any constituent or compound, its definition on each occurrence is independent of its definition at every other occurrence. Thus, for example, if

a group is shown to be substituted with 0 to 2 R, then such group is optionally substituted with up to two R groups and R at each occurrence is selected independently from the defined list of possible R. Such combinations of substituents and/or variables, however, are permissible only if such combinations result in stable compounds.

As used herein above and throughout this application, "nitrogen" and "sulfur" include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen.

Methods of Therapeutic Use

In accordance with the invention, there are provided novel methods of using the compounds of the formula (I). The compounds of the invention are effective in inhibiting the activity of IKKβ and/or IKKα. In particular, these compounds are useful in blocking disease processes exacerbated by IKKβ-mediated NF-κB activation and IKKα activation of B cell activity or the cell cycle regulatory gene Cyclin D1. In blocking NF-κB activation, compounds of the invention effectively block transcription of genes encoding inflammatory cytokines including IL-1, IL-2, IL-6, IL-8, TNFα, chemokines including IL-8 and RANTES as well as other pro-inflammatory molecules including COX-2 and cell adhesion molecules such as ICAM-1, VCAM-1 and E-selectin. These mediators play a key role in the etiology of inflammatory, autoimmune and cardiovascular disorders and cancer. Preventing the production of these mediators is a desirable means for treating these disorders. Thus there are provided methods for treating these conditions using the compounds of the invention. Such inflammatory and autoimmune conditions include but are not limited to osteoarthritis, reperfusion injury, asthma, chronic obstructive pulmonary disease (COPD), multiple sclerosis, Guillain-Barre syndrome, Crohn's disease, ulcerative colitis, psoriasis, graft versus host disease, systemic lupus erythematosus, rheumatoid arthritis, Alzheimer's disease, toxic shock syndrome, insulin-dependent diabetes mellitis, acute and chronic pain, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute glomerulonephritis, dermatoses with acute inflammatory components, acute purulent meningitis or other central nervous system disorders, Grave's disease, myasthenia gravis, scleroderma and atopic dermatitis. Such

cardiovascular disorders include but are not limited to atherosclerosis, myocardial infarction and stroke. Such cancers include but are not limited to lymphoid-, myeloid- and epithelial-derived malignancies including leukemia, lymphomas and breast, gastric, colorectal, lung, and pancreatic cancers. The compounds of the invention can also be used to treat other disorders associated with IKK activation of NF-κB unrelated to those listed above or discussed in the Background of the Invention. For example, the compounds of the invention may also be useful in the treatment of cancer by enhancing the effectiveness of chemotherapeutic agents. Therefore, the invention also provides methods of treating inflammatory and autoimmune diseases, and other diseases including cancer, comprising administering to a patient in need of such treatment a pharmaceutically effect amount of a compound according to the invention.

For therapeutic use, the compounds of the invention may be administered in any conventional dosage form in any conventional manner. Routes of administration include, but are not limited to, intravenously, intramuscularly, subcutaneously, intrasynovially, by infusion, sublingually, transdermally, orally, topically or by inhalation. The preferred modes of administration are oral and intravenous. Compositions comprising the compounds of the invention for each of the aforementioned routes of administration will be apparent to the skilled artisan. The invention also provides for pharmaceutical compositions including a therapeutically effective amount of the compounds according to the invention. Such pharmaceutical compositions will include pharmaceutically acceptable carriers and adjuvants as further described below.

The compounds of this invention may be administered alone or in combination with adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients. Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. Compounds of the invention may be physically combined with the conventional therapeutics or other

adjuvants into a single pharmaceutical composition. Advantageously, the compounds may then be administered together in a single dosage form. In some embodiments, the pharmaceutical compositions comprising such combinations of compounds contain at least about 15%, but more preferably at least about 20%, of a compound of the invention (w/w) or a combination thereof. Alternatively, the compounds may be administered separately (either serially or in parallel). Separate dosing allows for greater flexibility in the dosing regime.

As mentioned above, dosage forms of the compounds of this invention include pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art. These carriers and adjuvants include, for example, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes and cellulose-based substances. Preferred dosage forms include, tablet, capsule, caplet, liquid, solution, suspension, emulsion, lozenges, syrup, reconstitutable powder, granule, suppository and transdermal patch. Methods for preparing such dosage forms are known (see, for example, H.C. Ansel and N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)). Dosage levels and requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. In some embodiments, dosage levels range from about 10-1000 mg/dose for a 70 kg patient. Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 2000 mg/day may be required. As the skilled artisan will appreciate, lower or higher doses may be required depending on particular factors. For instance, specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto, and the judgment of the treating physician.

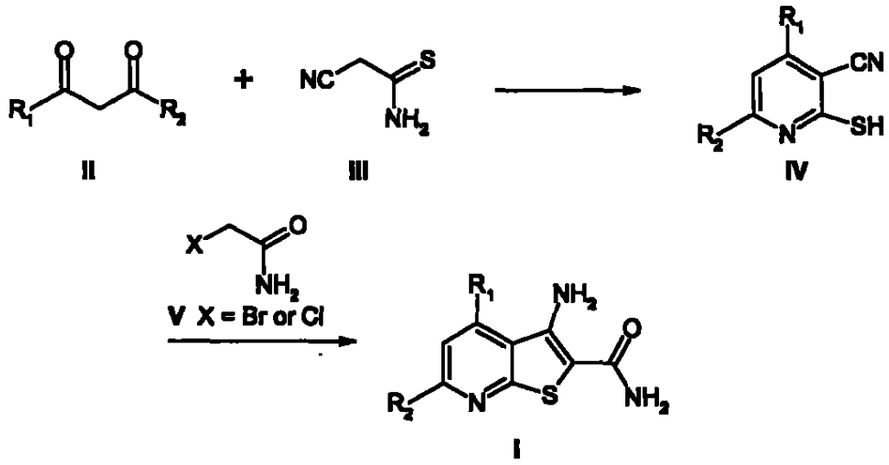
SYNTHETIC METHODS

The invention additionally provides for methods for making the compounds of the

formula (I). The compounds of the invention may be prepared by the general methods and examples presented below, and methods known to those of ordinary skill in the art. Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Reaction progress may be monitored by conventional methods such as thin layer chromatography (TLC). Intermediates and products may be purified by methods known in the art, including column chromatography, HPLC or recrystallization.

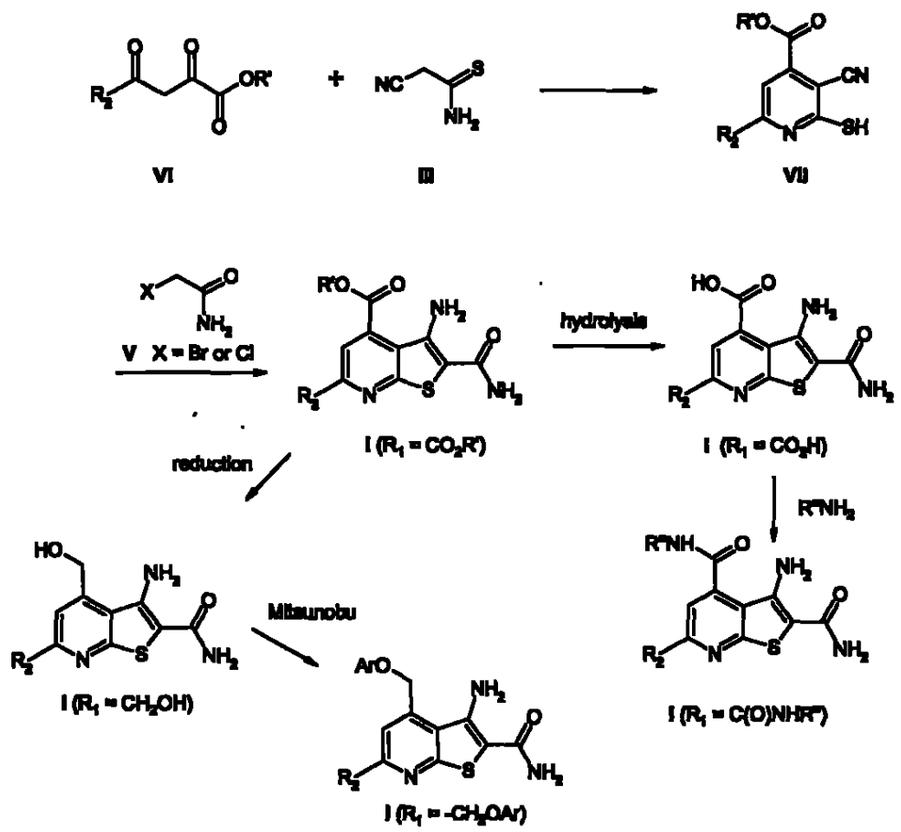
As illustrated in Scheme I, compounds of formula (I) may be prepared starting with a 1,3-dione bearing substituents R_1 and R_2 (II). Reaction of II with cyanothioacetamide (III) in a suitable solvent such as EtOH, in the presence of a suitable base such as triethylamine provides the substituted 2-mercaptonicotinonitrile IV. Reaction of IV with chloro- or bromoacetamide (V), in a suitable solvent such as DMF, THF or EtOH, in the presence of a suitable base such as sodium carbonate, sodium hydroxide or sodium ethoxide, provides the desired compound of formula (I). Substituents R_1 and R_2 may be further modified by methods known in the art to produce additional compounds of the invention.

Scheme I



For example, as illustrated in Scheme II, beginning with a diketo ester VI and using the procedure outlined above, one obtains ester I ($R_1 = CO_2R'$, where R' is an alkyl group such as methyl or ethyl). By using methods known in the art, R_1 may be modified to make other desired R_1. For example, hydrolysis provides the carboxylic acid I ($R_1 = CO_2H$) and reaction of the carboxylic acid with an amine $R''NH_2$ under standard coupling conditions provides the amide I ($R_1 = C(O)NHR''$). Alternatively, reduction of the ester with a suitable reducing agent such as lithium aluminum hydride provides an alcohol I ($R_1 = CH_2OH$). Reaction of the alcohol with a phenol ArOH under Mitsunobu conditions provides the aryl ether I ($R_1 = CH_2OAr$). These and other modifications are described in the Synthetic Examples section.

Scheme II



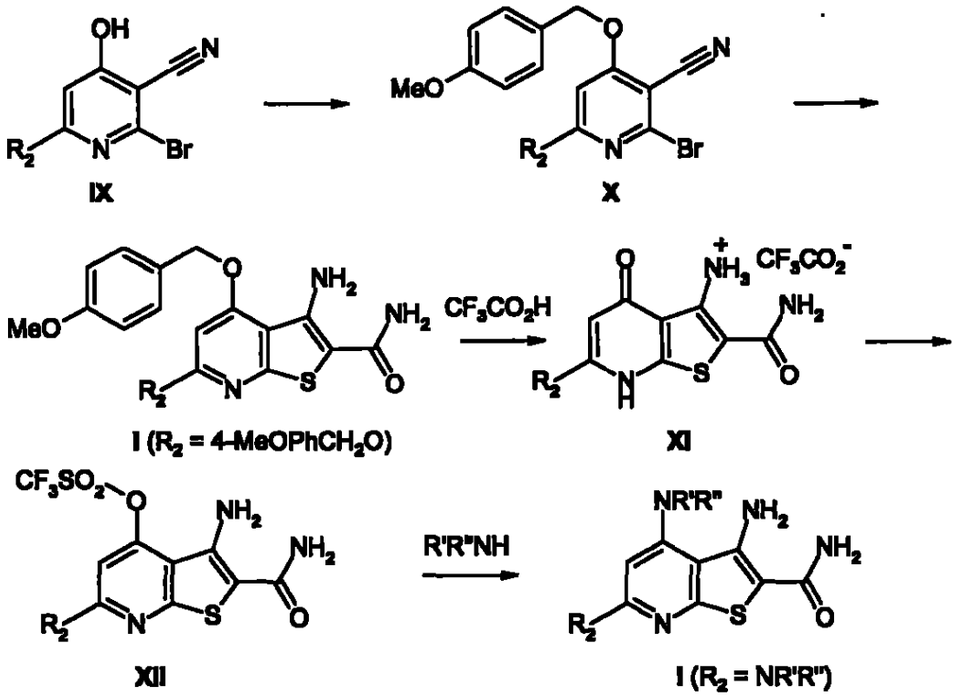
In a modification of the above procedure for preparing VII, one may begin with a 2-chloro or 2-bromo-3-cyano-isonicotinic acid ester (VIII, Scheme III). The 2-halo group may then be converted to a 2-mercapto group by methods known in the art, for example by reaction with thiourea in a suitable solvent such as EtOH providing the ester intermediate VII.

Scheme III



Scheme IV illustrates a procedure by which one may obtain compounds of formula (I) having an amine at R_1. 2-Bromo-4-hydroxy-nicotinonitrile (IX) is treated with 4-methoxybenzyl chloride in the presence of a suitable base such as sodium hydride in a suitable solvent such as DMF to provide the 4-methoxybenzyl ether X. This may then be converted to the 2-mercapto compound as described above in Scheme III. The resulting mercapto compound may then be reacted with a haloacetamide as described in Schemes I and II to provide I (R_1 = 4-methoxybenzyl ether). Alternatively, one may react X with mercaptoacetamide in the presence of a suitable base such as sodium hydride in a suitable solvent such as DMF to provide I (R_1 = 4-methoxybenzyl ether) directly. Treatment of the ether with trifluoroacetic acid provides the salt XI. Reaction of XI with N-phenyltrifluoromethanesulfonimide in the presence of a suitable base such as diisopropylethylamine in a suitable solvent such as dioxane provides the trifluoromethanesulfonate XII. Reaction of XII with an amine R'R''NH in a suitable solvent such as dioxane provides I (R_1 = NR'R''). The reaction may optionally be heated for less reactive amines such as aryl amines.

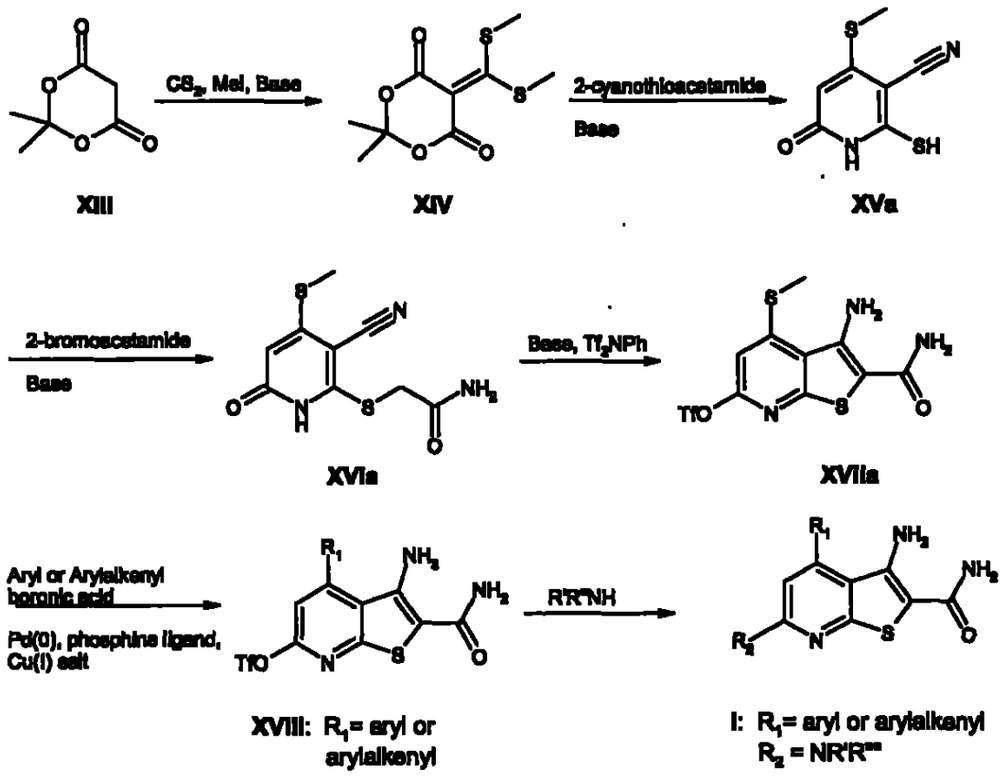
Scheme IV



A procedure that may be used to introduce a variety of aryl or arylalkenyl groups at R_1 and nucleophiles such as amines at R_2 is illustrated in Scheme V. Meldrum's acid (XIII) is treated with carbon disulfide, methyl iodide and a suitable base such as triethylamine, in a suitable solvent such as DMSO to provide the bis-methylsulfanylmethylene-dione XIV. Treatment of XIV with 2-cyanothioacetamide under suitable alkaline conditions such as sodium ethoxide in ethanol provides nitrile XVa. Reaction of XVa with 2-chloro or 2-bromoacetamide in the presence of a suitable base such as sodium hydride in a suitable solvent such as DMF provides XVIa. Cyclization to the triflate intermediate XVIIa may be achieved by reacting XVI with N-phenyltrifluoromethane-sulfonimide in the presence of a suitable base such as sodium hydride in a suitable solvent such as DMF. Reaction of XVIIa with the desired aryl boronic acid or arylalkenyl boronic acid in the presence of a suitable palladium catalyst, preferably tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct, a phosphine ligand, preferably tri-2-furylphosphine and a copper salt, preferably copper(I)thiophene-2-carboxylate, in a suitable solvent such as THF, provides

the desired aryl or arylalkenyl intermediate XVIII. Reaction of XVIII with the desired nucleophile such as an amine R'R"NH as shown, in a suitable solvent such as dioxane, provides the desired compound of formula (I). Alcohols (R'OH) or thiols (R'SH) in the presence of a suitable base could be used in place of an amine to obtain ethers or thioethers respectively at R_2.

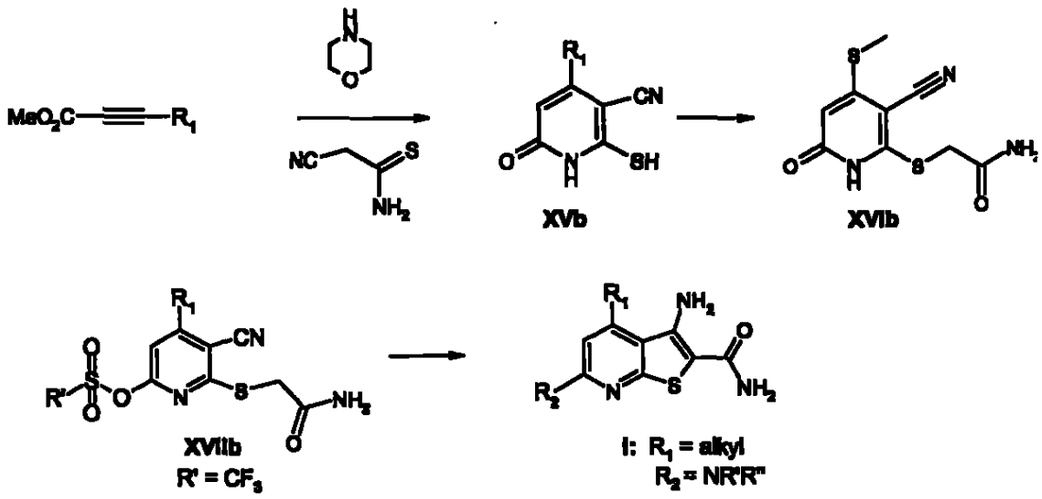
Scheme V



A modification of the above procedure that will provide an alkyl group at R_1 is illustrated in Scheme VI. An alkynoate ester, such as the methyl ester shown, is reacted with 2-cyanothioacetamide in the presence of a suitable base such as morpholine in a suitable solvent such as ethanol to provide XVb. Treatment of XVb as described for conversion of XVa to XVIa in Scheme V above provides XVIb. Reaction of XVIb with a suitable sulfonating reagent such as N-phenyltrifluoromethane-sulfonimide in the presence of a suitable base such as diisopropylethylamine in a suitable solvent such as dioxane provides

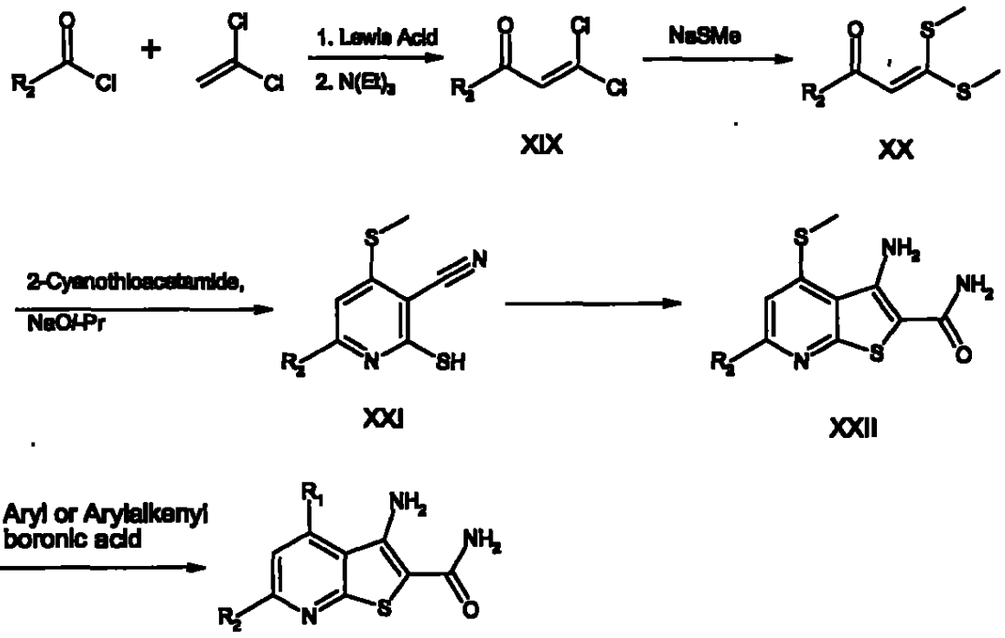
the sulfonyl ester XVIIb (R' = CF_3 in this case). Reaction of XVIIb with the desired nucleophile, such as an amine in the presence of a suitable base such as triethylamine, optionally while heating at about 50 °C to 100 °C results in displacement of the sulfonyl ester by the nucleophile. Cyclization *in situ* may be achieved by adding a second suitable base such as aqueous sodium carbonate followed by continued heating to provide the desired compound of formula (I).

Scheme VI



Another procedure that will provide aryl or arylalkenyl groups at R_1 and a variety of groups, such as aryl and alkyl, at R_2 is illustrated in Scheme VII. As illustrated in Scheme VII, an acid chloride bearing R_2 is reacted with vinylidene chloride in the presence of a Lewis acid such as $AlCl_3$, in a suitable solvent such as methylene chloride, followed by treatment with a suitable base such as triethylamine to provide XIX. Reaction of XIX with sodium thiomethoxide provides XX. Treatment of XX with 2-cyanothioacetamide in the presence of a suitable base such as sodium isopropoxide provides XXI. Reaction of XXI with 2-bromo or 2-chloroacetamide as described in Scheme I provides XXII. Treatment of XXII with an arylboronic acid or arylalkenylboronic acid as described in Scheme V provides the desired compound of formula (I).

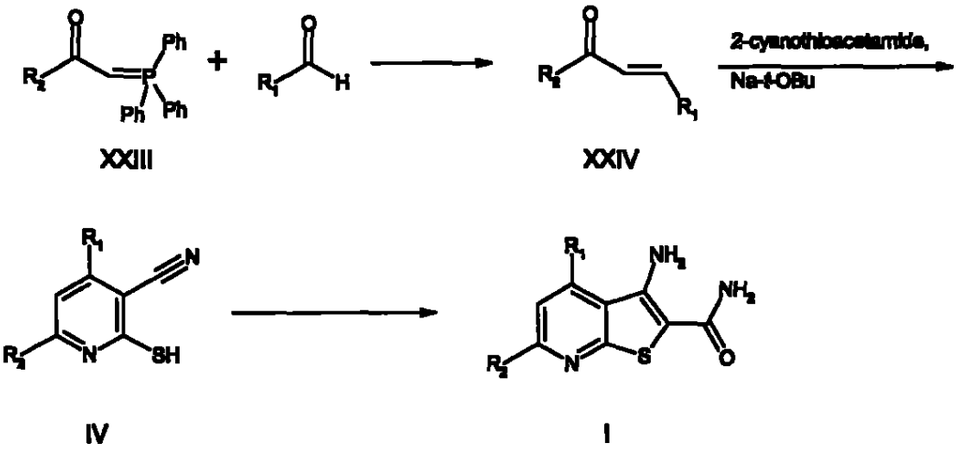
Scheme VII



I: R_1 = Aryl or Arylalkenyl

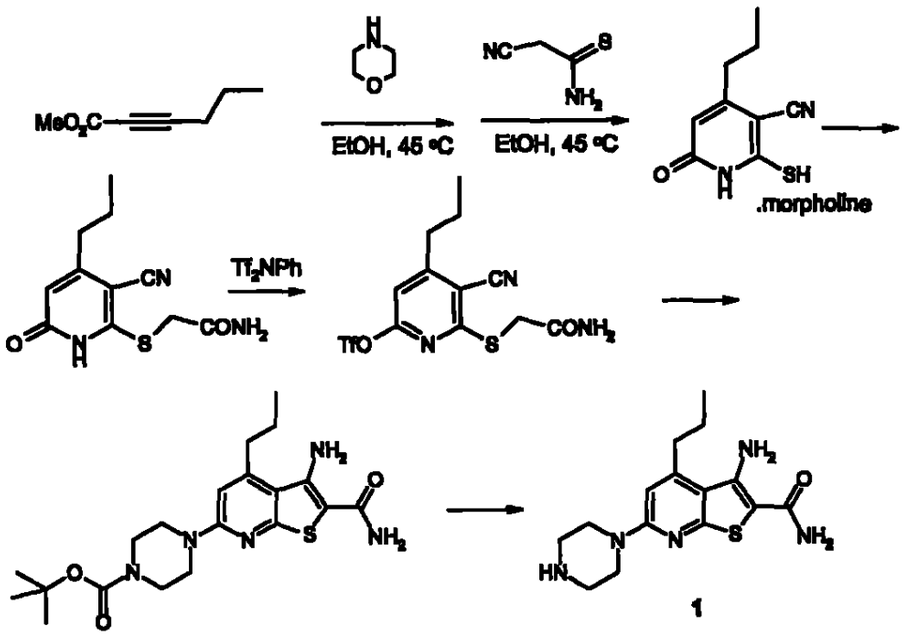
An additional procedure that may be used to prepare compounds of formula (I) is illustrated in Scheme VII. An aldehyde bearing R_1 is reacted with a triphenylphosphoranylidene bearing R_2 (XXIII) in the presence of a suitable acid such as acetic acid, in a suitable solvent such as toluene, to provide the alpha, beta-unsaturated ketone XXIV. Treatment of XXIV with 2-cyanothioacetamide in the presence of a suitable base such as soduim *t*-butoxide provides IV. This is converted to I as described in Scheme I.

Scheme VIII



SYNTHETIC EXAMPLES

Example 1: Synthesis of 3-amino-6-piperazin-1-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide



To a solution of methyl 2-hexynoate (15 g, 0.119 mol) in EtOH (40 mL) was added morpholine (10.5 g, 0.120 mol) dropwise at room temperature. The solution was then warmed to 45 °C for 4 h under nitrogen. Solid $NCCH_2C(S)NH_2$ (12.1 g, 0.120 mol) was then added in small portions. After stirring at 45 °C for 30 min, the mixture was stirred at room temperature overnight. The yellow precipitate was collected by filtration, giving 10.9 g of the desired mercaptopyridone as a complex with 1 molecule of morpholine.

A mixture of the above mercaptopyridone (5.25g, 18.68 mmol), 2-bromoacetamide (2.58 g, 18.68 mmol) and K_2CO_3 (2.58 g, 18.68 mmol) in dry DMF (50 mL) was heated under Ar at 70 °C for 4 h. The mixture was then cooled to 0 °C, and acidified to pH ~ 2 with 6 N HCl (~ 3 mL). The mixture was kept at 0 °C for 2 h, and the resulting white precipitate was collected by filtration. The product was washed with cold water to give 5.5 g of the desired mercaptoacetamide

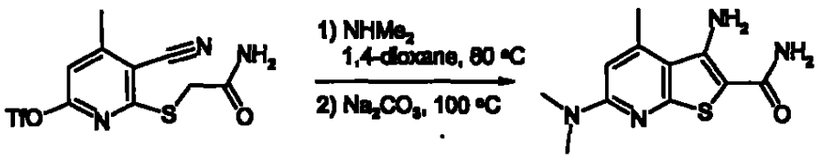
To a mixture of the above mercaptoacetamide (4.15 g, 16.54 mmol)) and iPr_2NEt (4.6 mL, 32.82 mmol) in dry dioxane (40 mL) was added in small portions N-phenyltrfluoromethane-sulfonimide (5.91 g, 16.54 mmol). The mixture was stirred under nitrogen for 16 h, concentrated and purified by silica gel column chromatography eluting with 50-80% EtOAc-hexane (gradient) to give 4.7 g of the desired 2-(3-cyano-4-*n*-propyl - 6-trifluoromethanesulfonylpyridin-2-ylmercapto)acetamide.

To a solution of 600 mg (1.57 mmol) of the above acetamide was added 542.4 mg (2.86 mmol) of 1-Boc-piperazine and 379.8 microL (2.72 mmol) of triethylamine. The resulting mixture was stirred for 2 h at 100 °C. A 2 M solution (4 mL) of sodium carbonate was then added. The stirring was continued overnight at 100 °C. The reaction mixture was then diluted with EtOAc, dried with sodium sulfate and concentrated. The crude product was chromatographed (preparative TLC on silica gel eluting with 10% MeOH/dichloromethane, rf=0.75) to afford 408.4mg (62.2%) of the desired N-Boc-piperazine intermediate.

To a suspension of 408.4 mg (0.97 mmole) of the above N-Boc intermediate in 9 mL of EtOAc was added 6 mL of a 6 M solution of HCl in MeOH. The resulting mixture was

stirred for 4 h at room temperature. The solvent was then removed *in vacuo*, the residue was suspended in dichloromethane, stirred for 10 min and filtered. The product was washed with methylene chloride twice. The solid was dried *in vacuo* to afford 295 mg of the title compound.

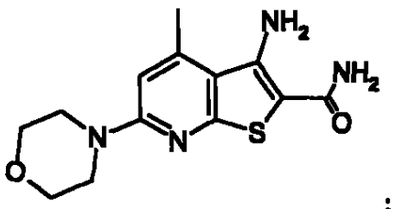
Example 2: Synthesis of 3-Amino-6-dimethylamino-4-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide



2-(3-Cyano-4-methyl-6-trifluoromethanesulfonylpyridin-2-ylmercapto)acetamide (30.0 mg, 0.08 mmol) (prepared as described in Example 1 for the *n*-propyl analog but using methyl 2-butynoate) and dimethylamine (170.0 microL, 0.34 mmol) were mixed in 1,4-dioxane (0.5 mL) in a preasure tube and heated at 80 °C for 1 h. 2.0 M Aqueous sodium carbonate (520 µL, 1.04 mmol) was added, and the reaction heated at 100 °C for 6 h, then cooled to room temperature overnight. The mixture was poured into saturated aqueous ammonium chloride, and extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford 23.0 mg of the crude product. This was purified via automated flash silica chromatography (4 g silica gel column, 30-100% EtOAc/hexanes) to afford 9.0 mg (0.02 mmol, 45% yield) of the title compound.

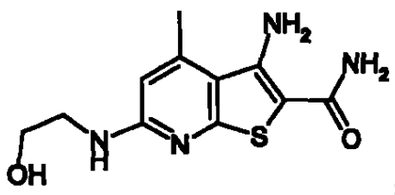
The following compounds were also made using the procedure described in Example 2 and the appropriate amine:

3-Amino-4-methyl-6-morpholin-4-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide



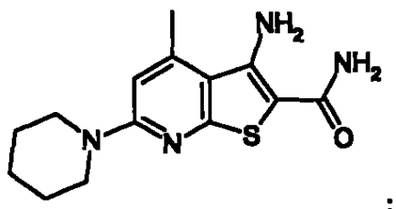
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3-Amino-6-(2-hydroxy-ethylamino)-4-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide



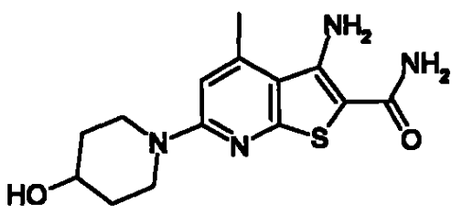
;

3-Amino-4-methyl-6-piperidin-1-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide

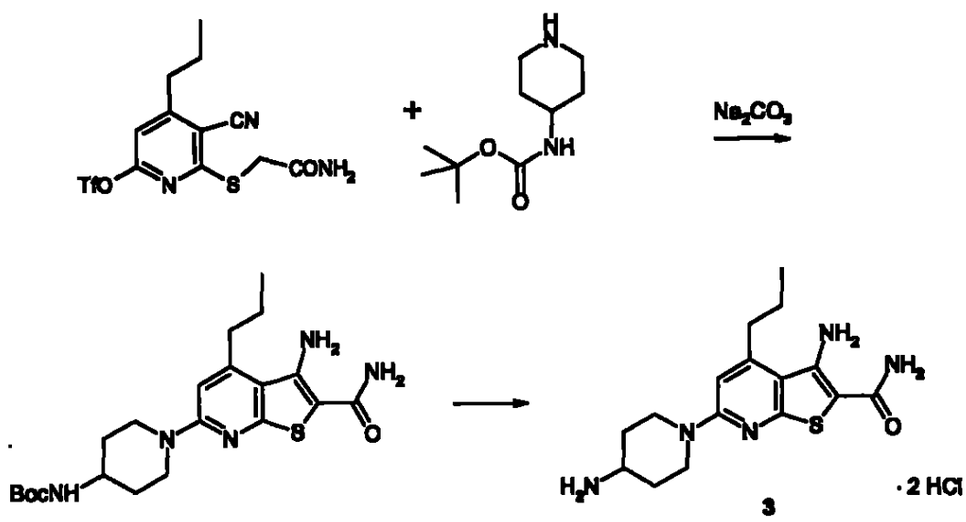


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3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide



Example 3: Synthesis of 3-Amino-6-(4-amino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide

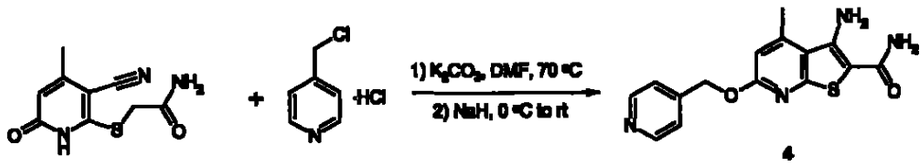


400 mg (1.04 mmol) of pyridine-triflate intermediate (see Example 1) was dissolved in 1,4-dioxane (10 mL), and placed in a dry pressure tube equipped with a magnetic stir bar and under Ar atmosphere. 4-N-Boc-aminopiperidine (640 mg, 3.13 mmol) was added, and the tube was sealed up. The reaction was stirred while heating at 80 °C for 35 min. TLC indicated the complete disappearance of starting triflate. The reaction was cooled to room temperature, and a 2.0 M aqueous solution of sodium carbonate (4.0 mL, 8.00 mmol) was added. The reaction was heated to 100 °C, where it stirred for 20 h, after which it was cooled to room temperature.

The reaction mixture was concentrated *in vacuo*, and the residue was taken up in acetone/MeOH (about 50:50). The resulting mixture was filtered and the filtrate was concentrated *in vacuo*. The material was pre-adsorbed onto diatomaceous earth and purified first via automated flash silica gel chromatography (10 g silica gel column, 30-70% EtOAc/hexanes gradient with EtOAc flush) to afford 274 mg of slightly crude product. This was further purified via regular flash chromatography on silica gel (30 mm *diameter* column by 4" *height*) *eluting with* 33%-50% EtOAc/*hexanes step gradient*, *then* an EtOAc flush, to afford 249.3 mg (55% yield) of [1-(3-Amino-2-carbamoyl-4-propyl-thieno[2,3-b]pyridin-6-yl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester.

249.3 mg (0.57 mmol) of the above compound was suspended in 10.0 mL of EtOAc. The material was completely dissolved by the addition of methanol (2.0 mL) and dichloromethane (2.0 mL). To this was added 5.0 mL (30.0 mmol) of a 6 M solution of hydrochloric acid in methanol. This reaction mixture stirred for 4 h at rt while a yellow solid slowly precipitated out of solution. TLC showed the complete disappearance of starting material, so the reaction was concentrated in vacuo. The residue was washed off the flask walls with a small amount of methanol, and then triturated with ethyl acetate. The yellow solid was collected via suction filtration, and washed successively with ethyl acetate, dichloromethane, and acetone. The solid was dried in vacuo to afford 191.3 mg of the title compound (83% yield).

Example 4: Synthesis of 3-Amino-4-methyl-6-(pyridin-4-ylmethoxy)-thieno[2,3-b]pyridine-2-carboxylic acid amide

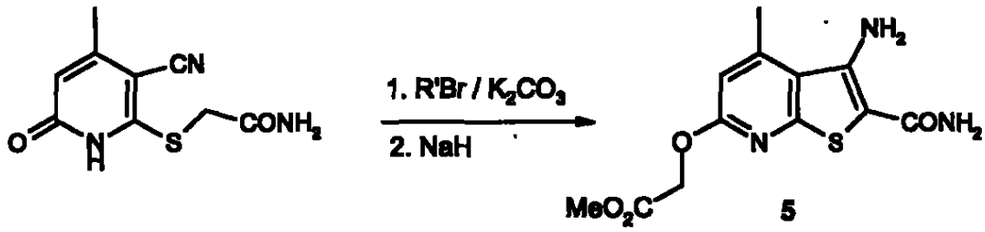


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4-Chloromethylpyridine hydrochloride (57.0 mg, 0.34 mmol) was combined with 50 mg of 4-methyl-mercaptopyridone intermediate (prepared analogous to Example 1) (0.22 mmol), and potassium carbonate (95.0 mg, 0.68 mmol) in DMF (1.0 mL) in a flame-dried pressure tube, under Ar. The tube was sealed and heated at 70 °C for 45 min. TLC showed

complete disappearance of starting material and a new spot formed. The reaction was cooled to 0 °C, and sodium hydride (9.0 mg, 0.23 mmol) was added. The reaction was warmed to room temperature and stirred for 30 min, after which it was cooled in an ice bath and quenched with aqueous sodium bicarbonate (saturated). The resulting mixture was extracted twice with EtOAc. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford 65.8 mg of the crude product which was purified via automated flash silica to afford 41.8 mg (0.13 mmol, 59% yield) of the title compound.

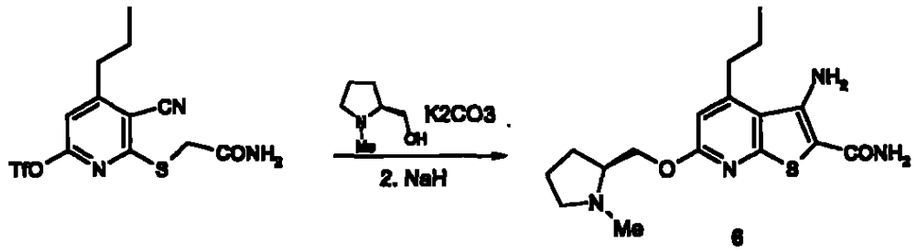
Example 5: Synthesis of (3-Amino-2-carbamoyl-4-methyl-thieno[2,3-b]pyridin-6-yloxy)-acetic acid methyl ester



5

To a mixture of the 4-methyl-mercaptopyridone intermediate (prepared analogous to Example 1) (62 mg) and K_2CO_3 (70 mg) in DMF (1 mL) was added methyl bromoacetate (50 mg). The mixture was heated under Ar at 70 °C for 2 h. After cooling to 0 °C, the mixture was treated with NaH (60%, 10 mg) and stirred at room temperature for 30 min. The mixture was then poured into ice - NH_4Cl mixture, extracted with EtOAc, dried with Na_2SO_4 and concentrated. The residue was purified by preparative TLC, providing 5 mg of the title compound (white solid).

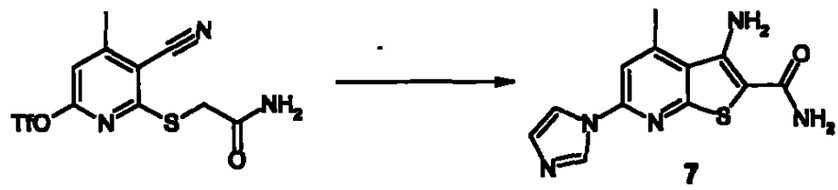
Example 6: Synthesis of 3-Amino-6-(1-methyl-pyrrolidin-2-ylmethoxy)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide



6

A mixture pyridine-triflate intermediate (see Example 1) (10 mg) and N-methyl-L-prolinol (40 mg) in dioxane was heated under Ar at 90 °C for 3 h. The mixture was cooled to room temperature, and Na_2CO_3 (2 M, 0.2 mL) was added. The mixture was heated at 100 °C under Ar for 10 h, cooled to room temperature and diluted with water (1 mL). The mixture was extracted with EtOAc, dried with Na_2SO_4 and concentrated. The residue was purified by preparative silica gel chromatography to give 6 mg of the title compound as a white solid.

Example 7: Synthesis of 3-Amino-6-imidazol-1-yl-4-methyl-thieno[2,3--b]pyridine-2-carboxylic acid amide

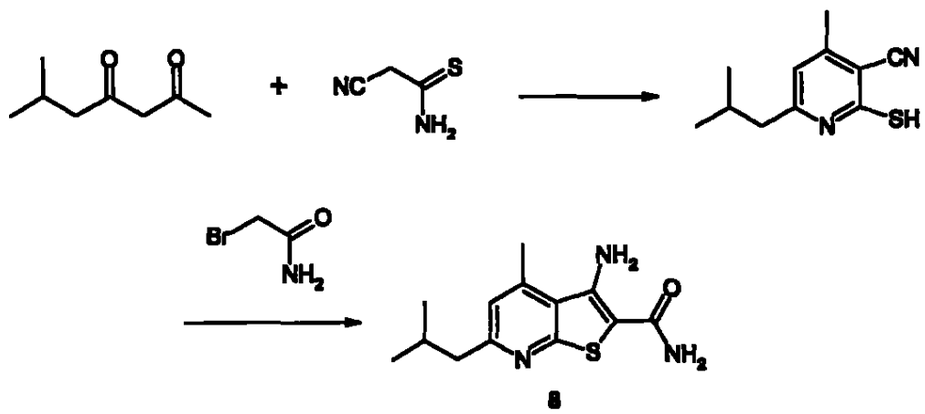


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To a solution of 20 mg (0.067 mmol) of starting 4-methylpyridine triflate intermediate (see Example 2) in 1.2 mL of 1,4-dioxane was added 9.2 mg of imidazole. The resulting mixture was stirred for 2 h at 80 °C. After that time 0.5 mL of 2M solution of sodium carbonate was added. The stirring was continued overnight at 100 °C. The reaction mixture was then cooled to room temperature, diluted with EtOAc, dried with sodium sulfate and concentrated. The crude product was chromatographed (preparative TLC on silica gel eluting with 10% MeOH/methylene chloride, Rf = 0.56) to afford 3.7 mg of

product, which was further purified by HPLC (reverse phase – solvent system: isocratic 60% water/acetonitrile providing 2.7 mg (14.7%) of the title compound.

Example 8: Synthesis of 3-amino-6-isobutyl-4-methyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide

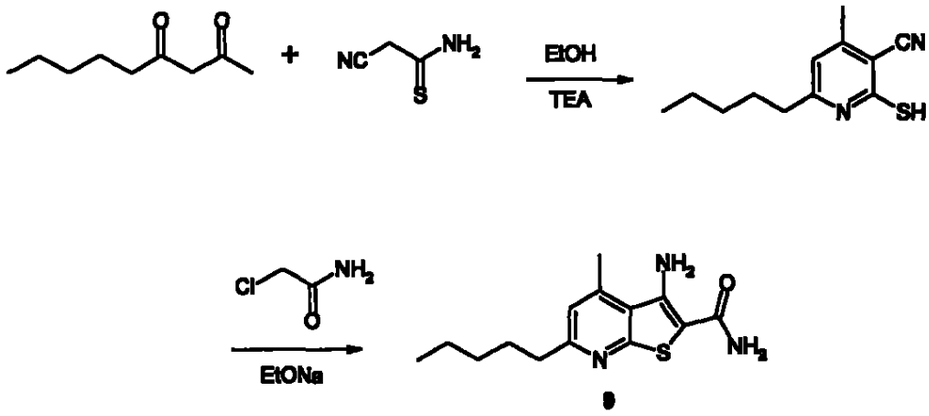


8

To a stirred solution of cyanothioacetamide (2.20 g, 22mmol) and 6-methyl-2,4-heptanediones (3.12 g, 22 mmol) in anhydrous EtOH (40 mL) was added triethylamine (0.4 mL) and the reaction was heated at 50 °C for 1 h before it was allowed to cool to room temperature. Filtration and washing of the precipitates with EtOH gave 6-isobutyl-2-mercapto-4-methylnicotinonitrile as a yellow solid (2.8 g, 61%).

A mixture of the above nitrile (1.00 g, 4.85 mmol), bromoacetamide (0.67 g, 4.85 mmol), and sodium ethoxide (0.68 g, 10 mmol) in DMF (20 mL) was heated at 70 °C for 1 h before it was allowed to cool to room temperature. The resulting mixture was diluted with water, filtrated and the precipitates washed with EtOH providing the title compound (0.5g, 39%).

Example 9: Synthesis of 3-amino-4-methyl-6-pentyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide



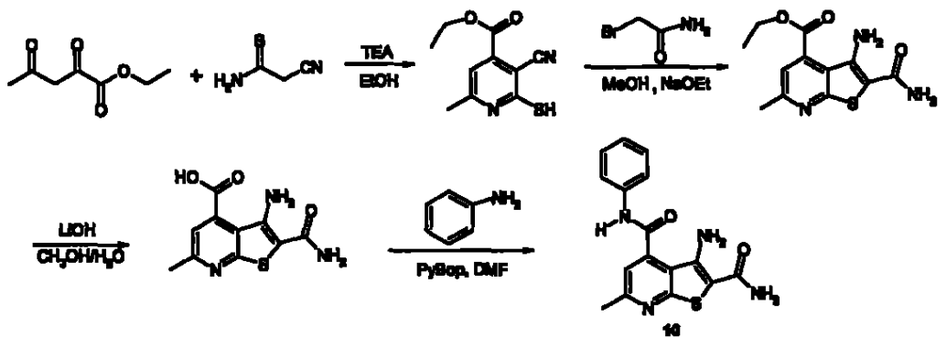
9

To a stirred solution of 2-cyanothioacetamide (1.4 g, 14 mmol) and 2,4-nonanedione (2.0 g, 13 mmol) in anhydrous EtOH (40 mL) was added triethylamine (0.5 mL) and the reaction was heated at 50 °C for 1 h and then was allowed to cool to room temperature. Filtration and washing of the precipitates with EtOH gave 6-pentyl-2-mercapto-4-methyl-nicotinonitrile as a yellow solid (1.84 g, 62.1%).

A mixture of the above nonitrile (1.84 g, 6.7 mmol), 2-chloroacetamide (0.63 g, 6.7 mmol) and sodium ethoxide (0.91 g, 13.4 mmol) in MeOH (35 mL) was heated at 75 °C for 2 h and then it was allowed to cool to room temperature. Filtration and washing of the precipitates with EtOH provided the title compound as a solid (1.31 g, 71.2%).

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Example 10: Synthesis of 3-amino-6-methyl-thieno[2,3-*b*]pyridine-2,4-dicarboxylic acid 2-amide 4-phenylamide

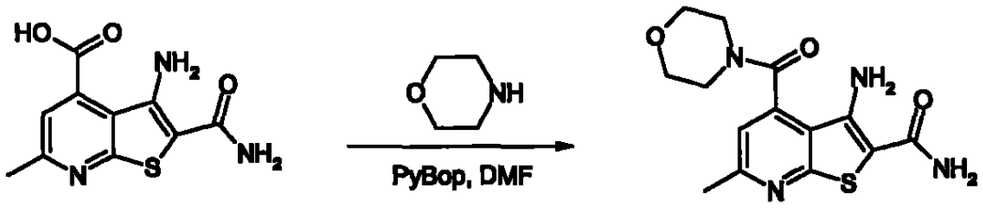


16

To a stirred solution of 2-cyanothioacetamide (3.52 g, 35 mmol) and ethyl 2,4-dioxovalerate (5.0 g, 32 mmol) in anhydrous EtOH (75 mL) at room temperature was added triethylamine (0.5 mL) and the reaction was stirred overnight. Filtration and washing of the precipitates with EtOH gave 3-cyano-2-mercapto-6-methyl-isonicotinic acid ethyl ester as a yellow solid (4.54 g, 64.5%). A mixture of this ester (3.54 g, 16 mmol), bromoacetamide (2.15 g, 16 mmol) and sodium ethoxide (2.18 g, 32 mmol) in MeOH was heated at reflux overnight. It was then allowed to cool to room temperature. Filtration and washing of the precipitates with EtOH provided 3-amino-2-carbamoyl-6-methyl-thieno[2,3-*b*]pyridine-4-carboxylic acid ethyl ester as a solid (0.94 g, 21.1%).

A mixture of the above ester (0.94 g. 3.4 mmol) and lithium hydroxide (0.11 g, 4.7 mmol) in MeOH/H_2O (100 mL, MeOH: H_2O = 3:1) was stirred for 2 h at room temperature. The reaction was neutralized with 2 *M* HCl and concentrated *in vacuo* to afford 3-amino-2-carbamoyl-6-methyl-thieno[2,3-*b*]pyridine-4-carboxylic acid as an orange solid (0.78 g, 63.2%). A mixture of this acid (0.3 g , 1.2 mmol), aniline (0.56 g , 6.0 mmol) and PyBop (0.63 g, 1.4 mmol) in DMF (10 mL) was stirred at room temperature overnight. The reaction was then diluted with water, filtered and the resulting solid washed with EtOH providing the title compound as a solid (0.27g, 73.6 %).

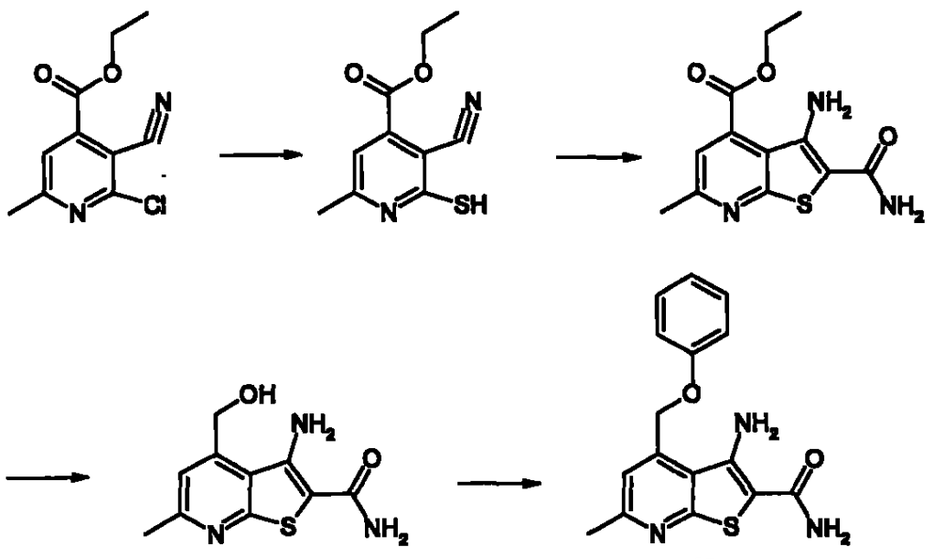
Example 11: 3-Amino-6-methyl-4-(morpholine-4-carbonyl)-thieno[2,3-*b*]pyridine-2-carboxylic acid amide



11

A mixture of 3-amino-2-carbamoyl-6-methyl-thieno[2,3-*b*]pyridine-4-carboxylic acid (see Example 10) (0.5 g, 2.0 mmol), morpholine (0.87 g, 10 mmol) and PyBop (0.88 g, 2.0 mmol) in DMF (10mL) was stirred at room temperature overnight. It was diluted with water and extracted with methylene chloride (50 mL). Concentration of the organic phase the title compound as an orange solid (0.45g, 70.3%).

Example 12: Synthesis of 3-Amino-6-methyl-4-phenoxymethyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide



12

Thiourea (339 mg, 4.46 mmol) was added to a solution of 2-chloro-3-cyano-6-methyl-isonicotinic acid ethyl ester (500 mg, 2.23 mmol) in EtOH (25 mL) at room temperature.

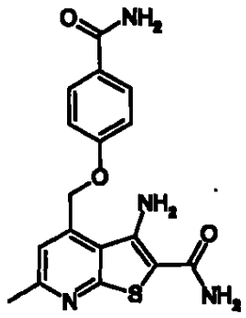
The mixture was heated to reflux for 24 h. The mixture was cooled (crystallization began upon cooling) to room temperature. The solid was collected by vacuum filtration giving 3-cyano-2-mercapto-6-methyl-isonicotinic acid ethyl ester (250 mg, 50%) as a yellow orange solid.

NaH (39 mg, 0.95 mmol) was added to a solution of the above ester (210 mg, 0.95 mmol) in THF (15 mL) at room temperature. After stirring for 5 min, α-bromoacetamide (134 mg, 0.97 mmol) and *n*-Bu_4NI (10 mg) were added. The mixture was stirred at room temperature for 1 h, then NaH (39 mg, 0.95 mmol) was added, and the mixture was stirred for an additional 0.5 h. The reaction was quenched by addition of saturated aqueous NH_4Cl, diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated giving an orange solid. The crude residue was recrystallized from MeOH giving 3-amino-2-carbamoyl-6-methyl-thieno[2,3-*b*]pyridine-4-carboxylic acid ethyl ester (160 mg, 60 %), m.p. 205-208 °C.

$LiBH_4$ (62 mg, 2.04 mmol) was added to a solution of 3-Amino-2-carbamoyl-6-methyl-thieno[2,3-*b*]pyridine-4-carboxylic acid ethyl ester (205 mg, 0.73 mmol) in 10:1 THF:MeOH (15 mL) at room temperature. After stirring for 2 h, the reaction was quenched by addition of 1M HCl. The mixture was buffered to a pH ≈ 7, diluted with EtOAc, washed sequentially with H_2O, brine, dried over Na_2SO_4, concentrated, and triturated with 50% EtOAc/hexane giving 3-amino-4-hydroxymethyl-6-methyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide (123 mg, 71%) as a yellow solid, m.p. > 210 °C.

Diisopropyl azodicarboxylate (DIAD) (14 mg, 0.069 mmol) was added to a solution of 3-amino-4-hydroxymethyl-6-methyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide (15 mg, 0.063 mmol), phenol (6 mg, 0.069 mmol), and Ph_3P (18 mg, 0.069 mmol) in THF (1.5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 24 h. The reaction mixture was concentrated and fractionated by preparative TLC (10% MeOH/CH_2Cl_2) providing the title compound (12 mg, 61%) as an orange solid, m.p. 194-196 °C.

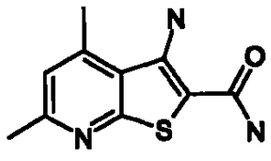
Example 13: Synthesis of amino-4-(4-carbamoyl-phenoxymethyl)-6-methyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide



13

DIAD (23 mg, 0.116 mmol) was added to a solution of 3-amino-4-hydroxymethyl-6-methyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide (see Example 12) (25 mg, 0.105 mmol), 4-hydroxy-benzamide (15 mg, 0.116 mmol), and Ph_3P (30 mg, 0.116 mmol) in THF (2.5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 24 h. The reaction mixture was concentrated and triturated with 2:1 EtOAc:MeOH giving the title compound (7 mg, 19%) as an orange solid, m.p. > 250 °C.

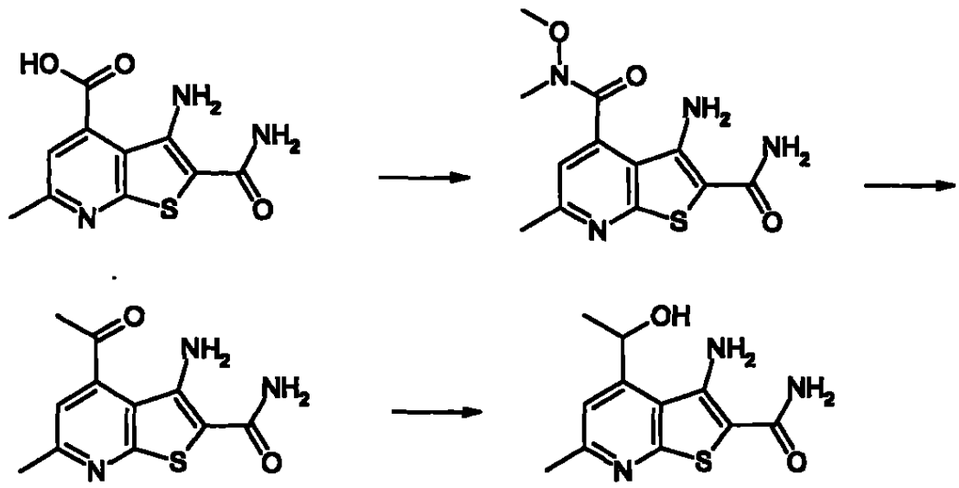
Example 14: Synthesis of 3-Amino-4,6-dimethyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide



α-Bromoacetamide (388 mg, 2.81 mmol) was added to a solution of 2-mercapto-4,6-dimethyl-nicotinonitrile (420 mg, 2.56 mmol) in MeOH (25 mL) at room temperature. This was followed by addition of sodium methoxide (1.76 mL, 25% NaOMe in MeOH, 7.7 mmol). The reaction mixture was heated to reflux. Heating at reflux was continued overnight, after which time the reaction mixture was cooled and filtered. The product was dried overnight providing 450mg (80%) of the title compound, m.p. 238-40°C.

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Example 15: Synthesis of 3-amino-4-(1-hydroxy-ethyl)-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide



15

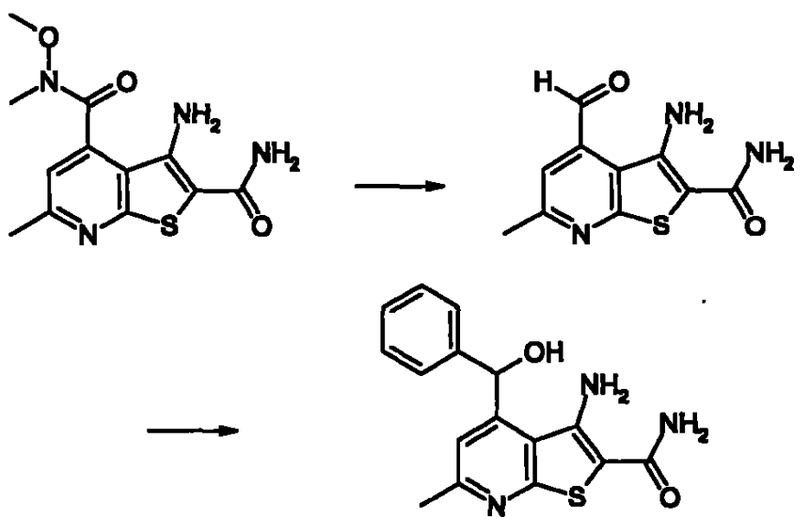
To a solution of 0.80 g 3-amino-2-carbamoyl-6-methyl-thieno[2,3-b]pyridine-4-carboxylic acid and 0.37 g N,O-dimethylhydroxylamine hydrochloride in DMF was added 1.8 mL diisopropylethylamine and 1.23 g O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate. The solution was stirred at room temperature overnight. The reaction was poured into aqueous NH_4Cl, extracted 4 times with EtOAc, washed 4 times with water and aqueous Na_2CO_3 , dried and concentrated *in vacuo* to 0.74 g. The aqueous phase was re-extracted 4 times with n-butanol, washed with aqueous Na_2CO_3, concentrated *in vacuo*, and azeotroped 3 times with toluene to get 0.71 g more product. The aqueous phase was made basic with Na_2CO_3, re-extracted 4 times with n-butanol, washed with water, concentrated *in vacuo*, and azeotroped 3 times with toluene to get a third crop of 0.52 g. The three crops were combined and flash-chromatographed on silica gel eluting with 5% MeOH-CH_2Cl_2 to provide 0.62 g 3-amino-6-methyl-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-(methoxy-methyl-amide) as a yellow solid.

To 100 mg 3-amino-6-methyl-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-(methoxy-methyl-amide) in 3 mL dry THF in an ice bath was added 0.68 mL 3 M methylmagnesium bromide and the reaction was stirred 1 h in the cold and at room

temperature overnight under argon. Aqueous NH_4Cl was added and the product was extracted 4 times into EtOAc, dried, and concentrated in vacuo. Purification on a 2 mm silica gel prep plate in 5% MeOH-CH2Cl2 afforded 12.2 mg of 4-acetyl-3-amino-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide.

A spatula tip full of $NaBH_4$ was added to a solution of 9.9 mg 4-acetyl-3-amino-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide in 1 mL MeOH. After 0.5 h, the reaction was concentrated *in vacuo*, quenched with aqueous NH_4Cl, extracted 4 times into EtOAc, concentrated *in vacuo*, dissolved in MeOH-CH_2Cl_2, filtered , concentrated and dried *in vacuo* at 60° C to provide 8.1 mg of the title compound as a beige solid.

Example 16: Synthesis of 3-amino-4-(hydroxy-phenyl-methyl)-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide



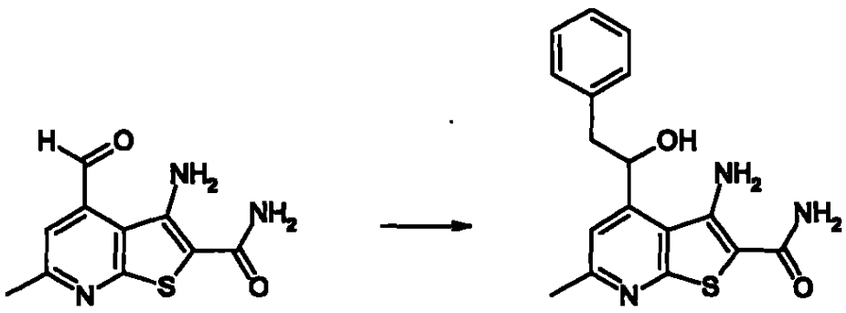
16

$LiAlH_4$ (0.31 g) was added to a suspension of 0.60 g of 3-amino-6-methyl-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-(methoxy-methyl-amide) (see Example 15) in 15 mL dry THF at –10° C and stirred 1 h under Ar. Aqueous NH_4Cl was added slowly and the mixture was filtered through diatomaceous earth, washing with H_2O and EtOAc. The

aqueous phase was separated and extracted 3 times with more with EtOAc and the combined organics were and concentrated *in vacuo* to a resin that was flashed chromatographed eluting with 30% acetone-petroleum ether to afford 163 mg 3-amino-4-formyl-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide as a dark resin.

To a suspension of 314 mg $CeCl_3$ in 3 mL dry THF at –78° C was added 0.425 mL 3M phenylmagnesium bromide and the reaction was stirred 1.5 h under Ar. Then, 50 mg of 3-amino-4-formyl-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide was added and the reaction was stirred 5 h in the cold and then allowed to warm to room temperature over 0.5 h. Aqueous NH_4Cl was added and the reaction was filtered through diatomaceous earth, washing with EtOAc, and the aqueous phase was separated and extracted 3 times with more with EtOAc. The combined organics were dried, and concentrated *in vacuo*, and the product was purified on a prep plate developed with 5% MeOH-CH_2Cl_2. Starting material impurity was removed by dissolving the product in EtOAc with a trace MeOH and washing 3 times with aqueous $NaHSO_3$. The organics were dried, concentrated *in vacuo*, re-dissolved in MeOH-CH_2Cl_2, filtered, concentrated and dried *in vacuo* at 60° C to provide 8.2 mg of the title compound as a yellow solid.

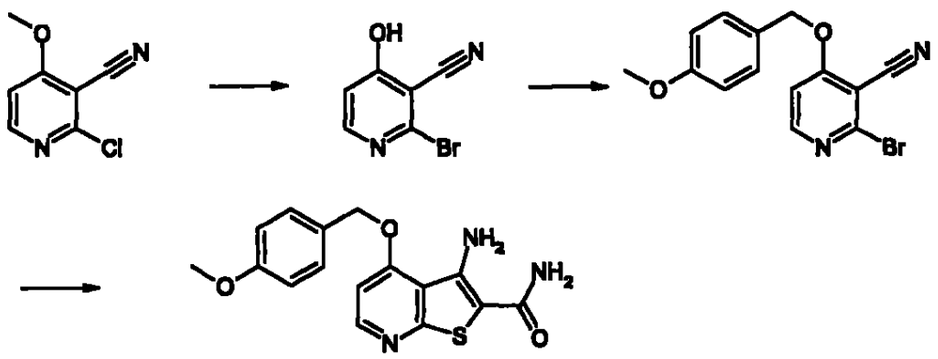
Example 17: Synthesis of 3-amino-4-(1-hydroxy-2-phenyl-ethyl)-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide



17

To a suspension of 344 mg $CeCl_3$ in 3 mL dry THF at –78° was added 0.70 mL 2 M benzylmagnesium chloride and the reaction was stirred 1.5 h under Ar. Then, 41 mg of 3-amino-4-formyl-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide (see Example 16) was added and the reaction was stirred 3.5 h in the cold and then allowed to warm to room temperature over 0.5 h. Aqueous NH_4Cl was added and the reaction was filtered through diatomaceous earth, washing with EtOAc, and the aqueous phase was separated and extracted 3 times more with EtOAc. The combined organics were dried, concentrated *in vacuo*, and re-dissolved in EtOAc with a trace MeOH and washed 3 times with aqueous $NaHSO_3$. This was dried, concentrated *in vacuo*, and the product was purified on a prep plate developed with 5% MeOH-CH_2Cl_2. The product was re-dissolved in MeOH-CH_2Cl_2, filtered, concentrated and dried *in vacuo* at 60° C providing 16.3 mg of the title compound as an orange solid.

Example 18: Synthesis of 3-amino-4-(4-methoxy-benzyloxy)-thieno[2,3-b]pyridine-2-carboxylic acid amide



18

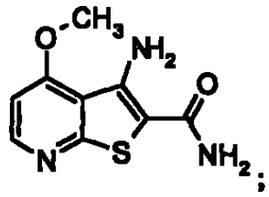
2-Chloro-4-methoxy-nicotinonitrile (M. Mittelbach *et al.*, Arch.Pharm.(Weinheim Ger.); 1985, GE, 318, 6, 481-486) (6.92 g) was suspended in 70 mL of 30% HBr in acetic acid in a pressure vessel and heated with stirring at 100° C for 2 h. The reaction was cooled to room temperature and filtered, washing well with H_2O, and dried *in vacuo* overnight at 50° C providing 4.85 g 2-bromo-4-hydroxy-nicotinonitrile as a white solid. Proton NMR(DMSO) indicated the product was a mixture of 69% bromo compound with 31% starting chloro analog.

To a solution of 5.85 g of the above mixture in 30 mL of dry DMF was added 1.52 g 60% NaH in mineral oil in portions and the brown reaction was stirred 15 min at room temperature under Ar. 4-Methoxybenzyl chloride (5.16 mL) was added and the reaction was heated at 60° C for 2.5 h and then quenched with aqueous NH_4Cl. Extraction into EtOAc, followed by washing with H_2O gave precipitation of a white solid side-product in the separatory funnel that was filtered off. The filtrate was dried and stripped to 9.4 g of a semisolid that was triturated in CH_2Cl_2 and filtered to afford 730 mg more side-product. The filtrate was concentrated and flash-chromatographed on silica gel eluting with CH_2Cl_2 providing 4.80 g of a white waxy solid. Proton NMR(DMSO) indicated the product was a 2:1 mixture of 2-bromo-4-(4-methoxy-benzyloxy)-nicotinonitrile with its 2-chloro analog.

A mercaptoacetamide solution in MeOH (6.80 mL) was concentrated *in vacuo* providing 928 mg. 2.75g of the above 2:1 mixture was added and dissolved in 14 mL dry DMF under a N_2 purge. A 60% NaH suspension in mineral oil (723 mg) was added and stirred at 60° C overnight under Ar. Aqueous NH_4Cl was added and the product was filtered, washed with H_2O, and dried *in vacuo* at 50°C providing 1.97 g crude product that was recrystallized from MeOH to afford 1.25 g of the title compound as a yellow solid.

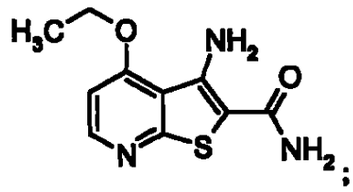
The following compounds were prepared in the manner described above from 2-bromo-4-hydroxy-nicotinonitrile and the appropriate alkyl halide. In the case of alkyl ethers, the alkyl bromide or iodide was used. In the case of benzyl ethers, the benzyl chloride or bromide was used.:

3-Amino-4-methoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide



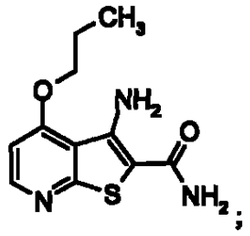
;

3-Amino-4-ethoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide

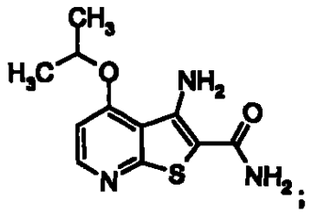


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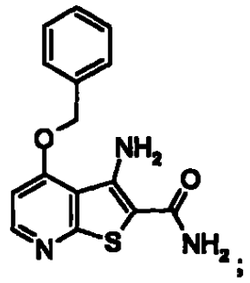
3-Amino-4-propoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide



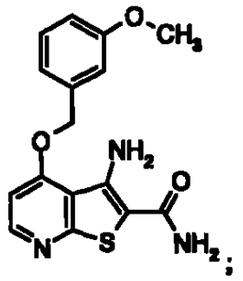
3-Amino-4-isopropoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide



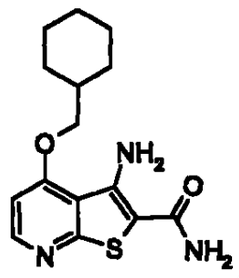
3-Amino-4-benzyloxy-thieno[2,3-b]pyridine-2-carboxylic acid amide



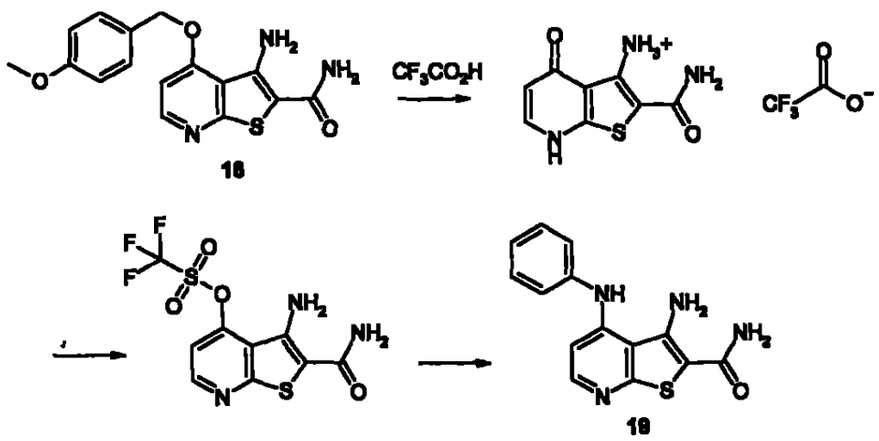
3-Amino-4-(3-methoxybenzyloxy)-thieno[2,3-b]pyridine-2-carboxylic acid amide



3-Amino-4-(cyclohexylmethoxy)-thieno[2,3-b]pyridine-2-carboxylic acid amide



Example 19: Synthesis of 3-amino-4-phenylamino-thieno[2,3-b]pyridine-2-carboxylic acid amide



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19

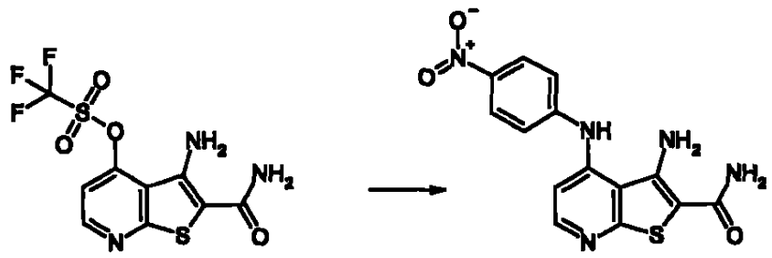
A solution of 2.43 g 3-amino-4-(4-methoxy-benzyloxy)-thieno[2,3-b]pyridine-2-carboxylic acid amide (Example 18) was stirred 6 h in 20 mL trifluoroacetic acid with a drying tube. The reaction was concentrated *in vacuo* and then co-evaporated 3 times with toluene and 2 times with CH_2Cl_2 to give a yellow resin. This was triturated in EtOAc and filtered to give 1.88 g 3-amino-4-oxo-4,7-dihydro-thieno[2,3-b]pyridine-2-carboxylic acid amide trifluoroacetic acid salt as a yellow solid.

A mixture of 1.0 g 3-amino-4-oxo-4,7-dihydro-thieno[2,3-b]pyridine-2-carboxylic acid amide trifluoroacetic acid salt and 2.76 g N-phenyltrifluoromethanesulfonimide and 1.35

mL diisopropylethylamine was stirred in 10 mL dioxane at room temperature under Ar overnight. EtOAc was added and the mixture was washed with H_2O, two times with aqueous NH_4Cl, and once with aqueous Na_2CO_3. The EtOAc solution was dried and concentrated *in vacuo* to 3.63 g yellow solid. Flash-chromatography, eluting with acetone-petroleum ether, afforded 1.05 g of trifluoromethanesulfonic acid 3-amino-2-carbamoyl-thieno[2,3-b]pyridin-4-yl ester as a yellow solid.

A solution of 20 mg trifluoromethanesulfonic acid 3-amino-2-carbamoyl-thieno[2,3-b]pyridin-4-yl ester and 27 microL aniline in 1 mL of THF was heated at 55° C overnight under Ar. The reaction was applied to a 2 mm silica gel prep plate that was developed twice in 5% MeOH-CH_2Cl_2. The band was eluted with 50% MeOH-CH_2Cl_2 to get 18 mg. This was dissolved in 5% MeOH-CH_2Cl_2, filtered, concentrated, and dried *in vacuo* at 60 °C overnight to provide 10.5 mg of the title compound as a yellow-green solid.

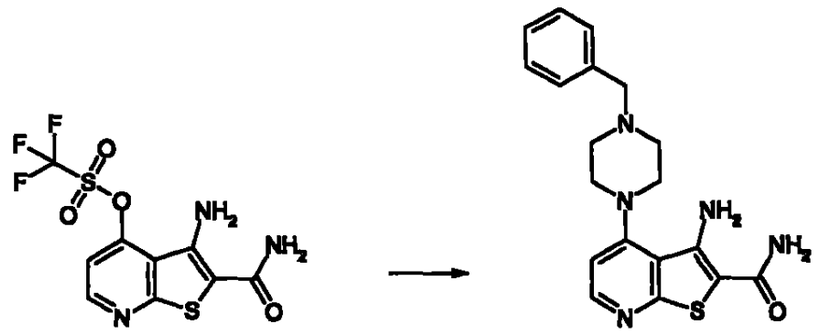
Example 20: Synthesis of 3-amino-4-(4-nitro-phenylamino)-thieno[2,3-b]pyridine-2-carboxylic acid amide



20

A solution of 20 mg trifluoromethanesulfonic acid 3-amino-2-carbamoyl-thieno[2,3-b]pyridin-4-yl ester (see Example 19) and 40.5 mg 4-nitroaniline in 1 mL of dry dioxane was heated at 95° C overnight under N_2. The reaction was concentrated and applied to a 2 mm silica gel prep plate that was developed twice in 7.5% MeOH-CH_2Cl_2. The band was eluted with 20% MeOH-CH_2Cl_2, concentrated *in vacuo*, re-dissolved in 5% MeOH-CH_2Cl_2, filtered, concentrated, and dried *in vacuo* at 60° overnight to get 2.2 mg of the title compound as an orange solid.

Example 21: Synthesis of 3-amino-4-(4-benzyl-piperazin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide

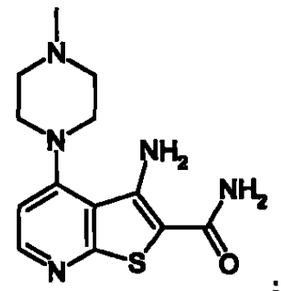


21

A mixture of 20 mg trifluoromethanesulfonic acid 3-amino-2-carbamoyl-thieno[2,3-b]pyridin-4-yl ester and 50 microL of N-benzylpiperazine in 1 mL of dry dioxane was purged with N_2 and capped and left at room temperature overnight. The reaction was diluted with EtOAc, washed four times with water, dried and concentrated to dryness *in vacuo*. The product was purified on a 2 mm silica gel prep plate, developing and eluting the band with MeOH-CH_2Cl_2 mixtures and then concentrating to dryness. The product was re-dissolved in 5-10% MeOH-CH_2Cl_2, filtered to remove silica gel, concentrated, and dried *in vacuo* at 60° C overnight to provide 7.9 mg of the title compound as a beige solid.

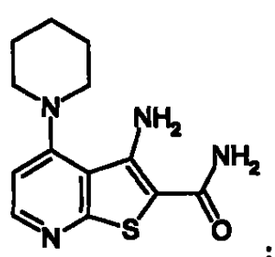
The following compounds were prepared using the same procedure described in the above Example. If the intermediate secondary amine was a solid, 50 molar equivalents were used rather than 50 microL. In some cases, if the product was thought to have appreciable solubility in water, the reaction mixture was concentrated without extraction and the residue purified by prep TLC as above. Other slight modifications are noted for particular compounds.

3-Amino-4-(4-methyl-piperazin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide



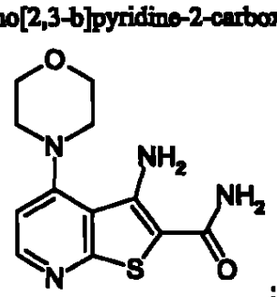
;

3-Amino-4-piperidin-1-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide



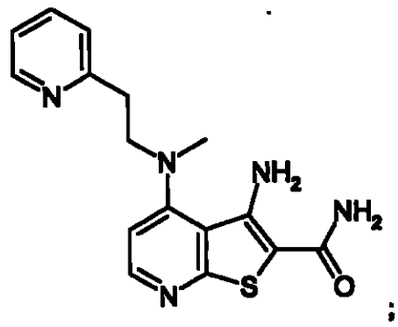
;

3-Amino-4-morpholin-4-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide



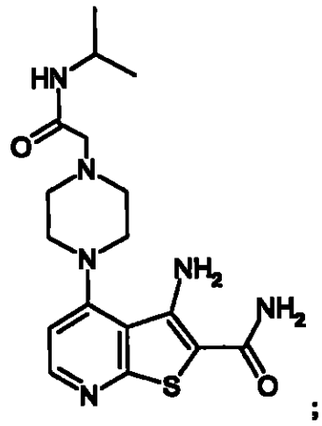
;

3-Amino-4-[methyl-(2-pyridin-2-yl-ethyl)-amino]-thieno[2,3-b]pyridine-2-carboxylic acid amide



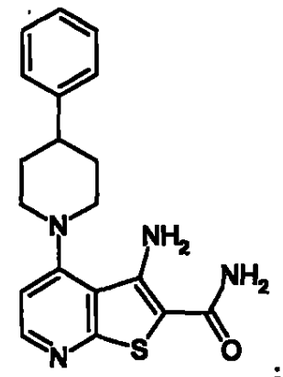
;

3-Amino-4-[4-(isopropylcarbamoyl-methyl)-piperazin-1-yl]-thieno[2,3-b]pyridine-2-carboxylic acid amide



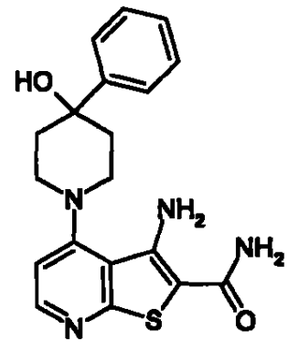
;

3-Amino-4-(4-phenyl-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide



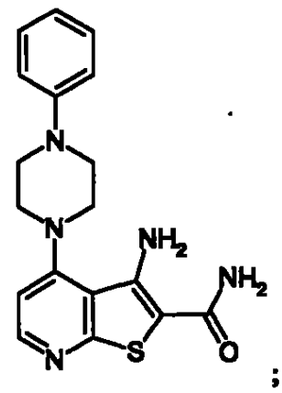
;

3-Amino-4-(4-hydroxy-4-phenyl-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide



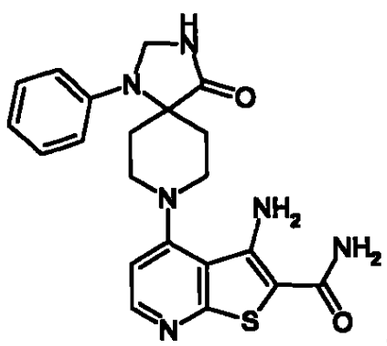
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3-Amino-4-(4-phenyl-piperazin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide



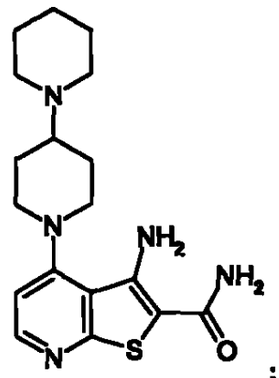
;

3-Amino-4-(4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide



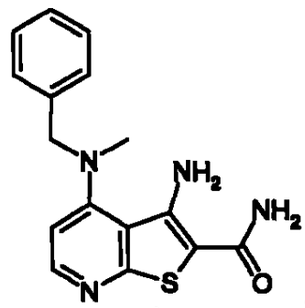
;

3-Amino-4-[1,4']bipiperidinyl-1'-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide



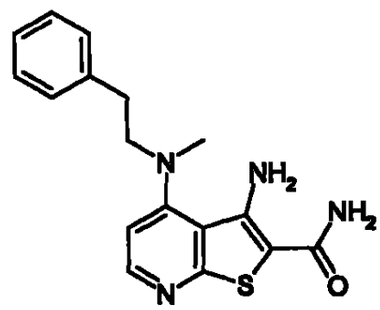
;

3-Amino-4-(benzyl-methyl-amino)-thieno[2,3-b]pyridine-2-carboxylic acid amide



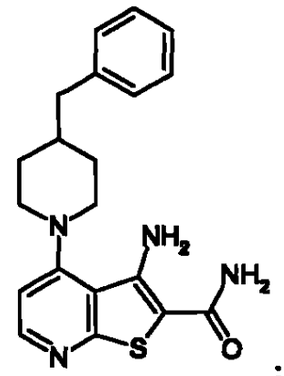
;

3-Amino-4-(methyl-phenethyl-amino)-thieno[2,3-b]pyridine-2-carboxylic acid amide



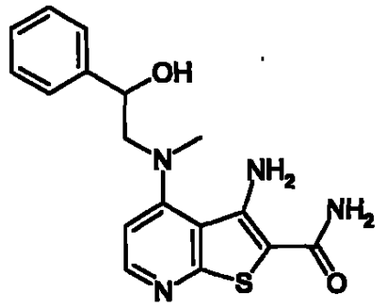
;

3-Amino-4-(4-benzyl-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide



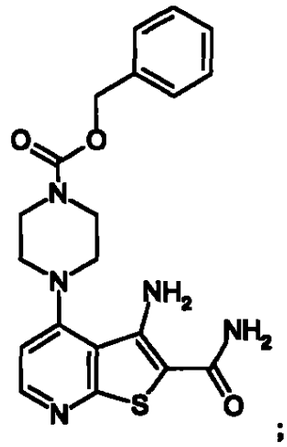
;

3-Amino-4-[(2-hydroxy-2-phenyl-ethyl)-methyl-amino]-thieno[2,3-b]pyridine-2-carboxylic acid amide



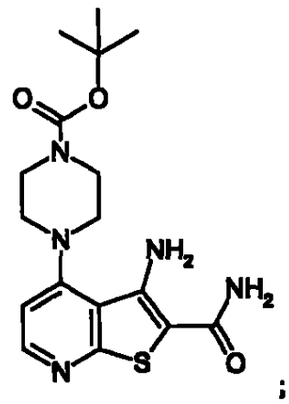
;

4-(3-Amino-2-carbamoyl-thieno[2,3-b]pyridin-4-yl)-piperazine-1-carboxylic acid benzyl ester



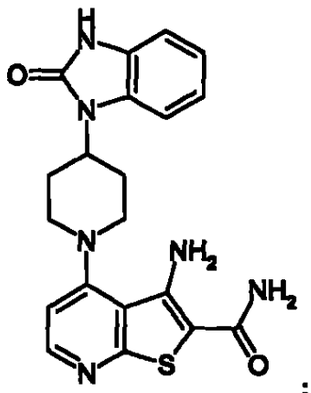
;

4-(3-Amino-2-carbamoyl-thieno[2,3-b]pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester



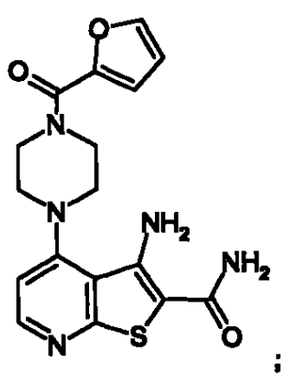
;

3-Amino-4-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-thieno[2,3-b]pyridine-2-carboxylic acid amide



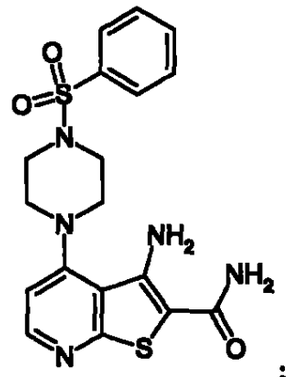
;

3-Amino-4-[4-(furan-2-carbonyl)-piperazin-1-yl]-thieno[2,3-b]pyridine-2-carboxylic acid amide



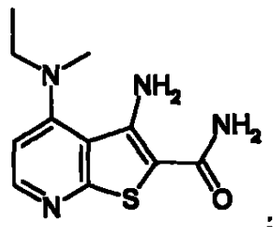
;

3-Amino-4-(4-benzenesulfonyl-piperazin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide



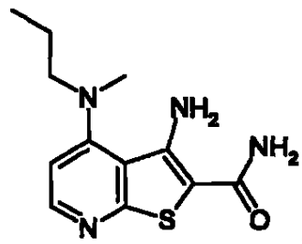
;

3-Amino-4-(ethyl-methyl-amino)-thieno[2,3-b]pyridine-2-carboxylic acid amide



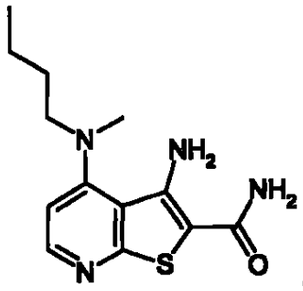
;

3-Amino-4-(methyl-propyl-amino)-thieno[2,3-b]pyridine-2-carboxylic acid amide



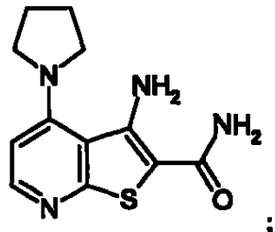
;

3-Amino-4-(butyl-methyl-amino)-thieno[2,3-b]pyridine-2-carboxylic acid amide



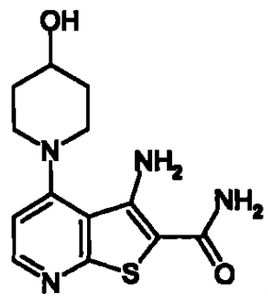
;

3-Amino-4-pyrrolidin-1-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide



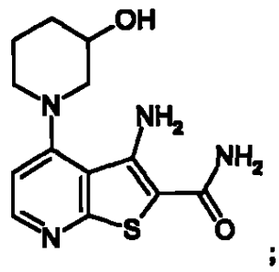
;

3-Amino-4-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide
This product was purified after the prep plate by HPLC on a C8 column eluting with 75% H_2O-25% acetonitrile



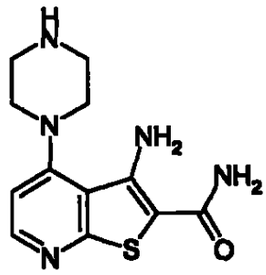
;

3-Amino-4-(3-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide
This product was purified after the prep plate by HPLC on a C8 column eluting with 65% H_2O-35% acetonitrile



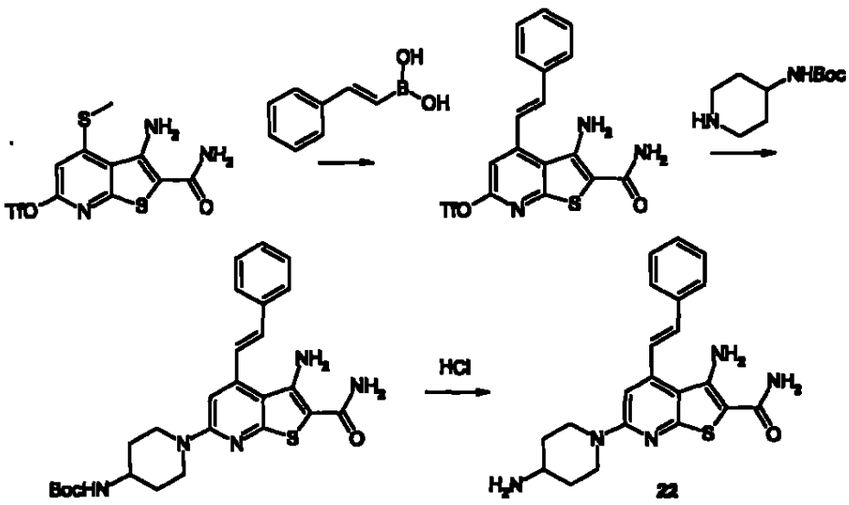
;

3-Amino-4-piperazin-1-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide



A solution of 18 mg 4-(3-amino-2-carbamoyl-thieno[2,3-b]pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester in 1 mL CH_2Cl_2 + 1 mL trifluoroacetic acid was stirred with a drying tube for 4 h at room temperature. The reaction was concentrated *in vacuo* and developed prep plate in 25% MeOH- CH_2Cl_2 -2% NH_4OH and the band was eluted with 50% MeOH- CH_2Cl_2 to get an oil that was re-dissolved 10% MeOH- CH_2Cl_2, filtered, concentrated, and dried *in vacuo* at 60° C to provide 4.6 mg of the product as a yellow solid.

Example 22: Synthesis of 3-amino-6-(4-amino-piperidin-1-yl)-4-((E)-styryl)-thieno[2,3-b]pyridine-2-carboxylic acid amide



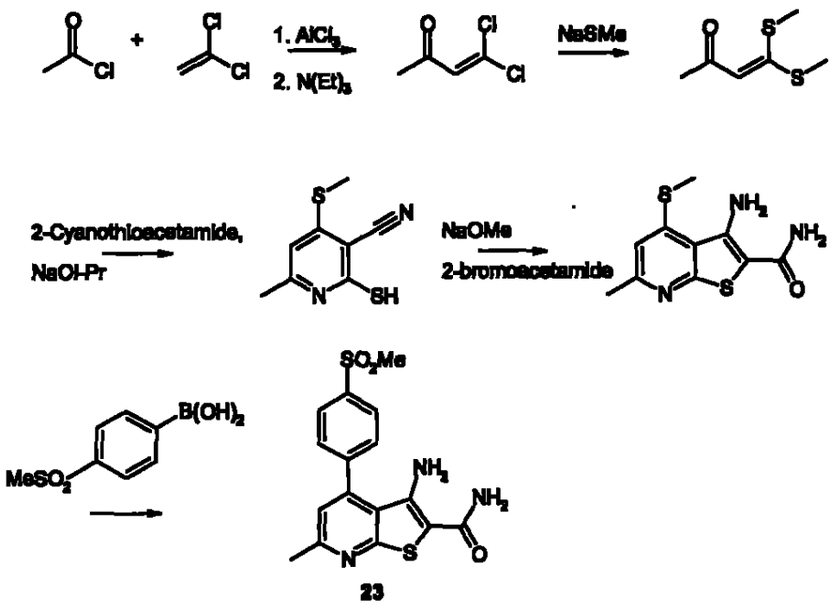
30 mL of dry THF was added into a sealable flask and a stream of Ar was bubbled through the solvent for 5 min. Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (76.1 mg, 73.5 μmol), tris-2-furylphosphine (121.9 mg, 0.5 mmol), copper(I) thiophene-2-carboxylate (541.2 mg, 2.7 mmol), *trans*-2-phenylvinylboronic acid (621.4 mg, 4.2 mmol), and 3-amino-4-methylthio-6-trifluoromethylsuflonyl-thieno[2,3-b]pyridine-2-carboxylic acid amide (800.0 mg, 2.1 mmol) were added and the sealed flask was heated at 40 °C for 20 h. The solution was diluted with CH_2Cl_2 and the organic phase was extracted with saturated $NaHCO_3$-solution. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic phases were washed with brine. The solution was dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on silica gel using a gradient (0 - 2.5 % MeOH/CH_2Cl_2 over 50 min). The fractions containing product were combined, evaporated and purified by preparative TLC (10 % acetone/Ether) to yield 415 mg (45%) of the 4-(E)-styryl intermediate.

The above intermediate was dissolved in dioxane (20 mL), 4-N-Boc-aminopiperidine (382.6 mg, 1.9 mmol) was added and the mixture was stirred for 8 h at 100 °C. The solution was cooled to room temperature and saturated NH_4Cl solution was added. The

aqueous phase was extracted with ethyl acetate and the combined organic phases were dried over $MgSO_4$. The compound was further purified by preparative TLC (5 % $MeOH/CH_2Cl_2$) to yield 220 mg (48%) of product.

The above carbamate was dissolved in dioxane (10 mL) and a 4 N solution of HCl dioxane (5 mL) was added. The suspension was stirred for 3 h after which the solvent was evaporated. The residue was purified by preparative TLC (10% 4N NH_3 in MeOH/90% CH_2Cl_2) to yield 115 mg (65 %) of the title compound.

Example 23: Synthesis of 3-amino-4-(4-methanesulfonyl-phenyl)-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide



Aluminum chloride (4.2 g, 32 mmol) was suspended in methylene chloride (5 mL) and acetyl chloride (2.44 mL, 34 mmol) was added dropwise over 30 min, while the internal temperature was kept below 30 °C. Stirring was continued for 15 min, after which vinylidene chloride was added over 10 min at 30 °C. After stirring for another 90 min at room temperature, the mixture was poured onto crushed ice. The mixture was stirred for 20

min and the aqueous phase was extracted twice with methylene chloride. The combined organic phases were washed with water. The methylene chloride solution was then cooled to 0 °C and triethylamine (4.21 mL, 30 mmol) was added while stirring the solution. After 30 min 10% HCl was added and the organic phase was washed with 5% HCl, water and brine. The volatiles were evaporated and the residue was distilled over a small path distillation apparatus to yield 3.28 g (78%) of the desired dichlorovinyl ketone.

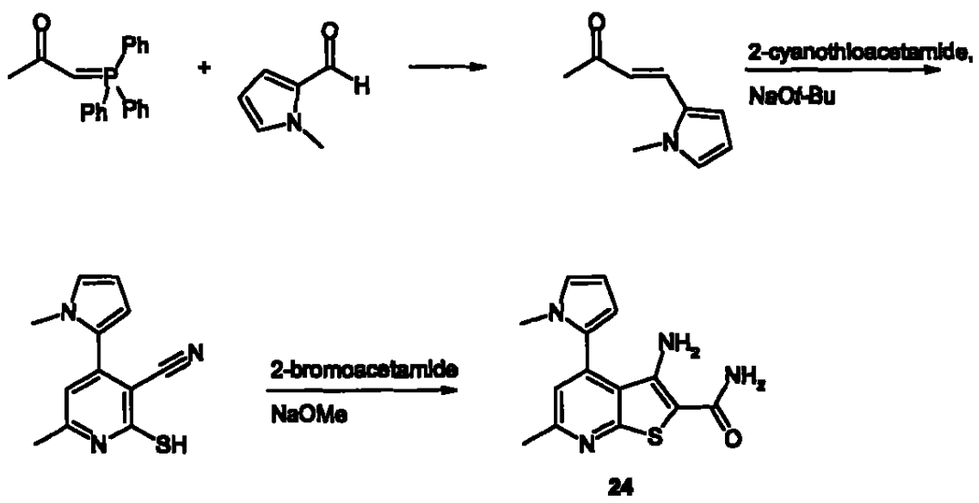
Sodium thiomethoxide (1.40 g, 20 mmol) was suspended in ether (20 mL) and the above dichlorovinyl ketone (10 mmol), dissolved in ether (10 mL), was added dropwise. The resulting solution was refluxed for 1 h, filtered, and the precipitate washed with ether. The combined filtrates were evaporated to yield 1.4 g (87%) of the desired dimethylthiovinyl ketone.

Sodium (533 mg, 23.2 mmol) was dissolved in isopropanol (50 mL) under heating. 2-Cyanothioacetamide (2.1 g, 21 mmol) was added and the solution was stirred for 5 min of at room temperature. The above dimethylthiovinyl ketone (3.4 g, 21 mmol) was added to the reaction mixture and the solution was refluxed until starting material disappeared (~ 30 h). The solvent was evaporated and the residue was dissolved in water. The aqueous solution was filtered, acidified to pH 3, and the precipitate was filtered off. The precipitate was washed with ether and then with hexane to give 3.9 g (95%) of the desired thiopyridine.

Sodium methoxide (2.16 g, 40 mmol) was dissolved in MeOH (60 mL) and the above thiopyridine (3.9 g, 20 mmol) was added. After 5 min, 2-bromoacetamide (2.76 g, 20 mmol) was added and the solution was refluxed for 2 h. The MeOH was partly evaporated and the residue was diluted with aqueous sodium bicarbonate solution. The aqueous phase was extracted several times with 10% MeOH/ methylene chloride and the combined extracts were dried over magnesium sulfate. The solvent was evaporated and the residue purified by column chromatography on silica gel to give 2.1 g (41%) of the desired thieno[2,3-b]pyridne intermediate.

Dry THF (3 mL) was added to a sealable tube and a stream of Ar was bubbled through the solvent for 5 min. The above thieno[2,3-b]pyridine intermediate (50 mg, 0.2 mmol), 4-methanesulfonylphenylboronic acid (48 mg, 0.24 mmol), tris(dibezylideneacetone)dipalladium(0)-chloroform adduct (4 mg, 4 μmol), tri-2-furylphosphine (7.5 mg, 32 μmol), and copper(I)thiophene-2-carboxylate (50 mg, 0.26 mmol) were added. The tube was sealed and then heated at 65 °C for 24 h. The solution was diluted with CH_2Cl_2 and the organic phase was extracted with aqueous sodium bicarbonate solution. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic phases were washed with brine. The solution was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography. All fractions containing product were combined, evaporated and re-purified by preparative TLC to give 23 mg (32%) of the title compound.

Example 24: Synthesis of 3-amino-6-methyl-4-(1-methyl-1H-pyrrol-2-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide



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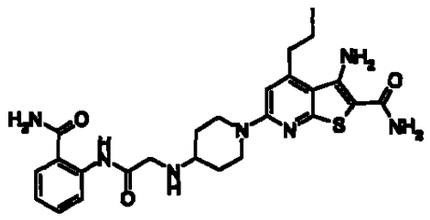
1-Methyl-2-pyrrolecarboxaldehyde (500 mg, 4.58 mmol) was dissolved in 10 mL of toluene followed by addition of 1-triphenylphosphoranylidene-2-propanone (1.53 g,

4.81mmol) and 10 drops of acetic acid. The reaction mixture was heated to 120 °C in a sealed tube for 16 h. The reaction mixture was cooled to room temperature and the solvent was evaporated. The residue was dissolved in EtOAc, and the organic phase was washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel to yield 565 mg (82.7%) of the vinyl ketone.

To a sealed tube was added 2-cyanothioacetamide (70.6 mg, 0.71 mmol) and sodium *t*-butoxide (71 mg, 0.74 mmol) in 2-propanol (4 mL). The mixture was stirred at room temperature for 5 min, followed by the addition of above vinyl ketone (100 mg, 0.67 mmol). The mixture was heated at 80 °C for 16 h. The solution was concentrated and the residue was dissolved in water. Dilute HCl was added to adjust the pH to 6. The solid that formed during acidification was filtered and washed with water. The solid was dried under high vacuum to afford 70 mg (45.5%) of the desired thiopyridine intermediate.

The above thiopyridine intermediate (70 mg, 0.31 mmol) was suspended in 2 mL of MeOH, followed by the addition of 2-bromoacetamide (42 mg, 0.3 mmol) and 1.22 mL of 0.5 N sodium methoxide solution in MeOH. The mixture was heated in a sealed tube at 70 °C for 2 h. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel to yield 36 mg (41%) of the title compound.

Example 25: Synthesis of 3-amino-6-(4-{[(2-carbamoyl-phenylcarbamoyl)-methyl]-amino}-piperidin-1-yl)-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide

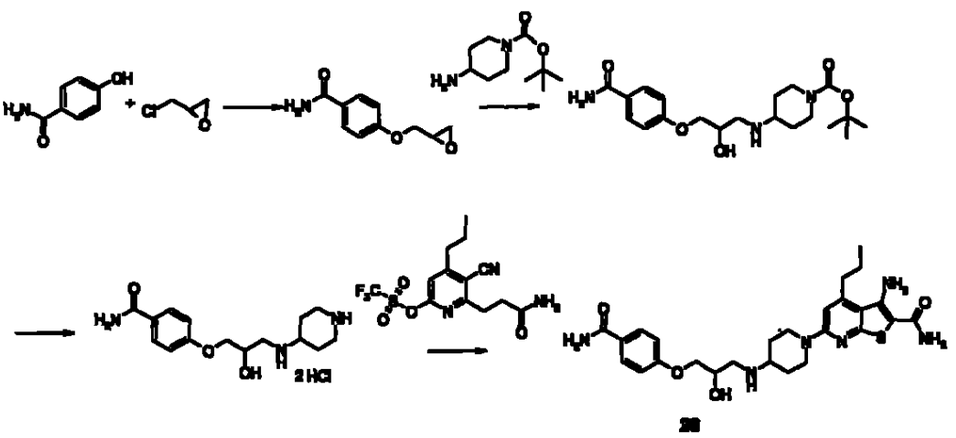


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To a solution of 2-aminobenzamide (2.00 g, 14.4 mmol) and triethylamine (2.4 mL, 17 mmol) in dry dioxane (20 mL) was added bromoacetyl bromide (1.33 mL, 15.0 mmol). This reaction mixture was stirred at room temperature for 1 h then poured into water. The resulting solid was collected by filtration and recrystallized from MeOH to give the diamide intermediate as a brown solid (2.02 g).

The above intermediate (70 mg, 0.21 mmol) and 3-amino-6-(4-amino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide (65 mg, 0.25 mmol), along with triethylamine (0.05 mL, 0.36 mmol), were stirred in 1 mL of DMF for 2 h. The solvent was removed in *vacuo*. The residue was triturated with water. The resulting solid was collected by filtration and recrystallized from acetonitrile to give the title compound (37 mg) as a pale colored solid.

Example 26: Synthesis of 3-amino-6-[4-[3-(4-carbamoyl-phenoxy)-2-hydroxy-propylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide



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To a sealed tube was added 4-hydroxybenzamide (200 mg, 1.458 mmol), epichlorohydrin (135 mg, 1.458 mmol) and potassium carbonate (403 mg, 2.916 mmol) in 7 mL of dry DMF. The reaction mixture was stirred at 70 °C for 18 h. The reaction mixture was filtered and concentrated. The residue was purified by flash chromatography, eluting with 0-5% 2M NH_3 in MeOH/CH_2Cl_2. The product fractions were collected and concentrated to afford 80 mg of 4-oxiranylmethoxy-benzamide as a white solid.

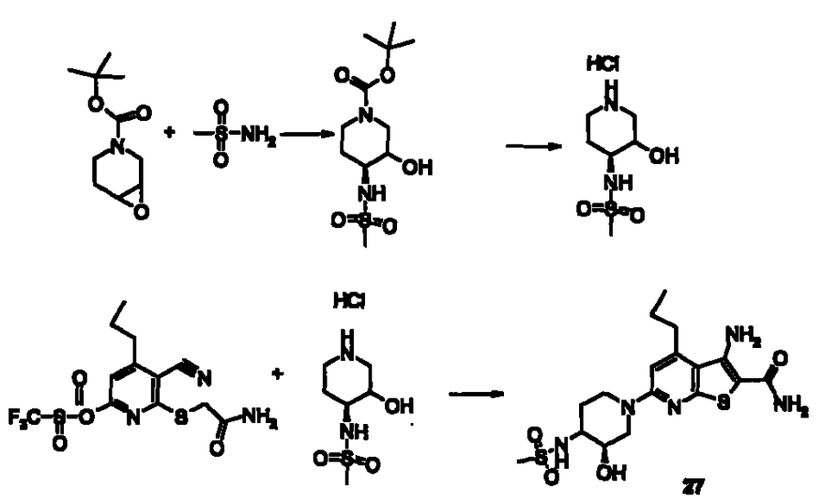
4-Oxiranylmethoxy-benzamide (76 mg, 0.393 mmol) was dissolved in 8 mL of dry DMF, followed by the addition of 4-amino-1-N-boc-piperidine (178 mg, 0.889 mmol). The reaction mixture was stirred at 80 °C for 48 h. The reaction mixture was concentrated and the residue was purified by flash chromatography eluting with 0-5% 2M NH_3 in MeOH/CH_2Cl_2. The product fractions were collected and concentrated to afford 62 mg of 4-[3-(4-carbamoyl-phenoxy)-2-hydroxy-propylamino]-piperidine-1-carboxylic acid *tert*-butyl ester as a colorless oil.

To a round bottom flask was added the above ester (62 mg, 0.158 mmol) in 5 mL of HCl, 4.0 M in 1,4-dioxane and 2 mL of MeOH. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated by high vacuum pump to

afford 57 mg of 4-[2-hydroxy-3-(piperidin-4-ylamino)-propoxy]-benzamide, hydrogen chloride salt as a white glass-solid product.

To a sealed tube was added trifluoro-methanesulfonic acid 6-(2-carbamoyl-ethyl)-5-cyano-4-propyl-pyridin-2-yl ester (54.2 mg, 0.141 mmol) in 5 mL of dry DMF, followed by the addition of the above hydrochloride salt (57 mg, 0.156 mmol) and N-N-diisopropylethylamine (91.4 mg, 0.707 mmol). The reaction mixture was stirred at 70 °C for 2 h. The reaction was concentrated and to the residue was added sodium methoxide, 0.5 M solution in MeOH (1.41 ml, 0.707 mmol) and 2 mL of MeOH. The reaction mixture was heated at 70 °C for 4 h. The reaction mixture was concentrated and the residue was purified by flash chromatography eluting with 0-10% 2M NH_3 in MeOH/CH_2Cl_2. The product fractions were collected and concentrated to afford 42 mg (56.4%) of the title compound as a light yellow crystalline solid.

Example 27: *Synthesis of* 3-amino-6-((S)-3-hydroxy-4-methanesulfonylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide



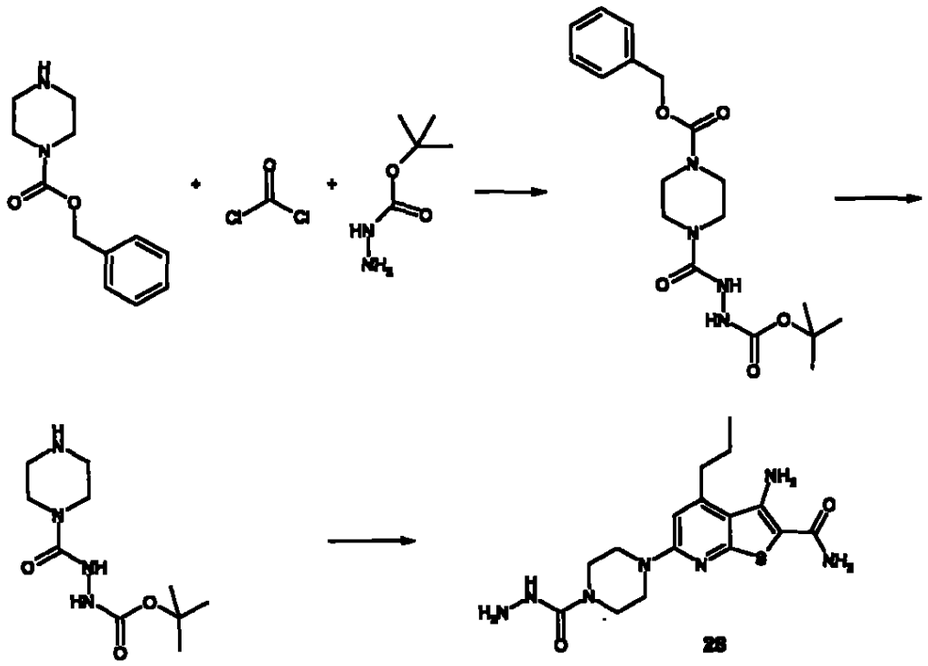
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A mixture of the 7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester (830 mg, 4.2 mmol), methylsulfonamide (1.2 g, 12.5 mmol), potassium carbonate (829 mg, 12.5 mmol), magnesium sulfate (1.5 g, 12.5 mmol) in MeOH (15 mL) was heated under Ar in a

pressure tube at 90 °C overnight. The mixture was then cooled to room temperature, diluted with CH_2CL_2 (10 mL), filtered through diatomaceous earth and concentrated. The crude product was further purified by column chromatography on silica gel using EtOAc as elutant to give 504 mg the desired hydroxypiperidine intermediate.

The above intermediate (118 mg, 0.4 mmol) was dissolved in MeOH (1mL). To this solution was added 4M HCL (0.2 mL in dioxane) dropwise. The mixture was stirred at room temperature overnight and concentrated. The product thus obtained was dissolved in dioxane, basified with 300 microL of triethylamine, and reacted with 144 mg (0.376 mmol) of 2-(3-cyano-4-*n*-propyl -6-trifluoromethanesulfonylpyridin-2-ylmercapto)acetamide, by the procedure described in Example 26, to provide 73 mg of the title compound.

Example 28 : Synthesis of 3-amino-6-(4-hydrazinocarbonyl-piperazin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide



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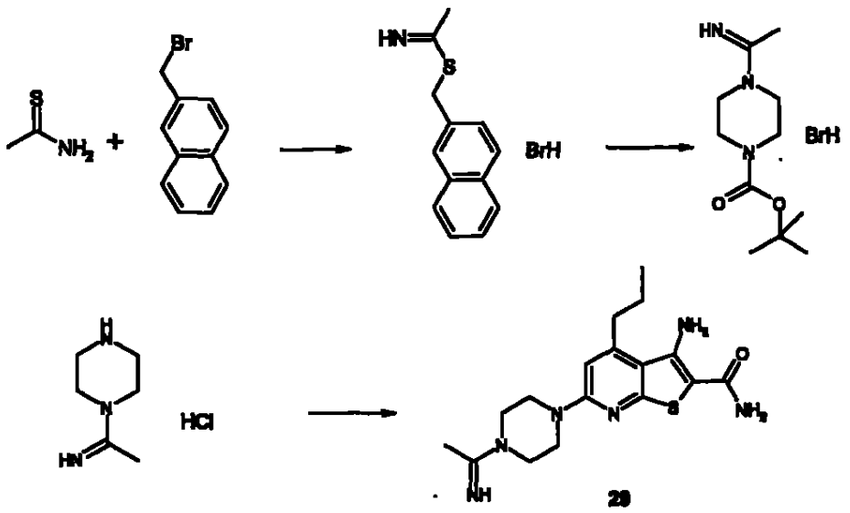
To a phosgene solution (20% solution in toluene) at 0 °C was added piperazine-1-carboxylic acid benzyl ester (0.385 mL, 1.996 mmol) and diisopropylethyl amine (0.383

mL, 4.397 mmol) in 5 mL of CH_2Cl_2 dropwise. The resulting pale yellow mixture was stirred 2 h warming to room temperature under Ar. The phosgene solution was removed by vacuum distillation. 20 mL of anhydrous CH_2Cl_2 was added. The reaction vessel was cooled to 0 °C and hydrazinecarboxylic acid *tert*-butyl ester and diisopropylethyl amine (0.383 mL, 4.397 mmol) was added in one portion. The reaction was warmed to room temperature and stirred for 1 h. The reaction was quenched with 10 mL of saturated $NaHCO_3$, diluted with 30 mL of EtOAc, then washed with 2 x 30 mL of saturated NH_4Cl solution and 30 mL of brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to provide 720 mg of 4-(*N*-*tert*-butoxycarbonyl-hydrazinocarbonyl)-piperazine-1-carboxylic acid benzyl ester as a white solid.

The above benzyl ester (720 mg, 1.913 mmol) was dissolved into 10 mL of EtOH and placed in a round-bottom flask. 10% Pd/C (300 mg) was added and the reaction was placed under 1 atm of H_2 in a balloon. The reaction was allowed to stir overnight, then was filtered through a plug of diatomaceous earth and concentrated to give 465 mg of 4-(*N*-*tert*-butoxycarbonyl-hydrazinocarbonyl)-piperazine as a pale white solid.

N'-[4-(3-Amino-2-carbamoyl-4-propyl-thieno[2,3-*b*]pyridin-6-yl)-piperazine-1-carbonyl]-hydrazinecarboxylic acid *tert*-butyl ester was prepared from the above intermediate as described in Example 26. Removal of the *t*-Boc protecting group by dissolving in EtOAc/CH_2Cl_2 and treatment with 4 N HCl in dioxane provided the title compound.

Example 29: Synthesis of 3-amino-6-[4-(1-imino-ethyl)-piperazin-1-yl]-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide

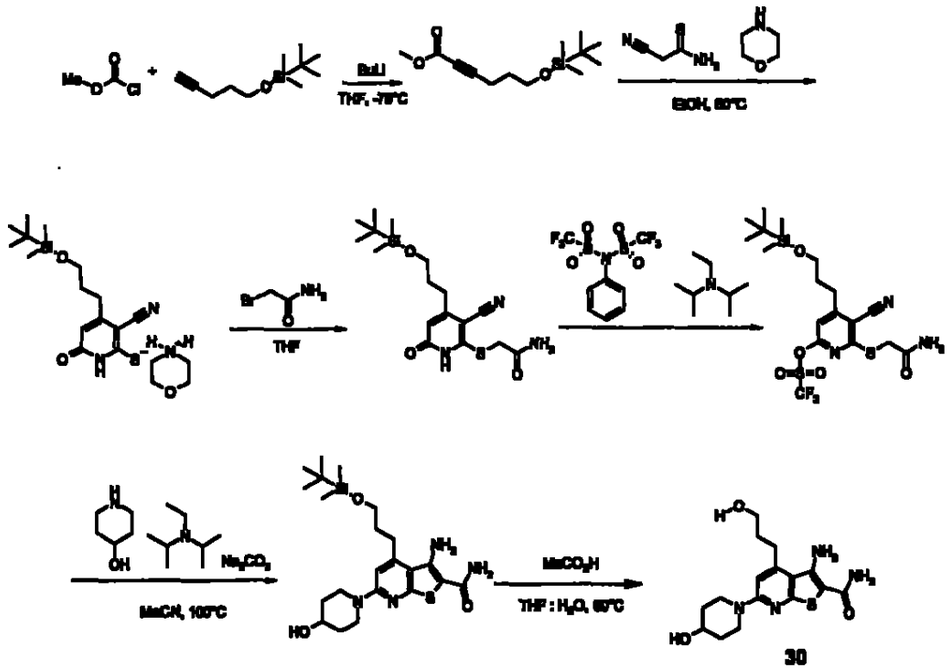


Thioacetamide (326.0 mg, 4.339 mmol) and 2-bromomethyl-naphthalene (959.0 mg, 4.337 mmol) were placed in a 50 mL round-bottom flask. 20 mL of $CHCl_3$ were added and the mixure was refluxed for 3 h at which time a white precipitate formed. The mixture was cooled and the precipitate collected. The precipitate was washed with 20 mL of CH_2Cl_2 and placed under vacuum for drying to give 1.01 g of thioacetimidic acid naphthalen-2-ylmethyl ester hydrobromide salt as a fine white powder.

The above hydrobromide salt (850.0 mg, 2.869 mmol) was placed into a 25 mL round-bottom flask. To this was added 10 mL of EtOH resulting in a suspension. The flask was placed in an ice bath and piperazine-1-carboxylic acid *tert*-butyl ester (534.4 mg, 2.869 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stirred an additional 3 h. The heterogenous solution was diluted with 40 mL of EtOAc and washed with 2 x 30 mL of H_2O. The aqueous phase was concentrated to near dryness, azeotroped with 2 x 20 mL of toluene to give a white solid. The solid was suspended in CH_2Cl_2/hexane and concentrated to dryness. The material was placed under vacuum overnight, affording 769 mg of 4-(1-imino-ethyl)-piperazine-1-carboxylic acid *tert*-butyl ester hydrobromide salt as a white solid.

The *t*-Boc protecting group of the above intermediate was removed as described in Example 28 and the resulting intermediate reacted further as described in Example 26 to provide the title compound.

Example 30: Synthesis of 3-amino-6-(4-hydroxy-piperidin-1-yl)-4-(3-hydroxy-propyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide



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To a solution of 7.98 g (40.2 mmol) of *t*-Butyl-dimethyl-pent-4-ynyloxy-silane (J.A. Marshall and B.S. DeHoff, *J. Org. Chem.*, 1986, *51*, 863) in THF (100 mL), cooled to –78 °C, was added a solution of *n*-butylithium in hexanes (28.0 mL of a 1.6 M solution). The mixture was stirred at –78 °C for 1 h then transferred, via cannula, to a flask containing a solution of 4.5 mL (58 mmol) of methyl chloroformate in THF (100 mL) cooled to –78 °C. The reaction was stirred at –78 °C for 2 h then excess base was consumed by addition of a saturated aqueous solution of NH_4Cl. The mixture was diluted with H_2O and washed with Et_2O. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography

using a 5% solution of EtOAc in hexanes as the eluent to provide, after concentration of the solvent, 6.18 g (60%) of the desired ester as a clear oil.

To a solution of 6.18 g (24.1 mmol) of the above ester in EtOH (120 mL) was added 2.2 mL (25 mmol) of morpholine. The mixture was heated at 60 °C for 3 h. The reaction mixture was cooled to room temperature and 2.5 g (25 mmol) of 2-cyanoacetamide was added as a solid in one portion. The reaction mixture was then heated at 60 °C for 15 h then cooled to room temperature and concentrated under reduced pressure. The residue was suspended in Et_2O and washed with H_2O. The combined aqueous phase was back extracted with Et_2O. The aqueous phase was lyophilized to provide 3.5 g (30.8%) of 4-[3-(*t*-butyl-dimethyl-silanyloxy)-propyl]-3-cyano-6-oxo-1,6-dihydro-pyridine-2-thiolate morpholine salt; as a yellow powder.

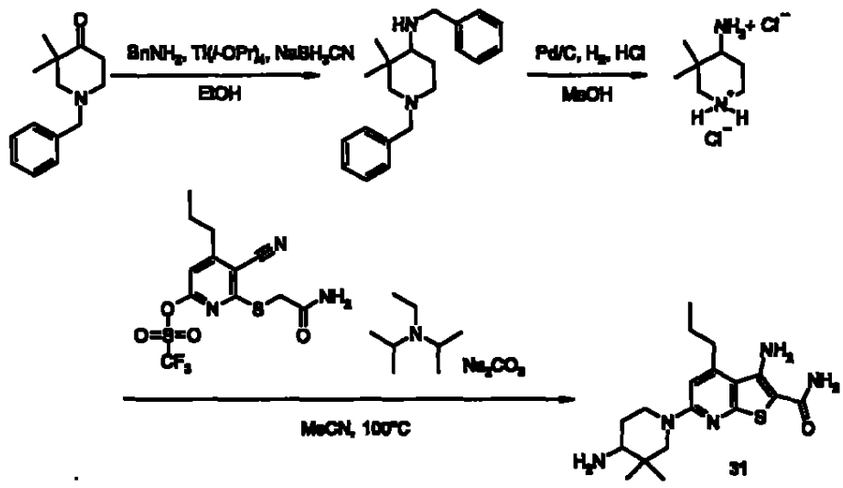
To a solution of 0.940 g (2.28 mmol) of the above morpholine salt in THF (15 mL), cooled to 0 °C, was added 0.315 g (0.280 mmol) of 2-bromoacetamide as a solid in one portion. The mixture was stirred and allowed to slowly warm to room temperature over a 2 h period during which time salts precipitated from solution. The mixture was filtered through diatomaceous earth to remove solids and the filter pad was washed with EtOAc. The mixture was concentrated under reduced pressure to provide 0.385 g (44%) of 2-{4-[3-(*t*-butyl-dimethyl-silanyloxy)-propyl]-3-cyano-6-oxo-1,6-dihydro-pyridin-2-ylsulfanyl}-acetamide as an orange foam.

To a solution of 2.32 g (6.08 mmol) of the above acetamide in THF (25 mL), cooled to 0 °C, was added 2.2 g (6.2 mmol)of *N*-phenyltrifluoromethanesulfonimide and 1.2 mL (6.7 mmol) of *N,N*-diisopropylethylamine. The mixture was stirred for 3 h as it slowly warmed to room temperature. The mixture was poured into H_2O and washed with EtOAc. The combined organic phase were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using a 0-50% gradient of A (10% MeOH in CH_2Cl_2) to B (CH_2Cl_2) to provide, after concentration of the eluent, 0.832 g (26%) of the desired trifluoromethanesulfonyl ester as an orange oil.

To a solution of 0.832 g (1.62 mmol) of the above trifluoromethanesulfonyl ester in 1,4-dioxane (30 mL) was added 0.175 g (1.73 mmol) of 4-hydroxypipiridine and 0.32 mL (1.79 mmol) of *N,N*-diisopropylethylamine. The mixture was heated to 80 °C for 5 h. The reaction was cooled to room temperature and an aqueous solution of Na_2CO_3 (8.0 mL of a 2.0 M solution) was added. The mixture was heated to 100 °C for 3 days then cooled to room temperature and diluted with H_2O. The mixture was washed with CH_2Cl_2 and the combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using a 0-50% gradient of A (10% MeOH in CH_2Cl_2) to B(CH_2Cl_2) to provide, after concentration of the eluent, 0.232 g (31%) of 3-amino-4-[3-(*t*-butyl-dimethyl-silanyloxy)-propyl]-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide as a yellow powder.

To a solution of 0.23 g (0.49 mmol) of the above amide in a 1 : 1 mixture of THF : H_2O (1.0 mL) was added 0.50 mL (8.7 mmol) of glacial acetic acid. The mixture was heated to 50 °C for 15h then cooled to room temperature and concentrated under reduced pressure which cause a solid to precipitate from solution. The material was collected by filtration and washed with H_2O and CH_2Cl_2 then dried under vacuum to provide 0.106 g (61%) of the title compound as a white solid.

Example 31: Synthesis of 3-Amino-6-(4-amino-3,3-dimethyl-piperidin-1-yl)-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide (5).



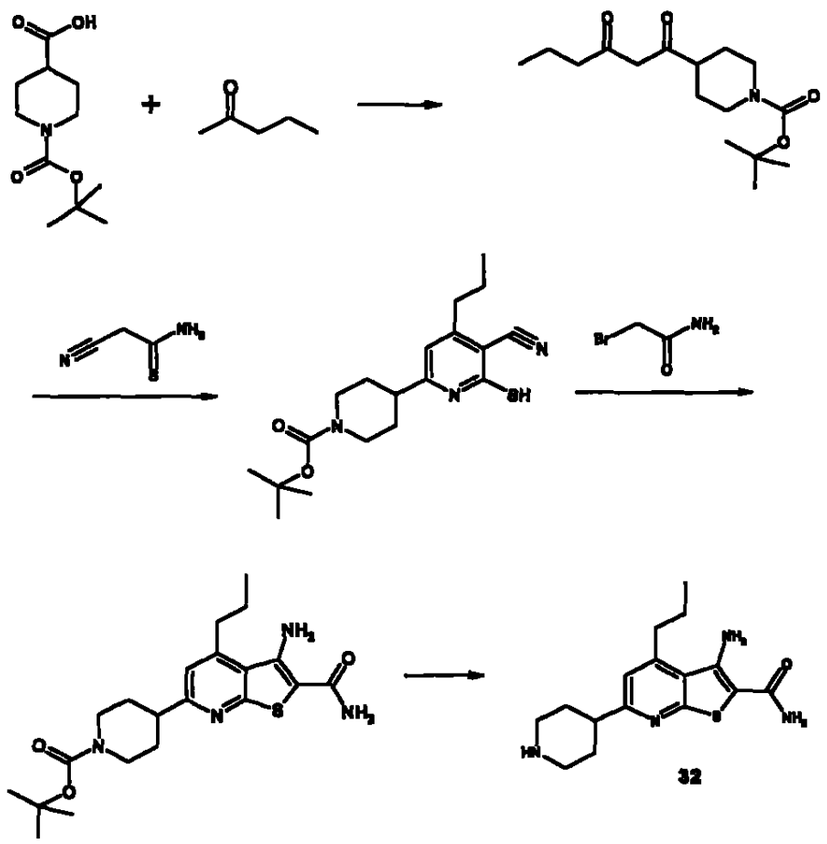
A mixture of 0.10 g (0.46 mmol) of 1-benzyl-3,3-dimethyl-piperidin-4-one, 0.055 mL (0.50 mmol) of benzyl amine, and 0.19 mL (0.64 mmol) of titanium isopropoxide was stirred at room temperature for 1h. The mixture was diluted with EtOH (1 mL) which caused the yellow solution to turn cloudy. To the reaction was added 0.031 g (0.49 mmol) of sodium cyanoborohydride and the mixture was stirred at room temperature for 20h. The mixture was diluted with H_2O (1 mL) then filtered through diatomaceous earth to remove precipitates. The filter pad was washed with MeOH and the mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using a 0-40% graident of A (10% MeOH in CH_2Cl_2) to B (CH_2Cl_2) to provide, after concentration of the eluent, 0.069 g (44 %) of the desired benzyl amine as a clear oil.

To a solution of 0.069 g (0.22 mmol) of the above benzyl amine in MeOH (5 mL) placed in a heavy walled pressure vessel was added 0.049 g (0.046 mmol) of palladium on carbon and 0.050 mL (0.60 mmol) of concentrated HCl. The mixture was placed under an atmosphere of hydrogen (50 psi) and shaken for 24h. The mixture was filtered through a plug of diatomaceous earth and the filter pad was washed with MeOH. The organic phase

was concentrated under reduced pressure to provide 0.041 g (91%) of the desired 4-amino-3,3-dimethylpiperidine diHCl salt as a white solid.

To a solution of 0.075 g (0.20 mmol) of trifluoromethanesulfonic acid 6-carbamoylmethylsulfanyl-5-cyano-4-propyl-pyridin-2-yl ester in 1,4-dioxane (5 mL) was added 0.041 g (0.20 mmol) of the above diHCl salt and 0.11 mL (0.61 mmol) of *N,N*-diisopropylethylamine. The mixture was heated at 60 °C for 15 h then cooled to room temperature and an aqueous solution of Na_2CO_3 (0.5 mL of a 2M solution) was added. The mixture was heated to 100 °C for 3d then cooled to room temperature, diluted with H_2O and washed with CH_2Cl_2. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography using a 0-50% gradient of A (10% MeOH in CH_2Cl_2) to B (CH_2Cl_2) to provide, after concentration of the eluent, 0.019 g (27 %) of the title compound as a yellow solid.

Example 32: Synthesis of 3-amino-6-piperidin-4-yl-4-propyl-3a,7a-dihydro-thieno[2,3-*b*]pyridine-2-carboxylic acid amide dihydrochloride



1-Boc-piperidine-4-carboxylic acid (4.4 g, 19.2 mmol) in oxalyl chloride (50 mL) was heated at reflux for 3 h and then concentrated and dried in vacuo to give the acid chloride, 4-chlorocarbonyl-piperidine-1-carboxylic acid *tert*-butyl ester.

To a stirred solution of LDA (1.8 M in THF/heptane/ethylbenzene, 21.3 mL, 38.4 mmol) in dry THF (50 mL) at -50 °C was added 2-pentanone (4.1 mL, 38.4 mmol), and after 10 min, a solution of the above acid chloride in dry THF (50 mL) was added. The reaction was allowed warming to room temperature and stirred overnight. It was diluted with 1 N HCl (500 mL), extracted with dichloromethane, washed with saturated sodium bicarbonate

and brine, dried over sodium sulfate, concentrated. It was purified by chromatography on silica gel (EtOAc/dichloromethane = 1/10) to give the desired diketone intermediate: 4-(3-oxo-hexanoyl)-piperidine-1-carboxylic acid *tert*-butyl ester (2.1 g).

A stirred mixture of the dikstone (2.1g, 7.1 mmol) and 2-cyanothioacetamide (1.42 g, 14.2 mmol) in EtOH (30 mL) was heated at 70 ^{o}C overnight. It was concentrated and chromatography on silica gel (MeOH/dichloromethane = 1/10) gave 1.8 g of 5-cyano-6-mercapto-4-propyl-3',4',5',6'-tetrahydro-2'*H*-[2,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester.

A stirred mixture of the above *tert*-butyl ester (0.9 g, 2.49 mmol) and bromoacetamide (0.38 g, 2.75 mmol) in dry dioxane (20 mL) was heated at 80 ^{o}C for 2 h. A solution of sodium carbonate (400 mg) in water (7 mL) was added and the reaction was heated at reflux overnight. It was diluted with water (100 mL) and the precipitates were filtered and dried to give 0.85 g of 4-(3-amino-2-carbamoyl-4-propyl-3a,7a-dihydro-thieno[2,3-*b*]pyridin-6-yl)-piperidine-1-carboxylic acid *tert*-butyl ester.

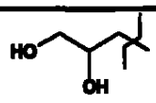
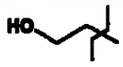
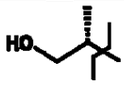
To a stirred solution of the above *tert*-butyl ester (600 mg, 1.43 mmol) in dry dichloromethane (35 mL) was added HCl/dioxane (4 N, 2 mL). Precipitates appeared immediately. It was concentrated and dried in vacuo to give the title compound as the dihydrochloride salt (570 mg).

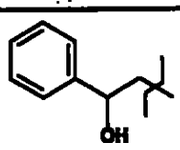
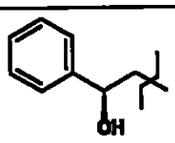
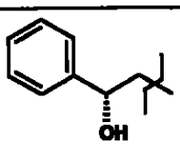
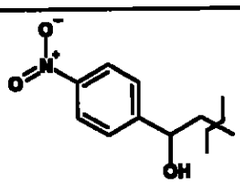
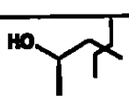
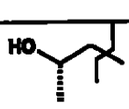
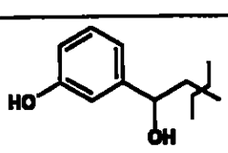
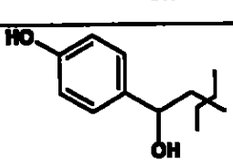
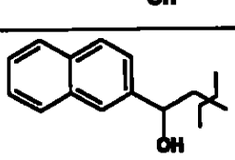
Example 33: Solid-Phase Reductive Amination

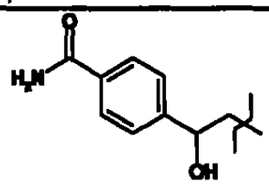
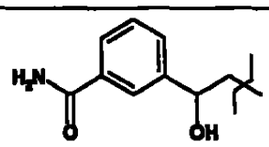
The following general procedure describes the method by which several 3-amino-6-(4-substituted amino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide compounds were made:



To 3-amino-6-(4-oxo-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide was added 1.5-3.00 equivalents of the desired amine, 1.42 solid-supported cyanoborohydride, and 8-9 equivalents acetic acid in THF. The reaction mixture was shaken on an orbital shaker for 15-72 h. The reaction was then filtered, and the solid-supported cyanoborohydride shaken with MeOH for 5-15 min, then filtered. To the combined filtrates was added 5 M NH_3 in MeOH and the resulting mixture was concentrated in vacuo. Purification was either via preparatory TLC (5-10% (5 M NH_3/MeOH)/EtOAc as eluant) or via flash silica chromatography (2.5-10% (5 M NH_3/MeOH)/CH_2Cl_2 as eluant) to afford compounds described in the table below:

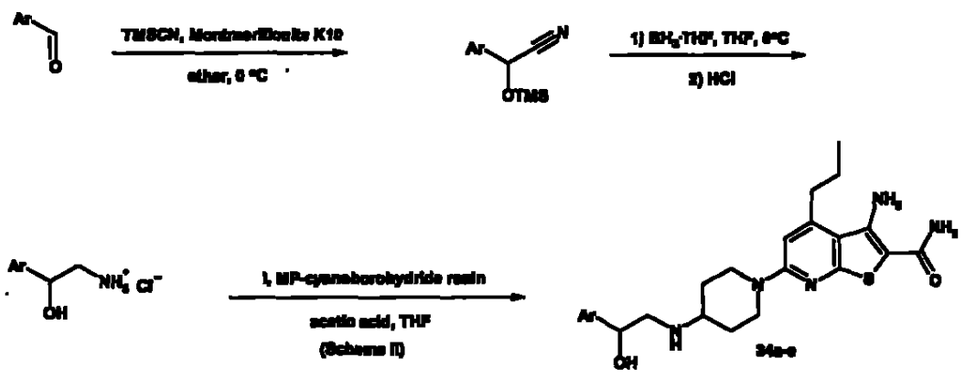
Cpd	R	Percent Yield
33a		45%
33b		65%
33c		51%

Cpd	R	Percent Yield
33d		44%
33e		56%
33f		53%
33g		26%
33h		18%
33i		9%
33j		41%
33k		54%
33l		62%

Cpd	R	Percent Yield
33m		34%
33n		55%

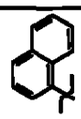
Example 34: Solid-Phase Reductive Amination

The following general procedure describes the method by which several amine intermediates were prepared for use in the preparation of 3-amino-6-(4-substituted amino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide compounds using the method in the Example above:

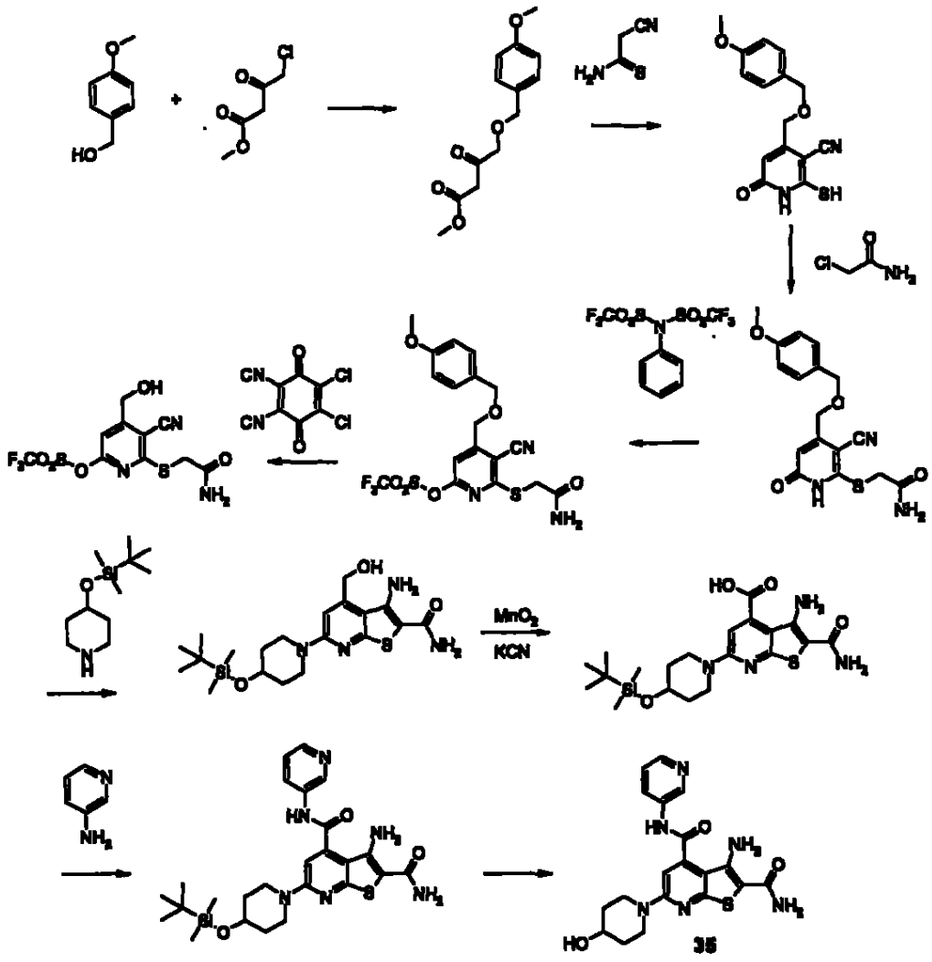


The desired aryl aldehyde was dissolved in ether and reacted with trimethylsilyl cyanide (1-2 eq.) at 0 °C using Montmorillonite K 10 (0.1-0.2 eq.) as an acidic catalyst. The reaction stirred 1-3 h, and then was filtered, and the filtrate concentrated in vacuo to afford compounds the corresponding trimethylsilyl ether. The ether was dissolved in THF and added to a solution of borane/THF at 0 °C. The reaction stirred for 17-24 h while the cold

bath expired. The reaction was cooled back down to 0 °C and quenched with MeOH, then concentrated in vacuo. The residue was taken up in EtOAc/CH_2Cl_2 and HCl/MeOH or HCl/dioxane was added. The white solid that resulted was isolated either by suction filtration or concentration in vacuo to afford the corresponding hydroxyl amine HCl salts. These HCl salts were then reacted and purified according to the method described in Example 33 to provide compounds 34a-34e shown in the table below:

	Ar	% yield
34a	*p*-MeOPh	13%
34b	*p*-ClPh	17%
34c	*p*-MeO_2CPh	61%
34d		58%
34e	*m*-MeO_2CPh	52%

Example 35: Synthesis of 3-amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-pyridin-3-ylamide



4-Methoxybenzyl alcohol (11.0 g, 79.7) was added in portions to a suspension of 6.38 g 60% NaH in 110 mL THF at 40° and the reaction was stirred 30 min under Ar. A solution of 10.00 g methyl 4-chloroacetoacetate in 40 mL THF was dripped in at 40° C and the reaction was stirred at room temperature overnight. aqueous NH_4Cl was added and the product was extracted into EtOAc, washed with aqueous NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated to 18.5 g oil. This was flash-chromatographed eluting with 15% acetone/petroleum ether to provide one fraction of 2.99 g oil, that was shown by

NMR(CDCl3) to contain showed 80% pure 4-(4-methoxy-benzyloxy)-3-oxo-butyric acid methyl ester. A second fraction of 12.01 g oil was obtained that contained 55% 4-(4-methoxy-benzyloxy)-3-oxo-butyric acid methyl ester by NMR with the rest being mostly unreacted starting material.

4-(4-Methoxy-benzyloxy)-3-oxo-butyric acid methyl ester was converted to 2-[3-cyano-6-trifluorometanesulfonyloxy-4-(4-methoxy-benzyloxymethyl)-pyridin-2-ylsulfanyl]-acetamide by procedures described above in Examples 8 and 30.

The above intermediate (9.00 g) was dissolved in 171 mL CH_2Cl_2 and 9 mL water. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (12.47 g) was added and the dark suspension was stirred for 6 h then another 4.16 g DDQ was added and the reaction was stirred overnight. The reaction was decanted and the remaining gummy red precipitate was triturated 2X with CH_2Cl_2 and decanted. The precipitate was dissolved in EtOAc, washed with water (4X) and aqueous $NaHCO_3$, dried and concentrated to a brown solid. This was triturated in CH_2Cl_2, filtered and dried to provide 4.61 (68%) of the desired hydroxymethylpyridine intermediate as a tan solid.

tert-Butyldimethylsilyl chloride (8.94 g) was added to a solution of 5.00 g 4-hydroxypiperidine in 25 mL DMF and the exothermic reaction was placed in an icebath for 10 min and then 10.10 g imidazole was added and the reaction was stirred at room temperature under Ar overnight. TLC showed mostly starting material. 4-Dimethylaminopyridine (0.60 g) and 7.45 g more *tert*-butyldimethylsilyl chloride were added and the reaction was stirred overnight. This was poured into aqueous Na_2CO_3, extracted with EtOAc (3X), washed with water (4X), dried and concentrated to 15.3 g yellow oil. This was flash-chromatographed eluting with 0-10% MeOH/CH_2Cl_2 to give several fractions of varying purity. The best contained 2.9g yellow oil that was determined by NMR(CDCl3) to contain 55 mol% 4-(*tert*-butyl-dimethyl-silanyloxy)-piperidine: 45 mol% *tert*-butyl-dimethylsilyl chloride .

The crude 4-(*tert*-butyl-dimethyl-silanyloxy)-piperidine was coupled with the 4-hydroxymethylpyridine intermediate from abpve by the procedure described in Example

30 to provide 3-amino-6-[4-(*tert*-butyl-dimethyl-silanyloxy)-piperidin-1-yl]-4-hydroxymethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide

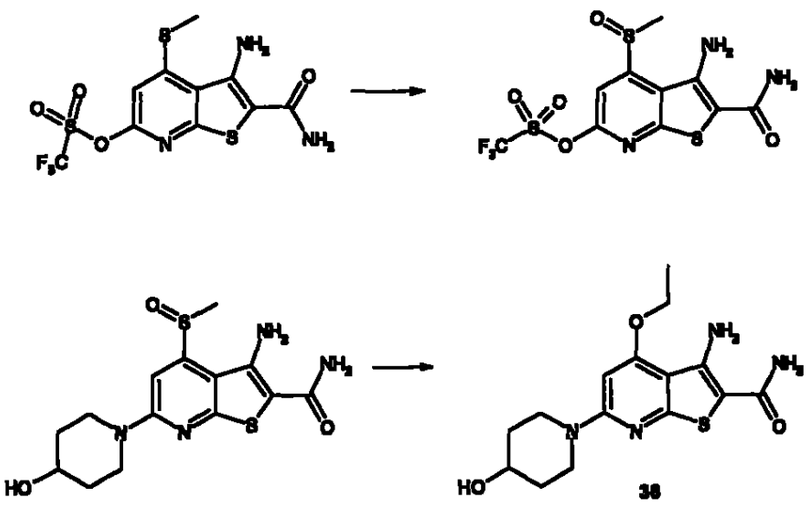
A mixture of 400 mg of the above amide, 298 mg KCN, 1.59 g MnO_2 and 157 microL acetic acid was suspended in 16 mL MeOH and the reaction was capped and stirred 2 days. The reaction mixture was filtered through diatomaceous earth, concentrated, and flash-chromatographed eluting with 5% MeOH/CH_2Cl_2 to provide 254 mg (60%) 3-amino-6-[4-(*tert*-butyl-dimethyl-silanyloxy)-piperidin-1-yl]-2-carbamoyl-thieno[2,3-b]pyridine-4-carboxylic acid methyl ester as determined by NMR(DMDO). Further elution with 25% MeOH/CH2Cl2/1% HOAc brought down 151 mg (36%) of the corresponding carboxylic acid as determined by NMR(DMDO).

81 mg 1-[Dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride was added a solution of 9.5 mg of the above carboxylic acid in 0.5 mL dry DMF at 0° C. After 15 min, 99 mg 3-aminopyridine was added and the reaction was stirred at room temperature overnight. This was diluted with EtOAc, washed with water (4X) and aqueous NH_4Cl (3X), dried, concentrated and purified by preparative TLC in 7.5%MeOH/CH_2Cl_2/0.5% NH_4OH. The major band was eluted with 50% MeOH/CH_2Cl_2 to provide 12.8 mg oil that was shown to be a mixture of 3-amino-6-[4-(*tert*-butyl-dimethyl-silanyloxy)-piperidin-1-yl]-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-pyridin-3-ylamide and unreacted starting material by NMR(CD_3OD). The mixture was dissolved in 0.5 mL CH_2Cl_2 and 50 microL HF-pyridine complex was added and the reaction was stirred overnight. The clear solution was decanted off the gummy precipitate that was washed and decanted 2X more with CH_2Cl_2. The precipitate was dissolved in 10% MeOH/CH_2Cl_2, neutralized with a drop of concentrated NH_4OH, applied to a preparative TLC plate and developed twice in 10% MeOH/CH_2Cl_2/1% NH_4OH. The band was eluted with 50% MeOH/CH_2Cl_2 to provide 2.0 mg (23%) the title compound.

3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-methylamide:

This compound was prepared from the above 3-amino-6-[4-(*tert*-butyl-dimethyl-silanyloxy)-piperidin-1-yl]-2-carbamoyl-thieno[2,3-b]pyridine-4-carboxylic acid methyl ester by combining of 10 mg of the ester in 1 mL CH_2Cl_2 with added 0.5 mL 2M methylamine in THF. The reaction was capped and stirred 2 days. The reaction was concentrated to give 3-amino-6-[4-(*tert*-butyl-dimethyl-silanyloxy)-piperidin-1-yl]-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-methylamide as a yellow solid. This was dissolved in 0.5 mL 10% MeOH/CH_2Cl_2 and 50 microL HF-pyridine complex was added and the reaction was capped and stirred overnight. The reaction was blown down with N_2, dissolved in EtOAc, washed with aqueous $NaHCO_3$ and queous NH_4Cl, dried, concentrated and purified by preparative TLC eluting with 10% MeOH/CH_2Cl_2. The band was eluted with 25% MeOH/CH_2Cl_2 to get 2.7 mg (35%) of the title compound as a yellow solid.

Example 36: Synthesis of 3-amino-6-(4-hydroxy-piperidin-1-yl)-4-ethoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide



Trifluoromethanesulfonic acid 3-amino-2-carbamoyl-4-methylsulfanyl-thieno[2,3-b]pyridin-6-yl ester (500 mg, 1.29 mmol) was dissolved in MeOH (10 mL), chilled to 0 °C, and potassium peroxymonosulfate (950 mg, 1.55 mmol) dissolved in water (15 mL) was

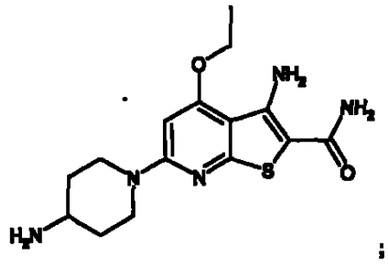
added. The mixture was stirred for 18 h after which it was filtered to give the desired trifluoromethanesulfonic acid 3-amino-2-carbamoyl-4-methanesulfinyl-thieno[2,3-b]pyridin-6-yl ester in 86 % yield.

The above ester (100 mg, 0.25 mmol) was dissolved in dioxane (5 mL), 4-hydroxypiperidine (100 mg, 1.0 mmol) was added and the mixture was stirred overnight at room temperature. The mixture was diluted with saturated ammonium chloride solution and the aqueous phase was extracted with dichloromethane several times. The combined organic phases were dried over $MgSO_4$ and evaporated. The product was finally purified by column chromatography to yield 43 mg of 3-amino-6-(4-hydroxy-piperidin-1-yl)-4-methanesulfinyl-thieno[2,3-b]pyridine-2-carboxylic acid amide (49 %).

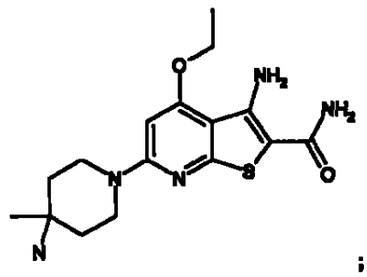
The above product was dissolved in EtOH and 235 microL of a 2.7 M solution of sodium ethoxide in EtOH was added. The solution was heated at 80 °C for 6 h. The mixture was poured into aqueous NH_4Cl solution and the aqueous phase was extracted three times with dichloromethane. The combined phases were dried over $MgSO_4$, filtered, and evaporated. The product was purified by column chromatography to yield 23 mg of the title compound (54 %).

The following compounds were prepared in the manner described above:

3-Amino-6-(4-amino-piperidin-1-yl)-4-ethoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide:

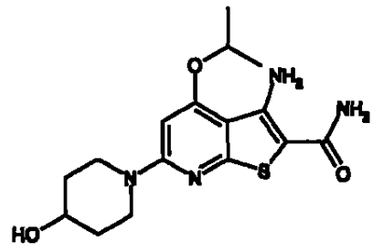


3-Amino-6-(4-amino-4-methyl-piperidin-1-yl)-4-ethoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide:



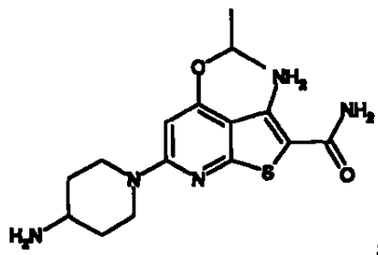
;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-isopropoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide:



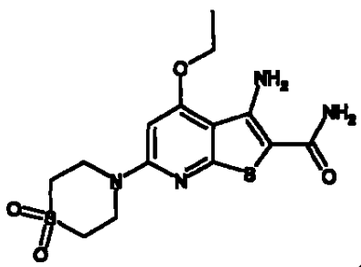
;

3-Amino-6-(4-amino-piperidin-1-yl)-4-isopropoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide:



;

3-Amino-6-(1,1-dioxo-1-thiomorpholin-4-yl)-4-ethoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide:



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ASSESSMENT OF BIOLOGICAL PROPERTIES

The inhibition of IKKα and IKKβ by the compounds of the present invention was determined with the following assay that measures the phosphorylation of the IκBα substrate by the respective kinases. The enzymes used in the assay were N-terminally flag-tagged versions of the human IKKβ or IKKα and the substrate was a GST fusion protein with IκBα (amino acids 1-54).

The reaction mixtures (60 µl) contained 20 mM HEPES pH 7.5, 10 mM $MgCl_2$, 2 mM $MnCl_2$, 100 mM NaCl, 100 µM Na_3VO_4, 20 mM ß-glycerophosphate, 1 mM DTT, 2% DMSO, 250 nM ATP, 0.4 nM [^{33}P]ATP (specific activity, 3000 Ci/mmol), IκBα substrate, IKK enzyme and test compound. The reaction mixtures contained either 3.6 µg/ml IKKα and 245 µg/ml IκBα or 0.9 µg/ml IKKβ and 53 µg/ml IκBα.

Reactions were initiated by adding a solution of IκBα substrate and ATP to polypropylene plates containing IKK enzyme that was pre-incubated for 5 minutes with test compound. Then the reaction mixtures were incubated for 1 hour at 25°C, placed on ice and quenched by the addition of 150 µl 10% trichloroacetic acid and 5% disodium pyrophosphate. After mixing, the entire contents of the quenched reaction mixtures were transferred to a pre-wetted Packard UniFilter filtration plate, aspirated and washed 6 times with 250 µl of ddH_2O using the Packard Filtermate Harvester. Filtration plates were then air dried, supplemented with 40 µl of Microscint 20 scintillation fluid and the ^{33}P-labeled reaction products were quantified using the Packard TopCount scintillation counter.

Compounds were tested in three-fold serial dilutions and inhibitor concentrations to achieve 50% inhibition of enzyme activity (i.e., IC_{50}) were derived from dose-reponse curves using SAS software (SAS Institute, Cary NC). A non-linear regression analysis based on the Hill equation was applied to the percent inhibition *versus* concentration data. In all cases, compound concentrations were verified by HPLC.

Compounds in the Tables in the Detailed Description of the Invention section were all evalnated in the assay for IKKβ inhibition and had IC_{50}'s of 10 μM or below. Compounds, listed below had IC_{50}'s below 1 μM in this assay:

3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-4-[(E)-2-(4-chloro-phenyl)-vinyl]-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-imidazol-1-yl-4-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-4-methyl-6-piperazin-1-yl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-carbamoyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-methyl-piperazin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-piperazin-1-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-methanesulfonyl-piperazin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(3-hydroxy-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-[4-(3-amino-propanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-4-(4-hydroxy-4-phenyl-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-[4-(2-amino-ethanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-

b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-oxo-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-carbamoyl-piperazin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-((S)-3-amino-pyrrolidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-((R)-3-amino-pyrrolidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-dimethylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-4-cyano-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

4-(3-Amino-2-carbamoyl-4-propyl-thieno[2,3-b]pyridin-6-yl)-piperazine-2-carboxylic acid methyl ester;

3-Amino-6-[4-(4-amino-butanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-((R)-2-amino-propanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-((S)-2-amino-propanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

6-(4-Acetylamino-piperidin-1-yl)-3-amino-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(piperidin-4-ylamino)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-4-methyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-methylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-methylsulfanyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-((E)-styryl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-nitro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-[(E)-2-(4-chloro-phenyl)-vinyl]-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-phenethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-aminomethyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-phenyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-[(E)-2-(2-chloro-phenyl)-vinyl]-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-fluoro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-methoxy-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-[1,4]diazepan-1-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-[4-(2,4-diamino-butanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-[4-(1-piperidin-4-yl-methanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-methyl-[1,4]diazepan-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-(3-nitro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-[(E)-2-(4-methoxy-phenyl)-vinyl]-

thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(3-amino-propylamino)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(3-carbamoyl-piperazin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(3-methyl-ureido)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

6-(4-Acetyl-[1,4]diazepan-1-yl)-3-amino-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(3-carbamoyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(3-amino-perhydro-azepin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(3-aminomethyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(2-aminomethyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-piperazin-1-yl-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide; and

3-Amino-6-(2-hydroxymethyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide.

Selected compounds from the Table in the Detailed Description of the Invention section were evaluated for IKKα inhibition. Compounds listed below had IC_{50}'s of 10 μM or below in this assay:

3-Amino-4-furan-2-yl-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-4-isopropoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide;

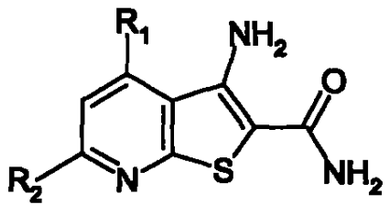
3-Amino-6-methyl-4-(4-nitro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-methyl-4-((E)-styryl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-4-(4-methanesulfonyl-phenyl)-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-4-[(E)-2-(4-fluoro-phenyl)-vinyl]-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-4-[(E)-2-(4-chloro-phenyl)-vinyl]-6-methyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-methyl-piperazin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-piperazin-1-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-((R)-3-amino-pyrrolidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-4-cyano-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-methylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-methylsulfanyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-((E)-styryl)-thieno[2,3-b]pyridine-2-carboxylic acid amide; and
3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-nitro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide.

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What is claimed is:

1. A compound of formula (I) :



(I)

wherein:

R_1 is

(a) phenyl or heteroaryl selected from furanyl, thienyl, pyridyl, pyrrolyl, imidazolyl and benzofuranyl, optionally substituted with one to two R_3,

(b) heterocyclyl selected from 1-piperidinyl, 1-piperazinyl, 1-pyrrolidinyl and 4-morpholinyl, optionally substituted with one to two groups selected from C_{1-6}alkyl, -CO_2C_{1-5}alkyl, phenyl, benzyl, -OH and -C(O)heteroaryl, wherein the heteroaryl is selected from furanyl, thienyl, pyridyl and pyrrolyl,

(c) $R_6(CH_2)_mO$-,

(d) R_6OCH_2-,

(e) $R_6(CH_2)_mNH$-,

(f) $R_6(CH_2)_p(CH{=}CH)_m$-,

(g) C_{1-6}alkyl, optionally partially of fully halogenated and optionally substituted with one to two R_9,

(h) C_{1-5}alkoxy, optionally partially of fully halogenated and optionally substituted with one to two R_9,

(i) C_{1-6}alkyl$S(O)_n$-, optionally partially of fully halogenated and optionally substituted with one to two R_9,

(j) $-N(R_4)(R_5)$, or

(k) $-C(O)NHR'$, wherein R' is R_6, pyridyl or $-CH_3$;

R_2 is

(a) C_{1-6}alkyl, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(b) C_{1-6}alkoxy, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(c) C_{1-6}alkylamino, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(d) C_{1-6}alkylthio, optionally partially or fully halogenated and optionally substituted with one to two R_{10},

(e) heterocyclyl$(CH_2)_m$- wherein said heterocycle is selected from piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, 1,4-diazacycloheptanyl, azepanyl, 2,5-diazabicyclo[2.2.1]heptanyl, oxazepanyl and thiomorpholino and is optionally substituted with one to three R_7,

(f) heterocyclylCH_2O- wherein the heterocyclyl is selected from 1-piperidinyl, 1-piperazinyl, 4-morpholinyl and 1-pyrrolidinyl, optionally substituted with C_{1-6}alkyl,

(g) phenyl, optionally substituted with one to three R_3,

(h) $-N(R_4)(R_5)$,

(i) heteroaryl selected from furanyl, thienyl, imidazolyl, pyridyl and pyrrolyl, or

(j) –H;

R_3 is chosen from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, halogen, -CN, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-S(O)_nC_{1-6}$alkyl, $-NO_2$, -OH, $-CF_3$, $-N(R_4)(R_5)$, $-NHC(O)NHC_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$ and phenyl optionally substituted with halogen, C_{1-6}alkyl, -CN or C_{1-6}alkoxy;

R_4 and R_5 are independently selected from H, C_{1-6}alkyl, -C(O)C_{1-6}alkyl, -SO_2C_{1-6}alkyl, phenyl, pyridyl, benzyl, piperidinyl, phenylethyl and $(CH_3)_3COC(O)$-;

R_6 is a phenyl group optionally substituted with one or two groups selected from halogen, C_{1-6}alkyl, -CN, -CO_2C_{1-6}alkyl, -C(O)NR_4R_5, -SO_2NH_2, -NO_2, -OH, -NH_2, -CF_3 and C_{1-6}alkoxy, or R_6 is C_{3-6}cycloalkyl, -CH_2OH, naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

R_7 is selected from –OH, -CN, oxo, -CO_2C_{1-6}alkyl, -CO_2H, -C(O)$N(R_4)(R_5)$, -$N(R_4)(R_5)$, -$CH_2N(R_4)(R_5)$, -CH_2OH, C_{1-6}alkyl, -CO_2benzyl, hydroxyC_{1-6}alkyl, -C(O)C_{1-6}alkyl$N(R_4)(R_5)$, -$NHCO_2C_{1-6}$alkyl, -NHC(O)$N(R_4)(R_5)$, -$S(O)_nC_{1-6}$alkyl, $(CH_3)_3COC(O)$-, phenyl, pyridyl, $H_2NCH(R_8)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- and -C(O)heterocyclyl, wherein said heterocyclyl is selected from piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl, hydroxyimino, hydrozinocarbonyl, sulfamoyl, methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, 2-hydroxy-1-methylethylamino, carbamoylmethylamino, N'-phenylhydrazinocarbonyl or toluene-4-sulfonylamino;

R_8 is selected from C_{1-6}alkyl, -$(CH_2)_{1-4}NH_2$, phenyl or benzyl;

R_9 is selected from oxo, -OH, -NR_4R_5, -CO_2H and C_{1-6}alkoxy;

R_{10} is selected from oxo, -OH, -$N(R_4)(R_5)$, C_{1-6}alkoxy, -C(O)C_{1-6}alkyl, -C(O)$N(R_4)(R_5)$, R_6, and heteroaryl selected from furanyl, thienyl, imidazolyl, pyridyl, indolyl and pyrrolyl;

m is 0 or 1;

n is 0, 1 or 2; and

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts, esters, tautamers, individual isomers, and mixtures of isomers thereof;

with the proviso that if R_1 is phenyl or heteroaryl, C_{1-6}alkyl, $-CF_3$, $-C(O)NR_4R_5$ or heterocyclyl, then R_2 is not C_{1-6}alkyl, phenyl, heteroaryl, $-CF_3$, or H.

2. The compound of Claim 1 wherein:

R_1 is

(a) phenyl or heteroaryl selected from furanyl, thienyl, pyridyl, pyrrolyl, imidazolyl and benzofuranyl optionally substituted with one to two R_3,
(b) $R_6(CH_2)_mO$-,
(c) R_6OCH_2-,
(d) $R_6(CH_2)_mNH$-,
(e) $R_6(CH_2)_p(CH=CH)_m$-,
(f) C_{1-6}alkyl, optionally partially of fully halogenated and optionally substituted with one to two R_9,
(g) C_{1-6}alkoxy, optionally partially of fully halogenated and optionally substituted with one to two R_9,
(h) C_{1-6}alkylthio,
(i) $-N(R_4)(R_5)$, or
(j) $-C(O)NHR'$, wherein R' is R_6, pyridyl or $-CH_3$,

R_2 is

(a) C_{1-6}alkyl, optionally substituted with R_{10},
(b) C_{1-6}alkoxy, optionally substituted with R_{10},
(c) C_{1-6}alkylamino, optionally substituted with R_{10},
(d) heterocyclyl selected from from 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, 1-pyrrolidinyl, 1,4-diazacycloheptan-1-yl, 1-azepanyl, 2,5-diazabicyclo[2.2.1]heptan-2-

yl, oxazepan-4-yl and 4-thiomorpholino and is optionally substituted with one to three R_7,

(e) heterocyclylCH$_2$O- wherein the heterocyclyl is selected from 1-piperidinyl, 1-piperazinyl, 4-morpholinyl and 1-pyrrolidinyl, optionally substituted with C$_{1-6}$alkyl, or

(f) –N(R_4)(R_5);

R_3 is chosen from C$_{1-6}$alkyl, C$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkyl, halogen, -CN, -CO$_2$H, -CO$_2$C$_{1-6}$alkyl, -S(O)$_n$C$_{1-6}$alkyl, -NO$_2$, -OH, -CF$_3$, -N(R_4)(R_5), -NHC(O)NHC$_{1-6}$alkyl, -C(O)N(R_4)(R_5) and phenyl optionally substituted with halogen, C$_{1-6}$alkyl, -CN or C$_{1-6}$alkoxy;

R_4 and R_5 are independently selected from H, C$_{1-6}$alkyl, -C(O)C$_{1-6}$alkyl, pyridyl, benzyl, piperidinyl and phenylethyl ;

R_6 is a phenyl group optionally substituted with one or two groups selected from Cl, F, C$_{1-6}$alkyl, -CN, CO$_2$C$_{1-6}$alkyl, C(O)NR_4R_5, -SO$_2$NH$_2$, -NO$_2$, -OH, -NH$_2$, -CF$_3$ and C$_{1-6}$alkoxy or R_6 is C$_{3-6}$cycloalkyl, -CH$_2$OH, naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

R_7 is selected from –OH, -CN, oxo, -CO$_2$C$_{1-6}$alkyl, -C(O)N(R_4)(R_5), -N(R_4)(R_5), -CH$_2$N(R_4)(R_5), CH$_2$OH, C$_{1-6}$alkyl, -C(O)C$_{1-6}$alkylN(R_4)(R_5), -NHC(O)N(R_4)(R_5), -S(O)$_n$C$_{1-6}$alkyl, H_2NCH(R_8)C (O)-, HO(CH$_2$)$_m$CH$_2$CH(NH$_2$)C(O)-, HOCH(R_6)CH$_2$NH- and -C(O)heterocyclyl, wherein said heterocyclyl is selected from piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl, hydroxyimino, hydrozinocarbonyl, sulfamoyl, methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, 2-hydroxy-1-methylethylamino, carbamoylmethylamino, N'-phenylhydrazinocarbonyl or toluene-4-sulfonylamino;

R_8 is selected from C$_{1-6}$alkyl, -(CH$_2$)$_{1-4}$NH$_2$, phenyl or benzyl;

R_9 is –OH;

R_{10} is selected from –OH, -N(R_4)(R_5), C$_{1-6}$alkoxy and heteroaryl selected from furanyl, thienyl and pyridyl;

m is 0 or 1;

n is 0, 1 or 2; and

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof;

with the proviso that if R_1 is phenyl or heteroaryl, C_{1-6}alkyl, $-CF_3$, $-C(O)NR_4R_5$ or heterocyclyl, then R_2 is not C_{1-6}alkyl, phenyl, heteroaryl, $-CF_3$, or H.

3. The compound of Claim 1 wherein:

R_1 is

(a) phenyl or heteroaryl selected from furanyl, thienyl and pyridyl, optionally substituted with one to two R_3,
(b) $R_6(CH_2)_mO$-,
(c) R_6OCH_2-,
(d) $R_6(CH_2)_mNH$-,
(e) $R_6(CH_2)_p(CH{=}CH)_m$-,
(f) C_{1-6}alkyl,
(g) C_{1-6}alkylOH,
(h) $-CF_3$,
(i) C_{1-6}alkoxy,
(j) $-OC_{1-6}$alkylOH,
(k) C_{1-6}alkylthio,
(l) $-N(R_4)(R_5)$, or
(m) $-C(O)NHR'$, wherein R' is R_6, pyridyl or $-CH_3$;

R_2 is heterocyclyl wherein said heterocycle is selected from 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, 1-azepanyl, 1-pyrrolidinyl, 1,4-diazacycloheptan-1-yl, 1-azepanyl 2,5-

diazabicyclo[2.2.1]heptan-2-yl, oxazepan-4-yl and 4-thiomorpholino and is optionally substituted with one to three R_7,

R_3 is chosen from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, halogen, -CN, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-S(O)_nC_{1-6}$alkyl, $-NO_2$, -OH, $-CF_3$, $-N(R_4)(R_5)$, $-NHC(O)NHC_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$ and phenyl optionally substituted with halogen, C_{1-6}alkyl, -CN or C_{1-6}alkoxy;

R_4 and R_5 are independently selected from H, C_{1-6}alkyl, $-C(O)C_{1-6}$alkyl, pyridyl, benzyl, piperidinyl and phenylethyl;

R_6 is a phenyl group optionally substituted with one or two groups selected from Cl, F, C_{1-6}alkyl, -CN, $-CO_2C_{1-6}$alkyl, $-C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ and C_{1-6}alkoxy, or R_6 is C_{3-6}cycloalkyl, $-CH_2OH$, naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

R_7 is selected from –OH, -CN, oxo, $-CO_2C_{1-6}$alkyl, $-CO_2H$, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, $-CH_2OH$, C_{1-6}alkyl, $-C(O)C_{1-6}$alkylN$(R_4)(R_5)$, $-NHC(O)N(R_4)(R_5)$, $-S(O)_nC_{1-6}$alkyl, phenyl, pyridyl, $H_2NCH(R_8)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_4)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- and -C(O)heterocyclyl, wherein said heterocyclyl is selected from piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl, hydroxyimino, hydrozinocarbonyl, sulfamoyl, methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, 2-hydroxy-1-methylethylamino, carbamoylmethylamino, N'-phenylhydrazinocarbonyl or toluene-4-sulfonylamino;

R_8 is selected from C_{1-6}alkyl, $-(CH_2)_{1-4}NH_2$, phenyl or benzyl;

m is 0 or 1;

n is 0, 1 or 2; and

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof.

4. The compound of Claim 1 wherein:

R_1 is

(a) phenyl, optionally substituted with one to two R_3,
(b) $R_6CH=CH-$
(c) C_{1-6}alkyl,
(d) $-C_{2-3}$alkylOH,
(e) $-CF_3$,
(f) $-C_{1-6}$alkoxy,
(g) $-OC_{2-3}$alkylOH,
(h) $-C_{1-6}$alkylthio, or
(i) $-C(O)NHR'$, wherein R' is R_6, pyridyl or $-CH_3$;

R_2 is heterocyclyl wherein said heterocycle is selected from 1-piperidinyl, 1-piperazinyl, 1-azepanyl, 1,4-diazacycloheptan-1-yl and 1-azepanyl and is optionally substituted with one to three R_7;

R_3 is chosen from $-CH_3$, $-OCH_3$, F, Cl, $-CO_2CH_3$, $-SO_2CH_3$ and $-NO_2$;

R_4 and R_5 are independently selected from H, $-CH_3$ and benzyl;

R_6 is a phenyl group optionally substituted with one or two groups selected from Cl, F, C_{1-6}alkyl, -CN, CO_2C_{1-6}alkyl, $C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ and C_{1-6}alkoxy or R_6 is C_{3-6}cycloalkyl, $-CH_2OH$, naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

R_7 is selected from –OH, -CN, oxo, $-CO_2C_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, CH_2OH, C_{1-6}alkyl, $-C(O)C_{1-6}$alkyl$N(R_4)(R_5)$, $-NHC(O)N(R_4)(R_5)$, $-S(O)_2C_{1-6}$alkyl, $H_2NCH(R_8)C(O)-$, $HO(CH_2)_mCH_2CH(NH_2)C(O)-$, $HOCH(R_6)CH_2NH-$, $R_6CH_2CH(OH)CH_2NH-$, $R_6OCH_2CH(OH)CH_2NH-$ and -C(O)heterocyclyl, wherein said

heterocyclyl is selected from piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl, hydroxyimino, hydrazinocarbonyl, sulfamoyl, methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, 2-hydroxy-1-methylethylamino, carbamoylmethylamino, N'-phenylhydrazinocarbonyl or toluene-4-sulfonylamino;

R_8 is selected from C_{1-6}alkyl, $-(CH_2)_{1-4}NH_2$, phenyl or benzyl;

and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof.

5. The compound of Claim 4 wherein

R_1 is

(a) $-CH_2CH_2CH_3$,
(b) $-OCH_2CH_3$,
(c) $-SCH_3$,
(d) $-C(O)NHR'$, where R' is 3-pyridyl, or phenyl substituted in the 4-position with -OH, $-C(O)NH_2$, or $-SO_2NH_2$;
(e) $-CF_3$

R_2 is heterocyclyl wherein said heterocycle is selected from 1-piperidinyl and 1-piperazinyl and is optionally substituted with one to three R_7;

R_4 and R_5 are independently selected from H, $-CH_3$ and benzyl;

R_6 is a phenyl group optionally substituted with one or two groups selected from Cl, F, $-CH_3$, -CN, $-CO_2CH_3$, $-C(O)NR_4R_5$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ and $-CH_3$, or R_6 is naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

R_7 is selected from –OH, -CN, oxo, $-C(O)NH_2$, $-NH_2$, $-CH_2NH_2$, $-CH_3$, $-NHC(O)NH_2$, $H_2NCH(R_8)C(O)$-, $HOCH(R_6)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$- and $R_6OCH_2CH(OH)CH_2NH$-, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl,

methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, carbamoylmethylamino or N'-phenylhydrazinocarbonyl;

R_8 is $-(CH_2)_{1-4}NH_2$;

and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof.

6. A compound selected from the group consisting of:

3-Amino-6-(4-oxo-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-4-cyano-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-methylsulfanyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-((E)-styryl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-nitro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-[1,4]diazepan-1-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide

3-Amino-6-[4-(2,4-diamino-butanoyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-[(E)-2-(4-methoxy-phenyl)-vinyl]-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(2-aminomethyl-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;
3-Amino-6-(4-amino-piperidin-1-yl)-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-piperazin-1-yl-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-((E)-2-p-tolyl-vinyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(2,3-dihydroxy-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(2-hydroxy-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-((E)-2-m-tolyl-vinyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-methanesulfonylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

4-[3-Amino-6-(4-amino-piperidin-1-yl)-2-carbamoyl-thieno[2,3-b]pyridin-4-yl]-benzoic acid methyl ester;

3-Amino-6-[4-(2-hydroxy-2-phenyl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-piperidin-4-yl-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-(2,5-difluoro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(N'-phenyl-hydrazinocarbonyl)-piperazin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-((S)-2-hydroxy-2-phenyl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-((R)-2-hydroxy-2-phenyl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-hydroxy-2-(4-nitro-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-ethoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-((S)-2-hydroxy-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-((S)-2-hydroxy-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-hydroxy-2-(3-hydroxy-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-hydroxy-2-(4-hydroxy-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-azepan-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-3-hydroxy-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-(2,4-difluoro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-(4-cyano-3-fluoro-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-amino-piperidin-1-yl)-4-isopropoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[(1H-indol-3-ylmethyl)-amino]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(4-amino-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-hydroxy-2-(4-methoxy-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(4-chloro-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-(4-methanesulfonyl-phenyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

4-{2-[1-(3-Amino-2-carbamoyl-4-propyl-thieno[2,3-b]pyridin-6-yl)-piperidin-4-ylamino]-1-hydroxy-ethyl}-benzoic acid methyl ester;

3-Amino-4-(4-cyano-3-fluoro-phenyl)-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-4-ethoxy-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-4-propyl-6-(4-ureido-piperidin-1-yl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-((S)-3,4-dihydroxy-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-methylsulfanyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-4-(3-hydroxy-propyl)-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(4-carbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-pyridin-3-ylamide;

3-Amino-6-((S)-3-hydroxy-4-methanesulfonylamino-piperidin-1-yl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(2-hydroxy-2-naphthalen-2-yl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(N'-methylsulfonyl-hydrazino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-[4-(2-hydroxy-2-naphthalen-1-yl-ethylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-{2-[1-(3-Amino-2-carbamoyl-4-propyl-thieno[2,3-b]pyridin-6-yl)-piperidin-4-ylamino]-1-hydroxy-ethyl}-benzoic acid methyl ester;

3-Amino-6-(4-amino-4-methyl-piperidin-1-yl)-4-ethoxy-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-hydroxy-2-(4-methylcarbamoyl-phenyl)-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(4-dimethylcarbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(4-benzylcarbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-{4-[2-(3-carbamoyl-phenyl)-2-hydroxy-ethylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-[(4-hydroxy-phenyl)-amide]

3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-[(4-carbamoyl-phenyl)-amide]

3-Amino-6-(4-hydroxy-cyclohexyl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-[(4-sulfamoyl-phenyl)-amide]

3-Amino-6-(4-hydroxy-piperidin-1-yl)-thieno[2,3-b]pyridine-2,4-dicarboxylic acid 2-amide 4-pyridin-4-ylamide

3-Amino-6-[4-(2-hydroxy-3-phenoxy-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide

3-Amino-6-[4-(2-hydroxy-3-phenyl-propylamino)-piperidin-1-yl]-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide

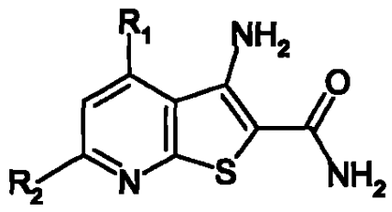
3-Amino-6-{4-[2-hydroxy-3-(4-methoxy-phenoxy)-propylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide

3-Amino-6-{4-[3-(4-carbamoyl-phenoxy)-2-hydroxy-propylamino]-piperidin-1-yl}-4-propyl-thieno[2,3-*b*]pyridine-2-carboxylic acid amide

3-Amino-6-(4-amino-3,3-dimethyl-cyclohexyl)-4-propyl-thieno[2,3-b]pyridine-2-carboxylic acid amide;

and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof.

7. A method of treating inflammatory and autoimmune conditions said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound according to formula (I):



(I)

wherein:

R_1 is

(a) phenyl or heteroaryl selected from furanyl, thienyl, pyridyl, pyrrolyl, imidazolyl and benzofuranyl, optionally substituted with one to two R_3,

(b) heterocyclyl selected from 1-piperidinyl, 1-piperazinyl, 1-pyrrolidinyl and 4-morpholinyl, optionally substituted with one to two groups selected from C_{1-6}alkyl, -CO_2C_{1-5}alkyl, phenyl, benzyl, -OH and -C(O)heteroaryl, wherein the heteroaryl is selected from furanyl, thienyl, pyridyl and pyrrolyl,

(c) $R_6(CH_2)_mO$-,

(d) R_6OCH_2-,

(e) $R_6(CH_2)_mNH$-,

(f) $R_6(CH_2)_p(CH{=}CH)_m$-,

(g) C_{1-6}alkyl, optionally partially or fully halogenated and optionally substituted with one to two R_9,

(h) C_{1-6}alkoxy, optionally partially or fully halogenated and optionally substituted with one to two R_9,

(i) C_{1-6}alkyl$S(O)_n$-, optionally partially or fully halogenated and optionally substituted with one to two R_9,

(j) $-N(R_4)(R_5)$, or

(k) –C(O)NHR', wherein R' is R_6, pyridyl or $–CH_3$;

R_2 is

(a) C_{1-6}alkyl, optionally partially of fully halogenated and optionally substituted with one to two R_{10},
(b) C_{1-6}alkoxy, optionally partially of fully halogenated and optionally substituted with one to two R_{10},
(c) C_{1-6}alkylamino, optionally partially of fully halogenated and optionally substituted with one to two R_{10},
(d) C_{1-6}alkylthio, optionally partially of fully halogenated and optionally substituted with one to two R_{10},
(e) heterocyclyl$(CH_2)_m$- wherein said heterocycle is selected from piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, 1,4-diazacycloheptanyl, azepanyl, 2,5-diazabicyclo[2.2.1]heptanyl, oxazepanyl and thiomorpholino and is optionally substituted with one to three R_7,
(f) heterocyclylCH_2O- wherein the heterocyclyl is selected from 1-piperidinyl, 1-piperazinyl, 4-morpholinyl and 1-pyrrolidinyl, optionally substituted with C_{1-6}alkyl,
(g) phenyl, optionally substituted with one to three R_3,
(h) $–N(R_4)(R_5)$,
(i) heteroaryl selected from furanyl, thienyl, imidazolyl, pyridyl and pyrrolyl, or
(j) –H;

R_3 is chosen from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, halogen, -CN, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-S(O)_mC_{1-6}$alkyl, $-NO_2$, -OH, $-CF_3$, $-N(R_4)(R_5)$, $-NHC(O)NHC_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$ and phenyl optionally substituted with halogen, C_{1-6}alkyl, -CN or C_{1-6}alkoxy;

R_4 and R_5 are independently selected from H, C_{1-6}alkyl, $-C(O)C_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, phenyl, pyridyl, benzyl, piperidinyl, phenylethyl and $(CH_3)_3COC(O)$-;

R_6 is a phenyl group optionally substituted with one or two groups selected from halogen, C_{1-6}alkyl, -CN, $-CO_2C_{1-6}$alkyl, $-C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, CF_3 and C_{1-6}alkoxy, or R_6 is C_{3-6}cycloalkyl, $-CH_2OH$, naphthalene-2-yl, naphthalene-1-yl or 2-thienyl;

R_7 is selected from –OH, -CN, oxo, $-CO_2C_{1-6}$alkyl, $-CO_2H$, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, $-CH_2OH$, C_{1-6}alkyl, $-CO_2$benzyl, hydroxyC_{1-6}alkyl, $-C(O)C_{1-6}$alkyl$N(R_4)(R_5)$, $-NHCO_2C_{1-6}$alkyl, $-NHC(O)N(R_4)(R_5)$, $-S(O)_nC_{1-6}$alkyl, $(CH_3)_3COC(O)$-, phenyl, pyridyl, $H_2NCH(R_8)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- and -C(O)heterocyclyl, wherein said heterocyclyl is selected from piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl, or R_7 is 2-hydroxyethylamino, methylcarbamimidoyl, hydroxyimino, hydrozinocarbonyl, sulfamoyl, methanesulfonylamino, methylsulfonylhydrazino, 2-hydroxypropylamino, 2,3-dihydroxypropylamino, 2-hydroxy-1-methylethylamino, carbamoylmethylamino, N'-phenylhydrazinocarbonyl or toluene-4-sulfonylamino;

R_8 is selected from C_{1-6}alkyl, $-(CH_2)_{1-4}NH_2$, phenyl or benzyl;

R_9 is selected from oxo, -OH, $-NR_4R_5$, $-CO_2H$ and C_{1-6}alkoxy;

R_{10} is selected from oxo, -OH, $-N(R_4)(R_5)$, C_{1-6}alkoxy, $-C(O)C_{1-6}$alkyl, $-C(O)N(R_4)(R_5)$, R_6, and heteroaryl selected from furanyl, thienyl, imidazolyl, pyridyl, indolyl and pyrrolyl;

m is 0 or 1;

n is 0, 1 or 2; and

p is 0, 1, 2 or 3 and pharmaceutically acceptable salts, esters, tautomers, individual isomers, and mixtures of isomers thereof.

8. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1.

9. A method of treating an inflammatory or autoimmune disease condition, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound according to claim 1.

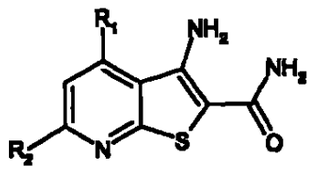
10. The method according to claim 9 wherein the inflammatory or autoimmune disease or condition is selected from the list consisting of osteoarthritis, reperfusion injury, asthma, multiple sclerosis, Guillain-Barre syndrome, Crohn's disease, ulcerative colitis, psoriasis, graft versus host disease, systemic lupus erythematosus, rheumatoid arthritis, Alzheimer's disease, toxic shock syndrome, insulin-dependent diabetes mellitis, acute and chronic pain, thermal injury, adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), multiple organ injury secondary to trauma, acute glomerulonephritis, dermatoses with acute inflammatory components, acute purulent meningitis or other central nervous system disorders, Grave's disease, myasthenia gravis, scleroderma and atopic dermatitis;

11. The method of claim 9 wherein the inflammatory or autoimmune disease is selected from osteoarthrists, rheumatoid arthritis, Chrohn's disease, ulcerative colitis, asthma, adult respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD).

12. A method of treating atherosclerosis, myocardial infarction or stroke, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound according to claim 1.

13. A method of treating cancer selected from lymphoid-, myeloid- and epithelial-derived malignancies, leukemia, lymphomas, breast cancer, gastric cancer, colorectal cancer, lung cancer, and pancreatic cancer, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound according to claim 1.

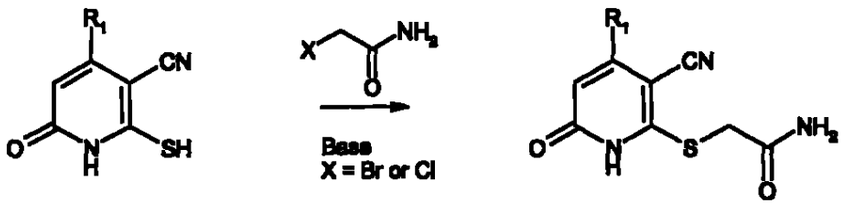
14. A method of making a compound of formula (I):



I

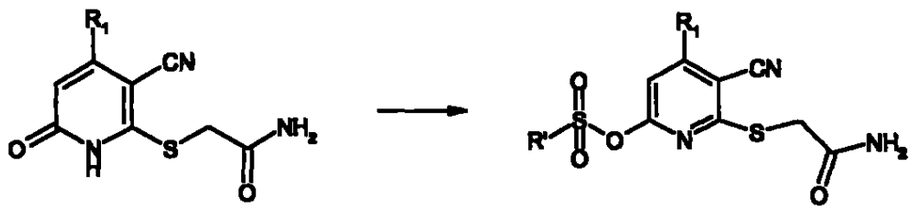
where R_1 and R_2 are as defined in claim 4, the method comprising:

(a) reacting a compound of formula (XVa) with 2-chloro or 2-bromoacetamide in the presence of a suitable base, in a suitable solvent to form the intermediate of formula (XVIb)



XVa XVI b ;

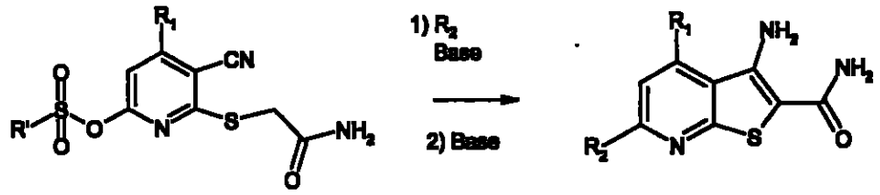
(b) reacting the intermediate of formula (XVIb) with a suitable sulfonating reagent in the presence of a suitable base in a suitable solvent to form the sulfonyl ester of formula (XVIIb)



XVI b XVII b ;

(c) reacting the intermediate of formula (XVIIb) with R_2 in the presence of a suitable base such as triethylamine, followed by addition of a second suitable base and further reaction

to form the desired compound of formula (I)



XVII b I

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PATENT COOPERATION TREATY

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.
9/244PCT		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/US 03/17343	[illegible]	[illegible]

Applicant

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the international Bureau.

This International Search Report consists of a total of 6 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.

INTERNATI NAL SEARCH REPORT

Inte[illegible]nal Application No
PCT/US 03/17343

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/38 A61K31/435 C07D495/04 A61P29/00
//(C07D495/04,333:00,221:00)

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 A61K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BEILSTEIN Data, CHEM ABS Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2001/020030 A1 (CONDROSKI KEVIN R ET AL) 6 September 2001 (2001-09-06) cited in the application page 2 -page 5; claims 8,9; examples 109,134 —/—	1-14

[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
18 September 2003	17/11/2003

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	Härtinger, S

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 03/17343

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GHORAB, M.-M. ET AL: "Synthesis of novel heterocyclic compounds for antitumor and radioprotective activities" retrieved from STN Database accession no. 133:58778 XP002254095 abstract & M.-M. GHORAB ET AL: PHOSPHORUS, SULFUR AND SILICON AND THE RELATED ELEMENTS (1998), 134/135, 447-462 ,	1-14
A	US 5 656 638 A (GAETA FEDERICO C A ET AL) 12 August 1997 (1997-08-12) cited in the application column 7, line 52 - line 64; claim 2	1-14
A	DATABASE WPI Section Ch, Week 199212 Derwent Publications Ltd., London, GB; Class B02, AN 1992-096796 XP002254099 -& WO 92 03427 A (JAPAN TOBACCO INC), 5 March 1992 (1992-03-05) abstract page 25, line 1 - line 5	1-14
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE ; Citation Number 6242573 Substances 28, 38, XP002254097 abstract & ATTABY ET AL: "SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SEVERAL NEW PYRIDINE, THIENOPYRIDINE AND PYRIDOTHIENOPYRAZOLE DERIVATIVES" PHOSPHOROUS, SULFUR SILICON RELATED ELEMENTS, vol. 149, 1999, pages 49-64,	8
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE ; BRN 7765365, XP002254098 abstract & KAIGORODOVA E I ET AL: CHEM. HETEROCYCL. COMPD: (ENGL. TRANSL.), vol. 32, no. 10, 1996, pages 1234-1238,	1

-/—

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 03/17343

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WAGNER ET AL: "SYNTHESE NEUER PRIM., SEK. UND TERT. 3-AMINO-THIENO(2,3-B)PYRIDIN-2-CARBONSAEUR EAMIDE AUF VERSCHIEDENEN WEGEN" PHARMAZIE, vol. 45, 1990, pages 102-109, XP001154945 ISSN: 0031-7144 cited in the application Scheme 1 page 102, left-hand column, paragraph 1	8,14

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/US 03/17343

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 7, 9-13 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

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.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 03/17343

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2001020030 A1	06-09-2001	US 6232320 B1	15-05-2001
		CA 2390948 A1	14-12-2000
US 5656638 A	12-08-1997	US 5760062 A	02-06-1998
		US 5703116 A	30-12-1997
		US 5863936 A	26-01-1999
WO 9203427 A	05-03-1992	WO 9203427 A1	05-03-1992
		JP 3341288 B2	05-11-2002
		JP 5004989 A	14-01-1993

PCT REQUEST 9/244PCT

Original (for SUBMISSION) - printed on 03.06.2003 11:24:59 AM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using:	PCT-EASY Version 2.92 (updated 01.04.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	9/244PCT
I	Title of invention	SUBSTITUTED 3-AMINO-THIENO[2,3-b]PYRIDINE-2-CARBOXYLIC ACID AMIDE COMPOUNDS AND PROCESSES FOR PREPARING AND THEIR USES
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States
II-4	Name	BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
II-5	Address:	900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	203-798-4868
II-9	Facsimile No.	203-798-4408
III-1	Applicant and/or inventor	
III-1-1	This person is:	inventor only
III-1-4	Name (LAST, First)	CYWIN, Charles, L.
III-1-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America

III-2	Applicant and/or inventor	
III-2-1	This person is:	inventor only
III-2-4	Name (LAST, First)	CHEN, Zhidong
III-2-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-3	Applicant and/or inventor	
III-3-1	This person is:	inventor only
III-3-4	Name (LAST, First)	EMEIGH, Jonathan
III-3-5	Address:	6 Kenmere Blvd. Danbury, CT 06810 United States of America
III-4	Applicant and/or inventor	
III-4-1	This person is:	inventor only
III-4-4	Name (LAST, First)	FLECK, Roman, Wolfgang
III-4-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-5	Applicant and/or inventor	
III-5-1	This person is:	inventor only
III-5-4	Name (LAST, First)	HAO, Ming-Hong
III-5-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-6	Applicant and/or inventor	
III-6-1	This person is:	inventor only
III-6-4	Name (LAST, First)	HICKEY, Eugene
III-6-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America

III-7	Applicant and/or inventor	
III-7-1	This person is:	inventor only
III-7-4	Name (LAST, First)	LIU, Weimin
III-7-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-8	Applicant and/or inventor	
III-8-1	This person is:	inventor only
III-8-4	Name (LAST, First)	MARSHALL, Daniel, Richard
III-8-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-9	Applicant and/or inventor	
III-9-1	This person is:	inventor only
III-9-4	Name (LAST, First)	MORWICK, Tina
III-9-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-10	Applicant and/or inventor	
III-10-1	This person is:	inventor only
III-10-4	Name (LAST, First)	NEMOTO, Peter
III-10-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-11	Applicant and/or inventor	
III-11-1	This person is:	inventor only
III-11-4	Name (LAST, First)	SORCEK, Ronald, John
III-11-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America

III-12	Applicant and/or inventor	
III-12-1	This person is:	inventor only
III-12-4	Name (LAST, First)	SUN, Sanxing
III-12-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-13	Applicant and/or inventor	
III-13-1	This person is:	inventor only
III-13-4	Name (LAST, First)	WU, Jiang-Ping
III-13-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	RAYMOND, Robert, P.
IV-1-2	Address:	Boehringer Ingelheim Corporation 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
IV-1-3	Telephone No.	203-798-9988
IV-1-4	Facsimile No.	203-798-4408
IV-1-5	Agent's registration No.	25,089
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	DEVLIN, Mary-Ellen, M.(27,928); STEMPEL, Alan, R.(28,991); BOTTINO, Anthony, P.(41,629); POCCHIARI, Susan, K.(45,016); DATLOW, Philip, I.(41,482); WITKOWSKI, Timothy, X.(40,232); DOW, David, A.(46,124)

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES.FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI 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 NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
V-3	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-8 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-8	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	06 June 2002 (06.06.2002)
VI-1-2	Number	60/386,312
VI-1-3	Country	US

PCT REQUEST 9/244PCT

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VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	26 March 2003 (26.03.2003)	
VI-2-2	Number	60/457,867	
VI-2-3	Country	US	
VI-3	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	7	-
IX-2	Description	138	-
IX-3	Claims	20	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	166	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	David Dow	
X-1-1	Name (LAST, First)	DOW, David, A.	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	

10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States of America

Date of mailing (day/month/year) 29 July 2003 (29.07.03)	
Applicant's or agent's file reference 9/244PCT	IMPORTANT NOTIFICATION
International application No. PCT/US03/17343	International filing date (day/month/year) 03 June 2003 (03.06.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 06 June 2002 (06.06.02)
Applicant BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
06 June 2002 (06.06.02)	60/386,312	US	07 July 2003 (07.07.03)
26 Marc 2003 (26.03.03)	60/457,867	US	07 July 2003 (07.07.03)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.88.65

Authorized officer

Nicole MILLIET

Telephone No. (41-22) 338 9686

005776616

received

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU DD

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To: 186

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

RECEIVED
JAN - 5 2004
PATENT SECTION

Date of mailing (day/month/year)	
18 December 2003 (18.12.03)	
Applicant's or agent's file reference	**IMPORTANT NOTICE**
9/244PCT	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US03/17343	03 June 2003 (03.06.03)	06 June 2002 (06.06.02)

Applicant
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

   AU, AZ, BY, CH, CN, CO, DE, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

   AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 18 December 2003 (18.12.03) under No. WO 03/103661

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

   The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19936, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

   In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

   It is the applicant's sole responsibility to monitor all these time limits.

   The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Judith Zahra
Facsimile No.(41-22) 740.14.35	Telephone No.(41-22) 338.91.11

Form PCT/IB/308 (April 2002)

National Phase 12/6/2004 PCT/US2003/017343

PATENT COOPERATION TREATY

DD 187

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States of America

Date of mailing (day/month/year)	
09 January 2004 (09.01.2004)	
Applicant's or agent's file reference	**IMPORTANT INFORMATION**
9/244PCT	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US2003/017343	03 June 2003 (03.06.2003)	06 June 2002 (06.06.2002)

Applicant
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP :AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IT,LU,MC,NL,PT,RO,SE,
   SI,SK,TR
   National :BG,CA,CN,DE,GB,IL,JP,KP,KR,MN,NO,PL,RO,RU,SK

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

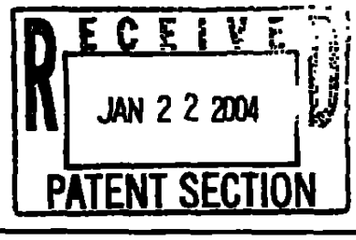
   AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
   National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BR,BY,BZ,CH,CO,CR,CU,CZ,DK,DM,DZ,EC,
   EE,ES,FI,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,
   MG,MK,MW,MX,MZ,NI,NZ,OM,PH,PT,SC,SD,SE,SG,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,UZ,
   VC,VN,YU,ZA,ZM,ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 36(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

received 1/20/04 BL



The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.88.85

Authorized officer:
James VANNIER

Telephone No. (41-22) 338 8464

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

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PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	*Date of receipt of DEMAND*

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 9/244PCT

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US03/17343	03 Jun 2003	06 Jun 2002

Title of invention: Substituted 3-Amino-Thieno[2,3-B]Pyridine-3-Carboxylic Acid Amide Compounds and Processes for Preparing and Their Uses

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)*

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 Ridgebury Road, P.O. Box 368
Ridgefield, Connecticut USA 06877-0368

Telephone No.: 203-798-9688
Facsimile No.: 203-798-4408
Teleprinter No.:
Applicant's registration No. with the Office:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

Sheet No. 2.

International application No.
PCT/US03/17343

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☑ agent ☐ common representative

and ☑ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RAYMOND, Robert P.; STEMPEL, Alan R.; DEVLIN, Mary-Ellen M.;
BOTTINO, Anthony P.; POCCHIARI, Susan K.; DATLOW, Philip I.;
WITKOWSKI, Timothy X.; DOW, David A.; MORRIS, Michael P.
c/o BOEHRINGER INGELHEIM CORPORATION
900 Ridgebury Road, P.O. Box 368
Ridgefield, Connecticut 06877-0368 USA

Telephone No.
203-798-9988

Facsimile No.
203/798-4408

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☑ the international application as originally filed

the description
☑ as originally filed
☐ as amended under Article 34

the claims
☑ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings
☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☑ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

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Sheet No. 3

International application No.
PCT/US03/17343

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)* Request For Detailed Exam	:	1 sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☑ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

David A. Dow, Agent

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and Item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PATENT COOPERATION TREATY

DEC 16 2003 PATENT SECTION

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PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
DOW, David A.
BOEHRINGER INGELHEIM CORPORATION
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

EXTRA Int'l PN - 12/8/2004

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)*	08-12-2003
Applicant's or agent's file reference: 9/244PCT	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/17343	03/06/2003	06/06/2002

Applicant

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

21/11/2003

2. This date of receipt is:

- [X] the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- [ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- [ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. [ ] **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

[ ] *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on:

_____

received 12/16/03

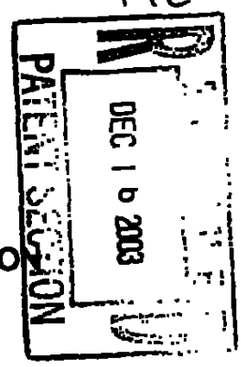
4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/	Authorized officer
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) 2399-2039

PATENT COOPERATION TREATY

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DD



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

DOW, David A.
BOEHRINGER INGELHEIM CORPORATION
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

ENTRE DM'L PA - 12/3/2004

03-12-04
LAST DAY

PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	12.12.2003
Applicant's or agent's file reference 9244PCT	REPLY DUE within 3 month(s) ✓ from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/17343	03.06.2003	06.06.2002

International Patent Classification (IPC) or both national classification and IPC
A61K31/38

Applicant
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

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	☒	Basis of the opinion
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 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 66.4 bis.
   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: 06.10.2004

received
12/16/03

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer
Härtinger, S

Formalities officer (incl. extension of time limits)
Hebert, W
Telephone No. +49 89 2399-2152

WRITTEN OPINION International application No. PCT/US03/17343

I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-138 as originally filed

Claims, Numbers

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 7,9-13 with respect to IA

because:

☒ the said international application, or the said claims Nos. 7,9-13 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

☐ *the written form has not been furnished or does not comply with the Standard.*

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1,7-14 no; 2-6 yes
Inventive step (IS)	Claims	1-14 no
Industrial applicability (IA)	Claims	1-6,8,14 yes

2. Citations and explanations

see separate sheet

Section III:

1. Claims 7, 9-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Section V:

1. The invention relates to the medical use of partly known 3-amino-thieno[2,3- b] pyrimidine-2-amides (in the following ATPA) for diseases which are associated with the interaction with I kappa B (IKK inhibitors; claims 7, 9-13). Further claims are drawn to a group of ATPA compounds (claims 1-6), pharmaceutical compositions comprising the same (claim 8) and a synthesis procedure for a group of ATPA compounds (claim 14).

   The relevant prior art has been cited in the International search report and will be named as follows.

   D1: US-A-2001/020030
   D2: XP002254095
   D3: US-A-5656638
   D4: WO-A-92 03427
   D5: XP002254097
   D6: XP00254098
   D7: XP001154945

2. a) The claimed matter represents a selection from what has been disclosed in D1 and D3. The area of overlap becomes evident from the comparison of the family of compounds as defined in claims 8 of D1, claim 2 of D3 and the present ATPA. Since ATPA has not been individualised in these prior art documents, the selection is regarded to be novel with respect to D1 and D3.

   b) Although the specific compounds disclosed in D2 (see in particular the Chemical Abstract record) have been disclaimed in the present compound claims,

the disclosure of their antitumour activity takes away the novelty of the present medical use claims and claims for pharmaceutical compositions. Therefore, it would appear that the subject-matter of claims 7-13 does not meet the requirements of Art. 33(2) PCT.

c) A further overlap situation is present between the ATPA of the invention and the compounds of formula VII of D4. Since, at the moment, no translation of the Japanese prior art is available to this authority, no reasonable preliminary opinion as to the novelty requirements can be given. This will be deferred to the time, when such translation will be available.

d) The products with the Beilstein Registry Numbers 8572893 and 8565530 have been disclosed in the context of antibacterial and antifungal products in D5. This disclosure is therefore considered to be detrimental to the novelty of claim 8.

e) The product with the Beilstein Registry Number 7765365 falls under the definition of the present ATPA of claim 1. This claim does therefore not comply with the requirements of Art. 33(2) PCT.

f) The products B of D7 have been disclaimed from the present compound claims. However, on page 102, left column, second last paragraph, their ability to act as anaphylactica is mentioned. This disclosure is therefore considered to be detrimental to the novelty of claim 8. Likewise, the synthesis procedures disclosed in Schema 1 and Schema 2 fall under the definition of present claim 14. This claim appears therefore not to meet the requirements of Art. 33(2) PCT.

3. Inventive step

For any novel subject-matter, the closest prior art compound is regarded to be the 3-amino-thieno[2,3-c]pyridine of schema 26 of D1, of which the 4-chlorophenoxy substituted derivative on page 10, paragraph 0453 is a specific example. This compound differs from the present ATPA merely in the fact that the pyridine ring nitrogen atom is in the 6-position of the ring system rather than in the 7-position in the present [2,3-b] isomers. Given the fact that the present group of [2,3-b] isomers is also individualised as an IKK inhibitor group (claim 8 and schemes 32 and 33 of D1), the skilled person would have expected that the present group of ATPA is likewise active. Hence, the present medical use and the respective ATPA

compounds are an obvious solution to the problem of providing further IKK inhibitors. In the absence of an allowable main claim for the medical use of the compounds, the claim directed to the synthesis of the present ATPA is likewise not allowable, or alternatively, solves a technical problem which is not so linked with the remaining claims as to form a single invention (Rule 13.1 PCT).

PATENT COOPERATION TREATY

DD

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

DOW, David A.
BOEHRINGER INGELHEIM CORPORATION
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

BIPAS D.P. – 12/13/2004

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	08.04.2004

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
9244PCT	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/17343	03.06.2003	06.06.2002

Applicant
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

   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 invention 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 international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Ullrich, J

Tel. +49 89 2399-8048

RECEIVED
APR 13 2004
PATENT SECTION

Form PCT/IPEA/416 (January 2004)

received
14 pkm

PATENT COOPERATION TREATY

PCT

199

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 9244PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/17343	International filing date *(day/month/year)* 03.06.2003	Priority date *(day/month/year)* 06.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/38, A61K31/38		
Applicant BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - 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 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

Date of submission of the demand	Date of completion of this report
21.11.2003	08.04.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Härtinger, S Telephone No. +49 89 2399-8289

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY EXAMINATION REP RT International application No. PCT/US 03/17343

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-138 as originally filed

Claims, Numbers

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/US 03/17343

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 7,9-13 with respect to IA

   because:

   ☒ the said international application, or the said claims Nos. 7,9-13 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-6
	No:	Claims	1,7-14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-6,8,14
	No:	Claims	

2. Citations and explanations

see separate sheet

Section III:

1. Claims 7, 9-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Section V:

1. The invention relates to the medical use of partly known 3-amino-thieno[2,3- b] pyrimidine-2-amides (in the following ATPA) for diseases which are associated with the interaction with I kappa B (IKK inhibitors; claims 7, 9-13). Further claims are drawn to a group of ATPA compounds (claims 1-6), pharmaceutical compositions comprising the same (claim 8) and a synthesis procedure for a group of ATPA compounds (claim 14).

   The relevant prior art has been cited in the International search report and will be named as follows.

   D1: US-A-2001/020030
   D2: XP002254095
   D3: US-A-5656638
   D4: WO-A-92 03427
   D5: XP002254097
   D6: XP00254098
   D7: XP001154945

2. a) The claimed matter represents a selection from what has been disclosed in D1 and D3. The area of overlap becomes evident from the comparison of the family of compounds as defined in claims 8 of D1, claim 2 of D3 and the present ATPA. Since ATPA has not been individualised in these prior art documents, the selection is regarded to be novel with respect to D1 and D3.

   b) Although the specific compounds disclosed in D2 (see in particular the Chemical Abstract record) have been disclaimed in the present compound claims, the disclosure of their antitumour activity takes away the novelty of the present medical use claims and claims for pharmaceutical compositions. Therefore, it

would appear that the subject-matter of claims 7-13 does not meet the requirements of Art. 33(2) PCT.

c) A further overlap situation is present between the ATPA of the invention and the compounds of formula VII of D4. Since, at the moment, no translation of the Japanese prior art is available to this authority, no reasonable preliminary opinion as to the novelty requirements can be given. This will be deferred to the time, when such translation will be available.

d) The products with the Beilstein Registry Numbers 8572893 and 8565530 have been disclosed in the context of antibacterial and antifungal products in D5. This disclosure is therefore considered to be detrimental to the novelty of claim 8.

e) The product with the Beilstein Registry Number 7765365 falls under the definition of the present ATPA of claim 1. This claim does therefore not comply with the requirements of Art. 33(2) PCT.

f) The products B of D7 have been disclaimed from the present compound claims. However, on page 102, left column, second last paragraph, their ability to act as anaphylactica is mentioned. This disclosure is therefore considered to be detrimental to the novelty of claim 8. Likewise, the synthesis procedures disclosed in Schema 1 and Schema 2 fall under the definition of present claim 14. This claim appears therefore not to meet the requirements of Art. 33(2) PCT.

3. Inventive step

For any novel subject-matter, the closest prior art compound is regarded to be the 3-amino-thieno[2,3-c]pyridine of schema 26 of D1, of which the 4-chlorophenoxy substituted derivative on page 10, paragraph 0453 is a specific example. This compound differs from the present ATPA merely in the fact that the pyridine ring nitrogen atom is in the 6-position of the ring system rather than in the 7-position in the present [2,3-b] isomers. Given the fact that the present group of [2,3-b] isomers is also individualised as an IKK inhibitor group (claim 8 and schemes 32 and 33 of D1), the skilled person would have expected that the present group of ATPA is likewise active. Hence, the present medical use and the respective ATPA compounds are an obvious solution to the problem of providing further IKK inhibitors. In the absence of an allowable main claim for the medical use of the compounds, the claim directed to the synthesis of the present ATPA is likewise not allowable, or alternatively, solves a technical problem which is not so linked

with the remaining claims as to form a single invention (Rule 13.1 PCT).

Traducción

TRATADO DE COOPERACIÓN DE PATENTES
PCT
INF RME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 del PCT)

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Referencia del expediente del agente o solicitante 9/244 PCT	PARA ACTUACIONES ADICIONALES	Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA416)
Solicitud Internacional No. PCT/US03/17343	Fecha de presentación internacional (*día/mes/año*) 03.06.2003	Fecha de prioridad (*día/mes/año*) 06.06.2002
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC A61K 31/38, A61K 31/38		
Solicitante BOEHRINGER INGELHEIM PHARMACEUTICALS, INC		

1. Este informe de examen preliminar internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.

2. Este **INFORME** consta de una total de 6 hojas, incluyendo la portada

   ☐ Este informe también se acompaña de **ANEXOS**, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas según el PCT)

   Estos anexos constan de un total de ____ hojas.

3. Este informe contiene indicaciones relativas a los siguientes aspectos:

   I ☒ Fundamentos del Informe
   II ☐ Prioridad
   III ☒ No se establece concepto relativo a la novedad, nivel inventivo y aplicación industrial
   IV ☐ Carencia de unidad de la invención
   V ☒ Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración
   VI ☐ Ciertos documentos citados
   VII ☐ Ciertos defectos de la solicitud internacional
   VIII ☐ Ciertas observaciones respecto a la solicitud Internacional

Fecha de presentación de la demanda	Fecha de terminación de este reporte
21.11.2003	08.04.2004
Nombre y dirección de correo de la autoridad encargada del examen preliminar Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Funcionario Autorizado Härtinger, S Teléfono No. +49 89 2399-8289

Formato PCT/IPEA/409 (portada) (julio 1998)

I. Base del Informe

1. Respecto a los **elementos** de la solicitud internacional: (*Las hojas de reemplazo que han sido entregadas a la Oficina receptora en respuesta a la invitación bajo el Artículo 14 se refieren en este informe como "originalmente presentadas" y no se anexan a este informe ya que ellas no contienen modificaciones (Regla 70.16 y 70.17)).*

La descripción, páginas

1-138 como se presentaron originalmente

Las reivindicaciones, números

1-14 como se presentaron originalmente

2. Respecto al **lenguaje**, todos los elementos marcados anteriormente estuvieron disponibles o fueron enviados a la Administración en el lenguaje en que se presentó la solicitud internacional, a menos que se indique otra cosa en este punto.

Estos elementos estuvieron disponibles o fueron enviados a esta Administración en el siguiente lenguaje _____ el cual es:

☐ el lenguaje de la traducción enviada para propósitos de la búsqueda internacional (bajo Regla 23.1 (b)).
☐ el lenguaje de la publicación de la solicitud internacional (bajo Regla 48.3(b)).
☐ el lenguaje de la traducción entregada con propósitos del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Respecto a cualquier **secuencia de nucleótido y/o amino ácidos** divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo con base en el listado de secuencias:

☐ contenido en la solicitud internacional en forma escrita
☐ presentado junto con la solicitud internacional en forma legible por computador
☐ entregado posteriormente a esta Administración en forma legible por computador
☐ La declaración de que el listado de secuencias posteriormente entregado no va más allá de lo divulgado en la solicitud internacional originalmente presentada, ha sido entregada.
☐ La declaración de que la información grabada en la forma legible por computador es idéntica al listado de secuencias escrito que se ha entregado.

4. ☐ Las modificaciones han dado como resultado la cancelación de:

☐ la descripción, páginas _____,
☐ las reivindicaciones, Nos. _____,
☐ los dibujos, página _____.

5. ☐ Este reporte ha sido establecido como si (parte de) las modificaciones no se hubieran realizado, ya que éstas han sido consideradas como una ampliación de lo inicialmente divulgado como se indica en la Casilla Suplementaria (Regla 70.2(c)).

(Cualquier hoja de reemplazo que contenga dichas modificaciones deberá ser referida bajo el punto 1 y anexada a este informe)

III. No-establecimiento de opinión con respecto a la novedad, nivel inventivo y aplicabilidad industrial.

1. La pregunta de si la invención reivindicada parece tener novedad, nivel inventivo (que no sea obvia), o que sea aplicable industrialmente no ha sido examinada con respecto a:

☐ la solicitud internacional completa
☒ las reivindicaciones Nos. 7,9-13, con respecto a IA

Porque

☒ la solicitud internacional, o las mencionadas reivindicaciones Nos. 7,9-13 se relacionan con los siguientes objetos, los cuales no requieren examen preliminar internacional *(especifique):*

Ver hoja separada

☐ la descripción, las reivindicaciones o los dibujos *(indique los elementos particulares abajo)* o las mencionadas reivindicaciones Nos. _____ son demasiado confusas que no se puede formar ninguna opinión significativa *(especifique):*

☐ la descripción, o las mencionadas reivindicaciones Nos. _____ no están adecuadamente soportadas por la descripción que no se puede formar ninguna opinión significativa.

☐ no se ha establecido un reporte de búsqueda para las mencionadas reivindicaciones Nos. _____

2. No se pudo realizar un examen preliminar internacional significativo debido a fallas en el listado de nucleótidos y/o aminoácidos para dar cumplimiento con los estándares del Anexo C de las Instrucciones Administrativas:

☐ El formato escrito no ha sido suministrado o no cumple con los estándares.

☐ El formato de lectura por computador no ha sido suministrado o no cumple con los estándares.

V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación industrial; citas y explicaciones que apoyan esta declaración.

1. Declaración

Novedad (N)	Reivindicaciones	2-6	SI
	Reivindicaciones	1, 7-14	NO
Nivel inventivo (NI)	Reivindicaciones		SI
	Reivindicaciones	1-14	NO
Aplicación industrial (AI)	Reivindicaciones	1-6, 8, 14	SI
	Reivindicaciones		NO

2. Citas y explicaciones (Regla 70.7)

Ver hoja separada

Sección III:

1. Las reivindicaciones 7, 9-13 se relacionan con un objeto que es considerado por esta Autoridad como que se encuentra cubierto por lo provisto en la Regla 67.1 (iv) PCT. Consecuentemente, no se formulará una opinión con respecto a la aplicabilidad industrial del objeto de las reivindicaciones (Artículo 34 (4)(a)(i) PCT).

Sección V:

1. La invención se relaciona con uso médico de 3-amino-tieno[2,3-b]pirimidina-2-amidas (a continuación ATPA) parcialmente conocidas para enfermedades que se encuentran asociadas con la interacción de I kappa B (inhibidores IKK; reivindicaciones 7, 9-13). Reivindicaciones adicionales se relacionan con un grupo de compuestos de ATPA (reivindicaciones 1-6), composiciones farmacéuticas que los comprenden (reivindicación 8) y una procedimiento de síntesis para un grupo de compuestos de ATPA (reivindicación 14).

   El arte previo relevante ha sido citado en el informe de búsqueda internacional y será llamado como sigue:

   D1: US-A-2001/020030
   D2: XP002254095
   D3: US-A-5656638
   D4: WO-A-92 03427
   D5: XP002254097
   D6: XP00254098
   D7: XP001154945

2.

   a) La materia reivindicada representa una selección de lo que ha sido revelado en D1 y D3. El área de superposición se hace evidente a partir de la comparación de la familia de compuestos como se definen en las reivindicaciones 8 de D1, reivindicación 2 de D3 y el presente ATPA. Debido a que ATPA no ha sido individualizado en estos documentos del arte previo, la selección se considera como novedosa con respecto a D1 y D3.

b) Sin embargo los compuestos específicos revelados en D2 (ver en particular el record del Chemical Abstract) han sido reclamados en los presentes compuestos, la divulgación de su actividad antitumoral le quita novedad a las presentes reivindicaciones de uso médico y reivindicaciones para las composiciones farmacéuticas. De esta forma, parecería que el objeto de las reivindicaciones 7-13 no cumple con los requerimientos del Artículo 33(2) del PCT.

c) Una situación de superposición adicional se presenta entre el ATPA de la invención y los compuestos de fórmula VII de D4. Debido a que, por el momento, no se encuentra disponible una traducción del arte previo en Japonés para esta Autoridad, no se puede dar una opinión razonable sobre los requerimientos de novedad. Este punto será diferido en el tiempo, cuando dicha traducción se encuentre disponible.

d) Los productos con Número de Registro Beilstein 8572893 y 8565530 han sido revelados en el contexto de los productos antibacteriales y antifúngicos en D5. Esta enseñanza se considera que va en detrimento de la novedad de la reivindicación 8.

e) El producto con el Número de Registro Beilstein 7765365 cae dentro de la definición del presente ATPA de la reivindicación 1. Esta reivindicación entonces no cumple con los requerimientos del Artículo 33(2) del PCT.

f) Los productos B de D7 han sido excluidos de las presentes reivindicaciones de compuesto. Sin embargo, en la página 102, columna izquierda, segundo último párrafo, se menciona su habilidad para actuar como anafiláctico. Esta revelación se considera entonces que va en detrimento de la novedad de la reivindicación 8. De la misma forma, los procedimientos de síntesis revelados en el Esquema 1 y Esquema 2 caen dentro de la definición de la presente reivindicación 14. Esta reivindicación entonces parece no cumplir con los requerimientos del Artículo 33(2) de PCT.

3. Nivel Inventivo

Para cualquier materia novedosa, el arte previo más cercano de compuestos se considera que es la 3-amino-tieno[2,3-c]piridina del esquema 26 de D1, del cual el

derivado 4-clorofenoxi en la página 10, párrafo 0453 es un ejemplo específico. Este compuesto difiere del presente ATPA meramente en el hecho de que el átomo de nitrógeno del anillo de piridina se encuentra en la posición 6 del sistema de anillos, y no en la posición 7 como en los presentes isómeros [2,3-b]. Dado que el presente grupo de isómeros [2,3-b] también son individualizados como un grupo inhibidor de IKK (reivindicación 8 y esquemas 32 y 33 de D1), una persona versada hubiera esperado que el presente grupo de ATPA sea igualmente activo. De esta forma, el presente uso médico y los correspondientes compuestos ATPA son una obvia solución al problema de proporcionar inhibidores adicionales de IKK. En ausencia de una reivindicación principal aceptable para el uso médico de los compuestos, la reivindicación dirigida a la síntesis de los presentes ATPA tampoco es aceptable, o alternativamente, resuelve un problema que no se encuentra tan relacionado con las reivindicaciones restantes para conformar una única invención (Regla 13.1 del PCT).

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COMPUESTOS DE AMIDAS DE ÁCIDO 3-AMINO-TIENO[2,3-b]PIRIDINO-2-CARBOXÍLICO SUSTITUIDO Y PROCEDIMIENTOS PARA PREPARARLOS Y SUS USOS.

CAMPO TÉCNICO DE LA INVENCIÓN

Esta invención se refiere a compuestos de amidas de ácido 3-amino-tieno[2,3-b]piridino-2-carboxílico sustituido útiles como inhibidores de la actividad de quinasa del complejo de quinasa IκB (IKK). Por lo tanto, los compuestos son útiles en el tratamiento de enfermedades mediadas por IKK que incluyen enfermedades autoinmunes, enfermedades inflamatorias y cáncer. La invención se refiere también a procedimientos para preparar estos compuestos y composiciones farmacéuticas que los comprenden.

ANTECEDENTES DE LA INVENCIÓN

El NF-κB o factor nuclear κB es un factor de transcripción que induce la expresión de un elevado número de genes pro-inflamatorios y anti-apoptóticos. Estos incluyen citoquinas como IL-1, IL-2, TNF-α e IL-6, quimioquinas que incluyen IL-8 y RANTES, así como otras moléculas pro-inflamatorias que incluyen COX-2 y moléculas de adhesión celular como ICAM-1, VCAM-1 y E-selectina. La familia del NF-κB incluye factores de transcripción homo- y hetero-dímeros compuestos por miembros de la familia Rel (véase, por ejemplo, P.A. Baeurle y D. Baltimore, Cell, 1996, 87, 13). Bajo condiciones de reposo, el NF-κB está presente en el citosol de las células en forma de un complejo con IκB. La familia de IκB de proteínas sirve como inhibidores deNF-κB, interfiriendo con la función de su señal de localización nuclear (véase, por ejemplo, U. Siebenlist et al., Ann. Rev. Cell Biol., 1994, 10, 405). Tras la descomposición del complejo IκB-NF-κB a continuación de la activación celular, el NF-κB se desplaza al núcleo y activa la transcripción génica. La descomposición del complejo IκB-NF-κB y la posterior activación del NF-κB es iniciada por la degradación de IκB.

Tras la activación celular mediante una diversidad de estímulos pro-inflamatorios que incluyen IL-1, TNF-α y LPS (lipopolisacárido bacteriano), dos residuos específicos de serina de IκB son fosforilados. Tras la fosforilación, el IκB experimenta una poliubiquinación y una posterior degradación por la 26S proteasoma (véase, por ejemplo, V.J. Palombella et al., Cell, 1994, 78, 773), eximiendo al NF-κB de trasladarse al núcleo. La fosforilación de IκB se lleva a cabo por las quinasas de IκB (véase, por ejemplo, un estudio de M. Karin y M. Delhase, Seminars in Immunology, 2000, 12, 85). El complejo de IKK tradicional incluye al menos tres subunidades, IKKα (también denominada IKK-1), IKKβ (o IKK-2) e IKKγ (o NEMO), aunque pueden existir otros complejos relevantes que incluyen IKKα e

IKKβ. Los IKKα e IKKβ son ambos subunidades catalíticas mientras que el IKKγ se cree que es una subunidad reguladora. Tanto el IKKα como el IKKβ pueden fosforilar el IκB. Para los fines de este documento, los términos IKK o complejo de IKK se refieren a cualquier complejo que tenga actividad de quinasa derivada de las subunidades IKKα y/o IKKβ.

In vivo, la activación de IKK se produce tras la fosforilación de su subunidad catalítica. Tanto el IKKα como el IKKβ pueden ser fosforilados sobre residuos de serina, S177 y S188 del bucle de activación en el caso de IKKβ, y S176 y S180 del bucle de activación de IKKα. Un mutante de IKKβ que tiene alaninas en lugar de serinas en 177 y 181 evitó la fosforilación de IKKβ y la posterior activación del complejo de IKK por TNFα, IL-1 y otros activadores aguas arriba. Estos resultados apoyan una función clave para el IKKβ en la fosforilación de IβB a continuación de la estimulación proinflamatoria.

Los estudios en los que la trayectoria de NF-κB ha sido inhibida en células y animales apoyan el concepto de que la inhibición de la fosforilación de IβB es una aproximación viable para el tratamiento de enfermedades inflamatorias, autoinmunes y otras. En estos estudios, la activación de NF-κB se evitó mediante la expresión de una versión no degradable de la proteína IβB. La expresión de este inhibidor en células sinoviales derivadas de pacientes con artritis reumatoide redujo la expresión de TNF-α, IL-6, IL-1β e IL-8 mientras que las moléculas antiinflamatorias IL-10, IL-1ra e IL-11 no se vio afectada. Las metaloproteinasas de matriz (MMP1 y MMP3) fueron también infra-reguladas (J. Bonderson et al., Proc. Natl. Acad. Sci. USA, 1999, 96, 5668). La expresión transgénica del inhibidor de IκB en células T provocó una reducción significativa en la gravedad y aparición de artritis inducida por colágeno en ratones (R. Seetharaman et al., J. Immunol 1999, 163, 1577). Estos experimentos indican que la supresión del NF-κB en la articulación enferma podría reducir tanto al gravedad como el progreso de RA. En células epiteliales intestinales primarias, el inhibidor de NF-κB bloqueó la expresión de IL-1, IL-8, iNOS y COX-2, mediadores que son sobre-regulados durante el transcurso de la enfermedad de inflamación intestinal (C. Jubin et al., J. Immunol., 1998, 160, 410). La expresión de este inhibidor en ciertas células tumorales aumenta la destrucción de estas células por reactivos quimioterapéuticos (A.A. Beg y D. Baltimore, Science, 1996, 274, 782).

Un análisis de biopsias de pulmones de pacientes con enfermedad de obstrucción pulmonar crónica (COPD) encontró una expresión aumentada de NF-κB que se correlacionaba con la gravedad de la enfermedad (A. Di Stefano et al., Eur.

Resp. J. 2002, 1, 437). La inhibición de la activación de NF-κB con inhibidores de IKK-β estuvo entre las aproximaciones anti-inflamatorias que se informó que eran potencialmente útiles en el tratamiento de la COPD (P.J. Barnes, Nature Rev. Drug Disc., 2002, 1, 437). Análogamente, la inhibición de la actividad de NF-κB ha sido mencionada como una aproximación terapéutica para el asma (A. Pahl and I. Szelenyi, Infl. Res., 2002, 51, 273).

Un reciente estudio describe la función esencial de los mediadores inflamatorios en el desarrollo de la enfermedad cardiovascular. Los mediadores inflamatorios y las células que reclutan se describe que desempeñan una función clave en el desarrollo de líneas y placas grasas que conducen a la aterosclerosis. Además, se describe que desempeñan una función clave en la posterior degradación del saliente fibroso que se forma sobre la placa, conduciendo a la ruptura y la formación de un coágulo. Si el coágulo crece y se hace suficientemente grande, puede conducir la infarto de miocardio o apoplejía. Por tanto, los fármacos anti-inflamatorios que pueden inhibir la producción de estos mediadores y el posterior reclutamiento y activación de estas células pueden ser ventajosos en el tratamiento de estas enfermedades (L. Libby, Scientific American, 2002, 46).

Un cierto número de estudios indica que la activación de NF-κB desempeña también una función clave en la patogénesis y desarrollo del cáncer (véanse, por ejemplo, los estudios de B. Haefner, Durg Disc. Today, 2002, 7, 653 y M. Karin et al., Nat. Rev. Cancer, 2002, 2, 301). Los estudios han mostrado que las células en las que el NF-κB es constitutivamente activo son resistentes a la apoptosis. Esto puede contribuir a la carcinogénesis previniendo la muerte celular en las células que han experimentado cambios o deterioro cromosomales. Además, las células tumorales con NF-κB constitutivamente activo son resistentes a las terapias anti-cancerígenas, incluidas la quimioterapia y radiación. Unos estudios adicionales han vinculado el NF-κB activado a una diversidad de enfermedades malignas derivadas de células linfoides, mieloides y epiteliales, incluidos leucemia, linfomas y cánceres de pecho, gástrico, colorrectal, de pulmón y pancreático. Por tanto, se sugiere que los inhibidores deNF-κB, incluidos los inhibidores de IKKα e IKKβ, pueden ser útiles solos o en combinación con otras terapias anti-cancerígenas para tratar el cáncer.

Colectivamente, los estudios anteriormente descritos proporcionan un apoyo en cuanto a que la inhibición de la función de NF-κB a través de la inhibición de IKK puede ser una aproximación terapéutica útil para el tratamiento de una enfermedad autoinmune e inflamatoria, una enfermedad cadiovascular y el cáncer.

Se han hecho también estudios en ratones con la ruptura dirigida a diana

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del gen del IKK. La desactivación del gen de IKKβ dio lugar a una mortalidad embriónica debida a la apoptosis de hepatocitos. Sin embargo, los fibroblastos de las desactivaciones de IKKβ no experimentaron activación de IKK y NF-κB tras una estimulación con IL-1 o TNFα (Q. Li et al., Science, 1999, 284, 321), apoyando una función clave para el IKKβ y la activación de NF-κB a continuación de estímulos inflamatorios.

Se generó una desactivación condicional expresando un transgen de IκBα negativo, dominante, inducible y específico para el hígado (I. Lavon et al., Nature Medicine, 2000, 6, 573). Estos ratones fueron viables sin indicios de disfunción hepática incluso después de un año, pero tuvieron la función inmune deteriorada. Este estudio apoya la idea de que la inhibición de IKKβ puede dar lugar a la supresión inmune sin deterioro del hígado.

Los ratones con desactivación de IKKα murieron poco después de nacer y exhibieron una diversidad de defectos del esqueleto y anormalidades en la piel. Los fibroblastos y timocitos de estos ratones mostraron una activación de IKK normal y degradación de IκB en respuesta a TNFα, IL-1 o LPS (Y. Hu et al., Science, 1999, 284, 316); K. Takeda et al., Science, 1999, 284, 313). Unos estudios recientes con ratones desactivados y activados han puesto de manifiesto las distintas funciones de IKKα en el desarrollo y la señalización celular. En contraste con los estudios con ratones de IKKα desactivado, los ratones que tenían una versión inactiva de quinasa de IKKα activada eran viables y fértiles, indicando que la mortalidad perinatal y las anormalidades observadas en ratones desactivados con IKKα no eran debidas a la falta de actividad de quinasa. Sin embargo, estos ratones tenían defectos en la maduración de células B y el desarrollo de órganos linfoides secundarios (U. Senftleben et al., Science, 2001, 293, 1495). Este fenotipo parece ser debido a un defecto en el tratamiento de la proteína de NF-κB2/p100 para p52, la forma de unión a DNA de este miembro de la familia REL de factores de transcripción. A su vez, esto conduce a un defecto en la activación de un subconjunto de genes diana de NF-κB en células B. Además, otros estudios con estos mismos ratones han mostrado que la actividad de IKKα-quinasa es necesaria para la activación del NF-κB en el epitelio de los mamíferos durante la preñez (Cao, Y., et al., Cell, 2001, 107, 763). Esta trayectoria es específicamente activada a través del miembro de la familia de receptores de TNF RANK, y requiere la fosforilación del IκBα del sustrato de IKK canónico, y culmina con la inducción del gen regulador del ciclo celular Cilina D1.

Estos estudios indican que un inhibidor de la actividad de IKKα-quinasa puede ser útil para tratar enfermedades asociadas con una activación inapropiada

de células B como lupus (O.T. Chan et al.,Immunological Res., 1999, 169, 107) y artritis reumatoide (A. Gause y C. Borek, Biodrugs, 2001, 15, 73). Además, un inhibidor de IKKα puede ser útil en el tratamiento del cáncer de mamas ya que el NF-κB es constitutivamente activo en un cierto número de tumores de mamas y muchos de estos tumores dependen de la ciclina D1 par ala proliferación.

Se han descrito algunos inhibidores de IKKβ. El documento WO 01/58890 describe derivados de carboxamidas heteroaromáticas como inhibidores de IKKβ. El documento WO 01/68648 describe β-carbolinas que tienen actividd inhibidora de IKKβ. Se describen indoles sustituidos que tienen actividad inhibidora de IKKβ en el documento WO 01/30774. El documento WO 01/00610 describe bencimidazoles sustituidos que tienen actividad inhibidora deNF-κB . La aspirina y los salicilatos se ha descrito que se unen a IKKβ y lo inhiben (M. Yin et al., Nature, 1998, 396, 77).

Se describen tienopiridinas sustituidas que tienen actividad inhibidora de la adhesión celular en el documento US 2001/0020030 A1 y por A.O. Stewart et al., J. Med. Cahem., 2001, 44, 988. Se describen tienopiridinas que exhiben actividad antagonizante de hormonas liberadoras de bonadotropinas en el documento US 6.313.301. Se describen tienopiridinas sustituidas como inhibidores de telomerasa en el documento US 5.656.638.

Se ha descrito un cierto número de amidas de ácido tieno[2,3-b]piridino-2-carboxílico en la bibliografía química. Ejemplos incluyen amida de ácido 3-amino-4,6-dimetil-tieno[2,3-b]piridin-2-carboxílico, diamida de ácido 3-amino-6-metil-tieno[2,3-b]piridin-2,4-dicarboxílico, 3-amino-4-metil-6-fenil-tieno[2,3-b]-piridin-2-carboxamida, amida de ácido 3-amino-6-metil-4-fenil-tieno[2,3-b]piridin-2-carboxílico, amida de ácido 3-amino-6-(4-bromo-fenil)-4-metil-tieno[2,3-b]piridin-2-carboxílico, amida de ácido 3-amino-4-(4-bromo-fenil)-6-metil-tieno[2,3-b]piridin-2-carboxílico, 2-amida-4-butilamida de ácido 3-amino-6-metil-tieno[2,3-b]piridin-2,4-dicarboxílico, amida de ácido 3-amino-6-furan-2-il-4-fenil-tieno[2,3-b]piridin-2-carboxílico, amida de ácido 3-amino-6-furan-2-il-4-piridin-3-il-tieno[2,3-b]piridin-2-carboxílico, amida de ácido 3-amino-4-(4-cloro-fenil)-6-fenil-tieno[2,3-b]piridin-2-carboxílico, amida de ácido 3-amino-4-(4-fluoro-fenil)-6-furan-2-il-tieno[2,3-b]piridin-2-carboxílico, amida de ácido 3-amino-4-(4-cloro-fenil)-6-furan-2-il-tieno[2,3-b]piridin-2-carboxílico, amida de ácido 3-amino-4-(4-bromo-fenil)-6-furan-2-il-tieno[2,3-b]piridin-2-carboxílico, amida de ácido 3-amino-4,6-bis-(4-cloro-fenil)-tieno[2,3-b]piridin-2-carboxílico, amida de ácido 3-amino-6-nafth-2-il-4-piridin-3-il-tieno[2,3-b]piridin-2-carboxílico, 2-amida-4-(2-hidroxietil)amida de ácido 3-amino-6-metil-tieno[2,3-b]piridin-2,4-dicarboxílico, 3-amino-6-metil-4-piperidin-1-il-tieno[2,3-

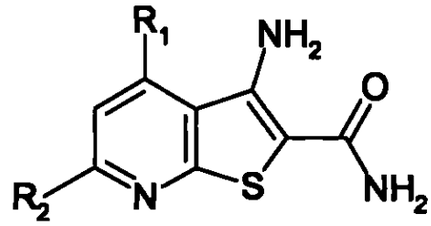
b]-piridin-2-carboxamida y 3-amino-4-metil-6-hidroxi-tieno[2,3-b]-piridin-2-carboxamide descritos como intermedios para la síntesis de heterociclos triciclicos y evaluados en cuanto a la actividad anti-alérgica (G. Wagner et al., Pharmazie, 1990, 45, 102).

Otros ejemplos incluyen amida de ácido 3-amino-4,6-difenil-tieno[2,3-b]piridin-2-carboxílico (A.M. Shestopalov et al., *J. Org. Chem. USSR,* (Engl. Transl.) 1984, *20*, 1382), amida de ácido 3-amino-6-metil-4-piridin-4-il-tieno[2,3-b]piridin-2-carboxílico y amida de ácido 3-amino-6-metil-4-piridin-3-il-tieno[2,3-b]piridin-2-carboxílico (G. Wagner et al., *Pharmazie*, 1993, *48*, 514), amida de ácido 3-amino-4-metoximetil-6-metil-tieno[2,3-b]piridin-2-carboxílico (E.I. Kaigorodova et al., *Chem. Heterocicl. Compd. (Engl. Transl.)*, 1996, *32*, 1234), amida de ácido 3-amino-6-fenil-4-tiofen-2-il-tieno[2,3-b]piridin-2-carboxílico, amida de ácido 3-amino-4-furan-2-il-6-metil-tieno[2,3-b]piridin-2-carboxílico, amida de ácido 3-amino-4-(4-cloro-fenil)-6-metil-tieno[2,3-b]piridin-2-carboxílico y amida de ácido 3-amino-4-furan-2-il-6-fenil-tieno[2,3-b]piridin-2-carboxílico (F.A. Attaby, *Phosphorus, Sulfur, Silicon Relat. Elem.*,1998, 139, 1), amida de ácido 3-amino-6-(4-cloro-fenil)-4-tiofen-2-il-tieno[2,3-b]piridin-2-carboxílico (Y. Sharanin et al., *J. Org. Chem. USSR,* (Engl. Transl.) 1996, *32*, 1207), amida de ácido 3-amino-6-fenil-4-piridin-3-il-tieno[2,3-b]piridin-2-carboxílico (A. Krauze, *Eur. J. Med. Chem. Chim. Ther.*, 1999, *34*, 301) y amida de ácido 3-amino-6-tiofen-2-il-4-trifluorometil-tieno[2,3-b]piridin-2-carboxílico (M.I. Abdel-Monem et al., *Pharmazie*, 2001, *56*, 41).

En ningún caso se describen estos compuestos por tener la capacidad de inhibir IKKα o IKKβ.

SUMARIO DE LA INVENCIÓN

Por lo tanto, es un objeto de esta invención proporcionar nuevos compuestos según la siguiente fórmula (I):



(I)

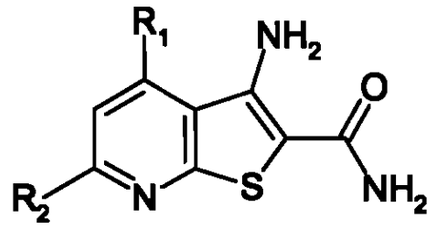
en la que las variables R_1 y R_2 se describen en la presente memoria descriptiva que inhiben IKK. Es un objeto adicional de la invención proporcionar métodos para tratar enfermedades y estados patológicos exacerbados por IKK como, pero sin limitación, enfermedades autoinmunes, enfermedades inflamatorias y cáncer. Es todavía un objeto adicional de la invención proporcionar nuevos proce-

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dimientos para la preparación de los nuevos compuestos anteriormente mencionados.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Un primer aspecto de la invención comprende un método para tratar un estado inflamatorio o autoinmune mediante la administración de ciertas moléculas nuevas y conocidas de fórmula (I):



(I)

en la cual:

R_1 es

(a) fenilo o heteroarilo seleccionado entre furanilo, tienilo, piridilo, pirrolilo, imidazolilo y benzofuranilo, opcionalmente sustituidos con uno a dos R_3,

(b) heterociclilo seleccionado entre 1-piperidinilo, 1-piperazinilo, 1-pirrolidinilo y 4-morfolinilo, opcionalmente sustituidos con uno a dos grupos seleccionados entre alquilo C_{1-6}, $-CO_2$-alquilo C_{1-5}, fenilo, bencilo, -OH y C(O)heteroarilo, en los que el grupo heteroarilo se selecciona entre furanilo, tienilo, piridilo y pirrolilo,

(c) $R_6(CH_2)_mO$-,

(d) R_6OCH_2-,

(e) $R_6(CH_2)_mNH$-,

(f) $R_6(CH_2)_p(CH=CH)_m$-,

(g) alquilo C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(h) alcoxi C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(i) alquilo C_{1-6}-$S(O)_n$-, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(j) $-N(R_4)(R_5)$, o

(k) -C(O)NHR', en donde R' es R_6, piridilo o $-CH_3$;

R_2 es

(a) alquilo C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(b) alcoxi C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(c) alquilamino C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10}

(d) alquiltio C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(e) heterociclil-$(CH_2)_m$- en donde dicho heterociclo se selecciona entre piperidinilo, piperazinilo, morfolinilo, azepanilo, pirrolidinilo, 1,4-diazacicloheptanilo, azepanilo, 2,5-diazabiciclo[2.2.1]heptanilo, oxazepanilo y tiomorfolino y está opcionalmente sustituido con uno o tres R_7,

(f) heterociclil-CH_2O- en donde el heterociclilo se selecciona entre 1-piperidinilo, 1-piperazinilo, 4-morfolinilo y 1-pirrolidinilo, opcionalmente sustituidos con alquilo C_{1-6},

(g) fenilo, opcionalmente sustituido con uno o tres R_3,

(h) -$N(R_4)(R_5)$,

(i) heteroarilo seleccionado entre furanilo, tienilo, imidazolilo, piridilo y pirrolilo, o

(j) -H;

R_3 se escoge entre alquilo C_{1-6}, alcoxi C_{1-6}, hidroxi-alquilo C_{1-6}, halógeno, -CN, -CO_2H, -CO_2-alquilo C_{1-6}, -$S(O)_n$-alquilo C_{1-6}, -NO_2, -OH, -CF_3, -$N(R_4)(R_5)$, -NHC(O)NH-alquilo C_{1-6}, -$C(O)N(R_4)(R_5)$ y fenilo opcionalmente sustituido con halógeno, alquilo C_{1-6}, -CN o alcoxi C_{1-6};

R_4 y R_5 se seleccionan independientemente entre H, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, -SO_2-alquilo C_{1-6}, fenilo, piridilo, bencilo, piperidinilo, feniletilo y $(CH_3)_3COC(O)$-;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre halógeno, alquilo C_{1-6}, -CN, -CO_2-alquilo C_{1-6}, -$C(O)NR_4R_5$, -SO_2NH_2, -NO_2, -OH, -NH_2, -CF_3 y alcoxi C_{1-6}, o R_6 es cicloalquilo C_{3-6}, -CH_2OH, naftalen-2-ilo, naftalen-1-ilo o 2-tienilo;

R_7 se selecciona entre –OH, -CN, oxo, -CO_2alquilo C_{1-6}, -CO_2H, -$C(O)N(R_4)(R_5)$, -$N(R_4)(R_5)$, -$CH_2N(R_4)(R_5)$, -CH_2OH, alquilo C_{1-6}, -CO_2bencilo, hidroxialquilo C_{1-6}, -C(O) alquil $C_{1-6}N(R_4)(R_5)$, -$NHCO_2$alquilo C_{1-6}, -$NHC(O)N(R_4)(R_5)$, -S(O)n-alquilo C_{1-6}, $(CH_3)_3COC(O)$-, fenilo, piridilo, $H_2NCH(R_6)C$ (O)-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$-$R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- y -C(O)heterociclilo, en donde dicho heterociclilo se selecciona entre piperidinilo, piperazinilo, morfolinilo y pirrolidinilo, o R_7 is 2-hidroxietilamino, metilcarbamidoilo, hidroxiimino, hidrazinocarbonilo, sulfamoilo, metanosulfonilamino, metilsulfonilhidrazino, 2-hidroxipropilamino, 2,3-dihidroxipropilamino, 2-hidroxi-1-metiletilamino, carbamoilmetilamino, N'-fenilhidrazinocarbonilo o tolueno-4-sulfonilamino;

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R_8 se selecciona entre alquilo C_{1-6}, $-(CH_2)_{1-4}NH_2$, fenilo o bencilo;

R_9 se selecciona entre oxo, -OH, $-NR_4R_5$, $-CO_2H$ y alcoxi C_{1-6};

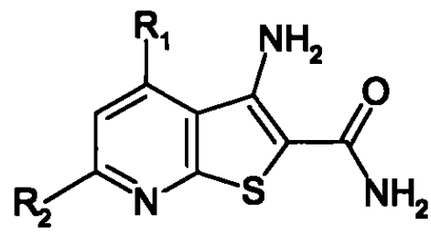
R_{10} se selecciona entre oxo, -OH, $-N(R_4)(R_5)$, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, $-C(O)N(R_4)(R_5)$, R_8 y heteroarilo seleccionado entre furanilo, tienilo, imidazolilo, piridilo, indolilo y pirrolilo;

m es 0 ó 1;

n es 0, 1 ó 2; y

p es 0, 1, 2 ó 3.

En su segundo aspecto, la invención proporciona nuevos compuestos de fórmula (I):



(I)

en la cual:

R_1 es

(a) fenilo o heteroarilo seleccionado entre furanilo, tienilo, piridilo, pirrolilo, imidazolilo y benzofuranilo, opcionalmente sustituidos con uno a dos R_3,

(b) heterociclilo seleccionado entre 1-piperidinilo, 1-piperazinilo, 1-pirrolidinilo y 4-morfolinilo, opcionalmente sustituidos con uno a dos grupos seleccionados entre alquilo C_{1-6}, $-CO_2$-alquilo C_{1-5}, fenilo, bencilo, -OH y -C(O)heteroarilo, en los que el heteroarilo se selecciona entre furanilo, tienilo, piridilo y pirrolilo,

(c) $R_8(CH_2)_mO$-,

(d) R_8OCH_2-,

(e) $R_8(CH_2)_mNH$-,

(f) $R_8(CH_2)_p(CH=CH)_m$-,

(g) Alquilo C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(h) alcoxi C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(i) alquil C_{1-6}-$S(O)_n$-, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(j) $-N(R_4)(R_5)$, o

(k) -C(O)NHR', en donde R' es R_8, piridilo o $-CH_3$;

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R_2 es

(a) alquilo C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(b) alcoxi C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(c) alquilamino C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(d) alquiltio C_{1-6}, opcional, parcial o completamente halaogenado y opcionalmente sustituido con uno a dos R_{10},

(e) heterociclil-$(CH_2)_m$- en el que dicho heterociclo se selecciona entre piperidinilo, piperazinilo, morfolinilo, azepanilo, pirrolidinilo, 1,4-diazacicloheptanilo, azepanilo, 2,5-diazabiciclo[2.2.1]heptanilo, oxazepanilo y tiomorfolino y está opcionalmente sustituido con uno a tres R_7,

(f) heterociclil-CH_2O- en el que el heterociclilo se selecciona entre 1-piperidinilo, 1-piperazinilo, 4-morfolinilo y 1-pirrolidinilo, opcionalmente sustituido con alquilo C_{1-6},

(g) fenilo, opcionalmente sustituido con uno a tres R_3,

(h) -$N(R_4)(R_5)$,

(i) heteroarilo seleccionado entre furanilo, tienilo, imidazolilo, piridilo y pirrolilo, o

(j) -H;

R_3 se escoge entre alquilo C_{1-6}, alcoxi C_{1-6}, hidroxi-alquilo C_{1-6}, halógeno, -CN, -CO_2H, -CO_2-alquilo C_{1-6}, -$S(O)_n$-alquilo C_{1-6}, -NO_2, -OH, -CF_3, -$N(R_4)(R_5)$, -NHC(O)NH-alquilo C_{1-6}, -$C(O)N(R_4)(R_5)$ y fenilo opcionalmente sustituido con halógeno, alquilo C_{1-6}, -CN o alcoxi C_{1-6};

R_4 y R_5 se seleccionan independientemente entre H, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, -SO_2-alquilo C_{1-6}, fenilo, piridilo, bencilo, piperidinilo, feniletilo y $(CH_3)_3COC(O)$-;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre alquilo C_{1-6}, -CN, -CO_2-alquilo C_{1-6}, -$C(O)NR_4R_5$, -SO_2NH_2, -NO_2, -OH, -NH_2, -CF_3 y alcoxi C_{1-6}, o R_6 es cicloalquilo C_{3-6}, -CH_2OH, naftaleno-2-ilo, naftaleno-1-ilo o 2-tienilo;

R_7 se selecciona entre –OH, -CN, oxo, -CO_2alquilo C_{1-6}, -CO_2H, -$C(O)N(R_4)(R_5)$, -$N(R_4)(R_5)$, -$CH_2N(R_4)(R_5)$, -CH_2OH, alquilo C_{1-6}, -CO_2bencilo, hidroxialquilo C_{1-6}, -C(O) alquil $C_{1-6}N(R_4)(R_5)$, -$NHCO_2$alquilo C_{1-6}, -$NHC(O)N(R_4)(R_5)$, -$S(O)_n$alquilo C_{1-6}, $(CH_3)_3COC(O)$-, fenilo, piridilo, $H_2NCH(R_6)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- y -C(O)heterociclilo,

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R_8 se selecciona entre alquilo C_{1-6}, $-(CH_2)_{1-4}NH_2$, fenilo o bencilo;

R_9 se selecciona entre -OH, $-NR_4R_5$, $-CO_2H$ y alcoxi C_{1-6};

R_{10} se selecciona entre oxo, -OH, $-N(R_4)(R_5)$, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, $-C(O)N(R_4)(R_5)$, R_8 y heteroarilo seleccionado entre furanilo, tienilo, imidazolilo, piridilo, indolilo y pirrolilo;

m es 0 ó 1;

n es 0, 1 ó 2;

p es 0, 1, 2 ó 3;

y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables.

En otra realización, se proporcionan nuevos compuestos de fórmula (I) como se describió anteriormente y en la cual:

R_1 es

(a) fenilo o heteroarilo seleccionado entre furanilo, tienilo, piridilo, pirrolilo, imidazolilo y benzofuranilo opcionalmente sustituidos con uno a dos R_3,

(b) $R_8(CH_2)_mO$-,

(c) R_8OCH_2-,

(d) $R_8(CH_2)_mNH$-,

(e) $R_8(CH_2)_p(CH=CH)_m$-,

(f) alquilo C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(g) alcoxi C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9;

(h) alquiltio C_{1-6},

(i) $-N(R_4)(R_5)$, o

(j) -C(O)NHR', en donde R' es R_8, piridilo o $-CH_3$,

R_2 es

(a) alquilo C_{1-6}, opcionalmente sustituido con R_{10},

(b) alcoxi C_{1-6}, opcionalmente sustituido con R_{10},

(c) alquilamino C_{1-6}, opcionalmente sustituido con R_{10},

(d) heterociclilo seleccionado entre 1-piperidinilo, 1-piperazinilo, 4-morfolinilo, 1-azepanilo, 1-pirrolidinilo, 1,4-diazacicloheptan-1-ilo, 1-azepanilo, 2,5-diazabiciclo[2.2.1]heptan-2-ilo, oxazepan-4-ilo y 4-tiomorfolino, y que está opcionalmente sustituido con uno a tres R_7,

(e) heterociclil-CH_2O- en donde el grupo heterociclilo se selecciona entre 1-piperidinilo, 1-piperazinilo, 4-morfolinilo y 1-pirrolidinilo, opcionamlente sustituidos con alquilo C_{1-6}, o

(f) $-N(R_4)(R_5)$;

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R_3 se escoge entre alquilo C_{1-6}, alcoxi C_{1-6}, hidroxi-alquilo C_{1-6}, halógeno, -CN, $-CO_2H$, $-CO_2$-alquilo C_{1-6}, $-S(O)_n$alquilo C_{1-6}, $-NO_2$, -OH, $-CF_3$, $-N(R_4)(R_5)$, -NHC(O)NHalquilo C_{1-6}, $-C(O)N(R_4)(R_5)$ y fenilo opcionalmente sustituido con halógeno, alquilo C_{1-6}, -CN o alcoxi C_{1-6};

R_4 y R_5 se seleccionan independientemente entre H, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, piridilo, bencilo, piperidinilo y feniletilo;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre Cl, F, alquilo C_{1-6}, -CN, $-CO_2$alquilo C_{1-6}, $-C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ y alcoxi C_{1-6}, o R_6 es cicloalquilo C_{3-6}, $-CH_2OH$, naftaleno-2-ilo, naftaleno-1-ilo o 2-tienilo; o

R_7 se selecciona entre –OH, -CN, oxo, $-CO_2$alquilo C_{1-6}, $-CO_2H$, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, $-CH_2OH$, alquilo C_{1-6}, -C(O) alquil $C_{1-6}N(R_4)(R_5)$, $-NHC(O)N(R_4)(R_5)$, $-S(O)_n$alquilo C_{1-6}, fenilo, piridilo, $H_2NCH(R_8)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- y -C(O)heterociclilo, en donde dicho heterociclilo se selecciona entre piperidinilo, piperazinilo, morfolinilo y pirrolidinilo, o R_7 es 2-hidroxietilamino, metilcarbamidoilo, hidroxiimino, hidrazinocarbonilo, sulfamoilo, metanosulfonilamino, metilsulfonilhidrazino, 2-hidroxipropilamino, 2,3-dihidroxipropilamino, 2-hidroxi-1-metiletilamino, carbamoilmetilamino, N'-fenilhidrazinocarbonilo o tolueno-4-sulfonilamino;

R_8 se selecciona entre alquilo C_{1-6}, $-(CH_2)_{1-4}NH_2$, fenilo o bencilo;

R_9 es -OH;

R_{10} se selecciona entre -OH, $-N(R_4)(R_5)$, alquilo C_{1-6} y heteroarilo seleccionado entre furanilo, tienilo y piridilo;

m es 0 ó 1;

n es 0, 1 ó 2;

p es 0, 1, 2 ó 3;

y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables.

Todavía, en otra realización de la invención, se proporcionan nuevos compuestos de fórmula (I) como se describió anteriormente, y en los cuales:

R_1 es

(a) fenilo o heteroarilo seleccionado entre furanilo, tienilo y piridilo, opcionalmente sustituido con uno a dos R_3,

(b) $R_6(CH_2)_mO$-,

(c) R_6OCH_2-,

(d) $R_6(CH_2)_mNH$-,

(e) $R_6(CH_2)_p(CH{=}CH)_m$-,

(f) alquilo C_{1-6},

(g) alquilo C_{1-6}-OH,

(h) -CF_3,

(i) alcoxi C_{1-6},

(j) -O-alquilo C_{1-6}-OH,

(k) alquiltio C_{1-6},

(l) –$N(R_4)(R_5)$, o

(m) –C(O)NHR', en donde R' es R_6, piridilo o –CH_3;

R_2 es heterociclilo en donde dicho heterociclo se selecciona entre 1-piperidinilo, 1-piperazinilo, 1-azepanilo, 1,4-diazacicloheptan-1-ilo y 1-azepanil-2,5-diazabiciclo[2.2.1]heptan-2-ilo y 4-tiomorfolino y está opcionalmente sustituido con uno a tres R_7,

R_3 se escoge entre alquilo C_{1-6}, alcoxi C_{1-6}, hidroxi-alquilo C_{1-6}, halógeno, -CN, -CO_2H, -CO_2-alquilo C_{1-6}, -$S(O)_n$-alquilo C_{1-6}, -NO_2, -OH, -CF_3, -$N(R_4)(R_5)$, -NHC(O)NH-alquilo C_{1-6}, -$C(O)N(R_4)(R_5)$ y fenilo opcionalmente sustituido con halógeno, alquilo C_{1-6}, -CN o alcoxi C_{1-6};

R_4 y R_5 se seleccionan independientemente entre H, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, piridilo, bencilo, piperidinilo y feniletilo;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre Cl, F, alquilo C_{1-6}, -CN, CO_2alquilo C_{1-6}, $C(O)NR_4R_5$, -SO_2NH_2, -NO_2, -OH, -NH_2, -CF_3 y alcoxi C_{1-6} o R_6 es cicloalquilo C_{3-6}, -CH_2OH, naftaleno-2-ilo, naftaleno-1-ilo o 2-tienilo;

R_7 se selecciona entre –OH, -CN, oxo, -CO_2alquilo C_{1-6}, -$C(O)N(R_4)(R_5)$, -$N(R_4)(R_5)$, -$CH_2N(R_4)(R_5)$, CH_2OH, alquilo C_{1-6}, -C(O) alquil $C_{1-6}N(R_4)(R_5)$, -NHC(O)$N(R_4)(R_5)$, -$S(O)_n$alquilo C_{1-6}, $H_2NCH(R_8)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$- , $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- y -C(O)heterociclilo, en donde dicho heterociclilo se selecciona entre piperidinilo, piperazinilo, morfolinilo y pirrolidinilo,, o R_7 es 2-hidroxietilamino, metilcarbamidoilo, hidroxiimino, hidrazinocarbonilo, sulfamoilo, metanosulfonilamino, metilsulfonilhidrazino, 2-hidroxipropilamino, 2,3-dihidroxipropilamino, 2-hidroxi-1-metiletilamino, carbamoilmetilamino, N'-fenilhidrazinocarbonilo o tolueno-4-sulfonilamino;

R_8 se selecciona entre alquilo C_{1-6}, -$(CH_2)_{1-4}NH_2$, fenilo o bencilo;

m es 0 ó 1;

n es 0, 1 ó 2;

p es 0, 1, 2 ó 3;

y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables.

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Todavía, en otra realización de la invención, se proporcionan nuevos compuestos de fórmula (I) como se describió anteriormente y en los cuales:

R_1 es

(a) fenilo, opcionalmente sustituido con uno a dos R_3,

(b) $R_6CH=CH-$

(c) alquilo C_{1-6},

(d) alquilo C_{2-3}-OH,

(e) $-CF_3$,

(f) alcoxi C_{1-6},

(g) -O-alquilo C_{2-3}-OH,

(h) alquiltio C_{1-6}, o

(i) -C(O)NHR', en donde R' es R_6, piridilo o $-CH_3$;

R_2 es

heterociclilo, en donde dicho heterociclo se selecciona entre 1-piperidinilo, 1-piperazinilo, 1-azepanilo, 1,4-diazacicloheptan-1-ilo y 1-azepanilo y está opcionalmente sustituido con uno a tres R_7;

R_3 se escoge entre $-CH_3$, $-OCH_3$, F, Cl, $-CO_2CH_3$, $-SO_2CH_3$ y $-NO_2$;

R_4 y R_5 se seleccionan independientemente entre H, $-CH_3$ y bencilo;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre Cl, F, alquilo C_{1-6}, -CN, CO_2alquilo C_{1-6}, $C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ y alcoxi C_{1-6} o R_6 es cicloalquilo C_{3-6}, $-CH_2OH$, naftalen-2-ilo, naftalen-1-ilo o 2-tienilo;

R_7 se selecciona entre –OH, -CN, oxo, $-CO_2$alquilo C_{1-6}, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, CH_2OH, alquilo C_{1-6}, -C(O) alquil $C_{1-6}N(R_4)(R_5)$, $-NHC(O)N(R_4)(R_5)$, $-S(O)_n$alquilo C_{1-6}, $H_2NCH(R_6)C(O)-$, $HO(CH_2)_mCH_2CH(NH_2)C(O)-$, $HOCH(R_6)CH_2NH-$, $R_6CH_2CH(OH)CH_2NH-$, $R_6OCH_2CH(OH)CH_2NH-$ y -C(O)heterociclilo, en los que dicho heterociclilo se selecciona entre piperidinilo, piperazinilo, morfolinilo y pirrolidinilo, o R_7 es 2-hidroxietilamino, metilcarbamidoilo, hidroxiimino, hidrazinocarbonilo, sulfamoilo, metanosulfonilamino, metilsulfonilhidrazino, 2-hidroxipropilamino, 2,3-dihidroxipropilamino, 2-hidroxi-1-metiletilamino, carbamoilmetilamino, N'-fenilhidrazinocarbonilo o tolueno-4-sulfonilamino;

R_8 se selecciona entre alquilo C_{1-6}, $-(CH_2)_{1-4}NH_2$, fenilo o bencilo;

y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables.

En una realización adicional de la invención, se proporcionan nuevos compuestos de fórmula (I) como se describieron anteriormente y en los cuales:

R_1 es

(a) $-CH_2CH_2CH_3$,

(b) $-OCH_2CH_3$,

(c) $-SCH_3$,

(d) -C(O)NHR', en donde R' es 3-piridilo o fenilo sustituido en la posición 4 con -OH, $-C(O)NH_2$ o $-SO_2NH_2$;

R_2 es heterociclilo en el que dicho heterociclo se selecciona entre 1-piperidinilo y 1-piperazinilo y está opcionalmente sustituido con uno a tres R_7;

R_4 y R_5 se seleccionan independientemente entre H, $-CH_3$ y bencilo;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre Cl, F, $-CH_3$, -CN, $-CO_2CH_3$, $-C(O)NR_4R_5$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ y $-CH_3$, o R_6 es naftalen-2-ilo, naftalen-1-ilo o 2-tienilo;

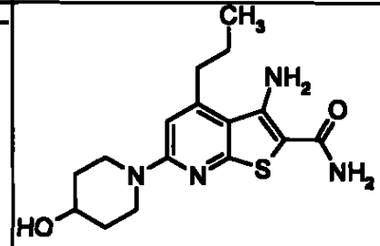
R_7 se selecciona entre –OH, -CN, oxo, $-C(O)NH_2$, $-NH_2$, $-CH_2NH_2$, $-CH_3$, $-NHC(O)NH_2$, $H_2NCH(R_8)C(O)$-, $HOCH(R_8)CH_2NH$- , $R_8CH_2CH(OH)CH_2NH$- y $R_8OCH_2CH(OH)CH_2NH$-, o R_7 es 2-hidroxietilamino, metilcarbamidoilo, metanosulfonilamino, metilsulfonilhidrazino, 2-hidroxipropilamino, 2,3-dihidroxipropilamino, carbamoilmetilamino o N'-fenilhidrazinocarbonilo;

R_8 es $-(CH_2)_{1-4}NH_2$;

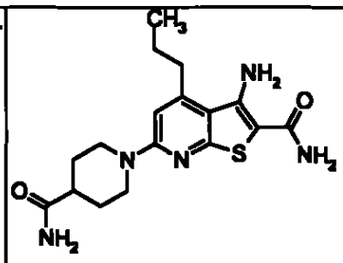
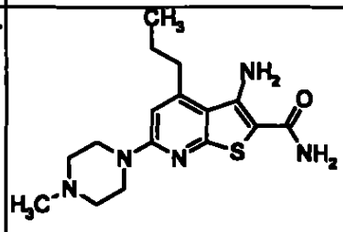
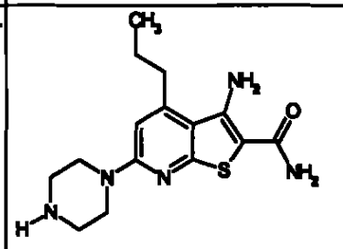
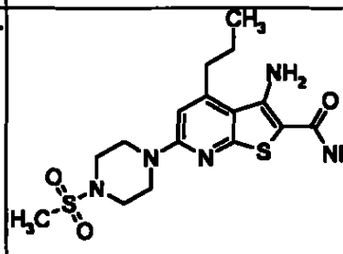
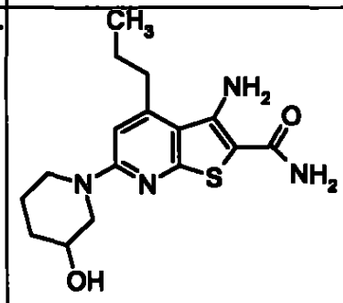
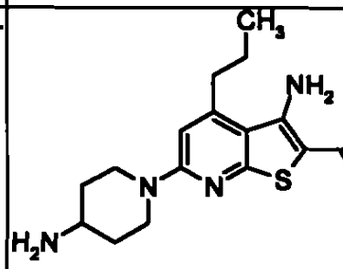
y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables;

con la condición de que en cada una de las realizaciones anteriores de los nuevos compuestos, si R_1 es fenilo o heteroarilo, alquilo C_{1-6}, $-CF_3$, $-C(O)NR_4R_5$ o heterociclilo, entonces R_2 no es alquilo C_{1-6}, fenilo, heteroarilo, $-CF_3$ o H. En el primer aspecto de la invención relacionado con un método para tratar un estado inflamatorio o autoinmune con compuestos de fórmula (I), esta condición no se aplica.

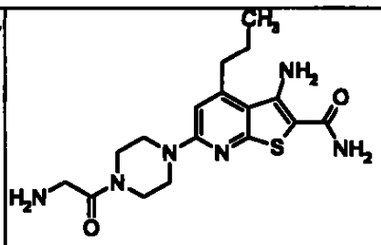
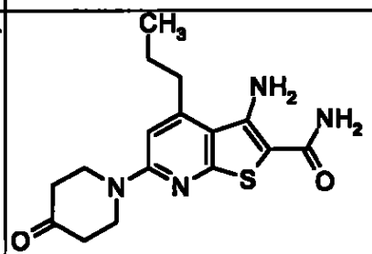
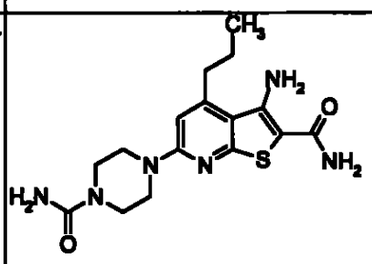
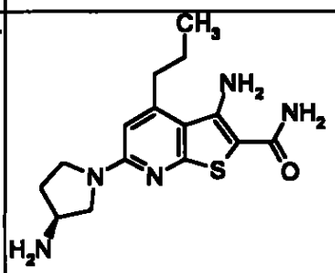
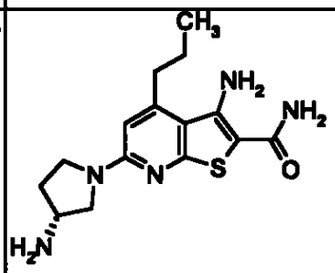
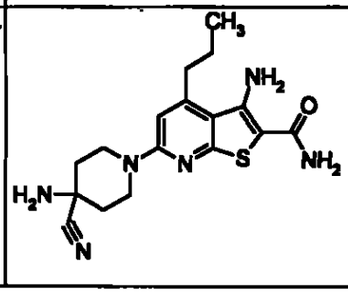
En una realización adicional de la invención, se proporcionan los siguientes compuestos:

	Nombre	Estructura
	Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	

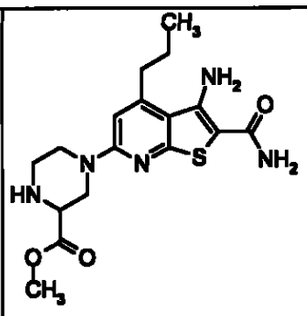
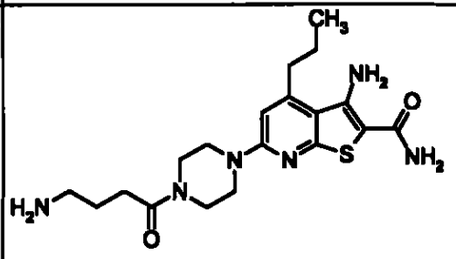
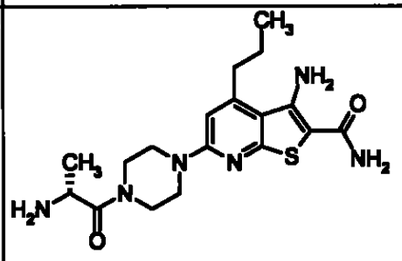
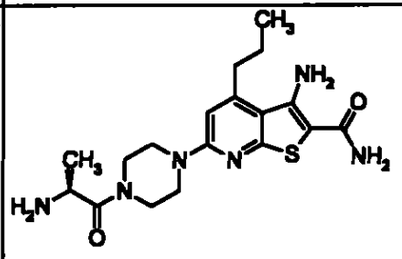
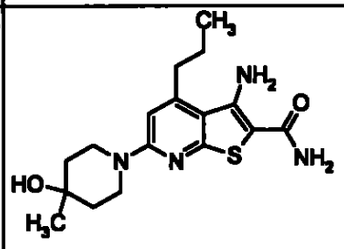
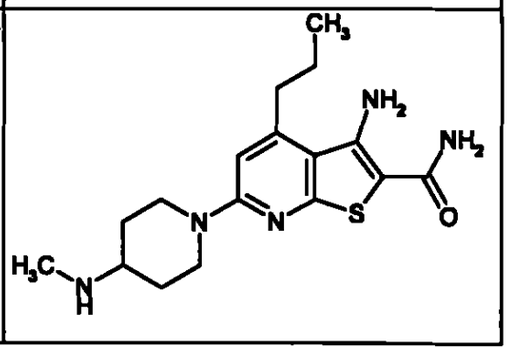
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	Amida de ácido 3-amino-6-(4-carbamoil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-metil-piperazin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-piperazin-1-il-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-metanosulfonil-piperazin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(3-hidroxi-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	

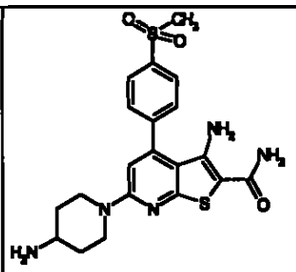
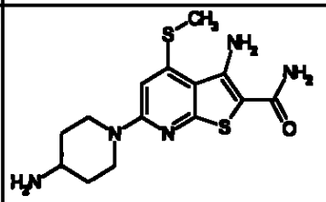
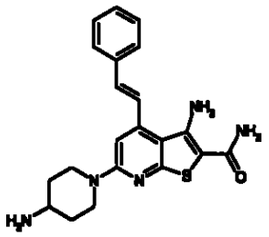
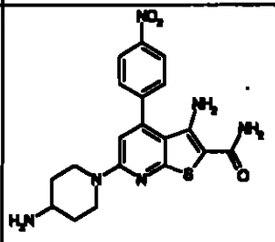
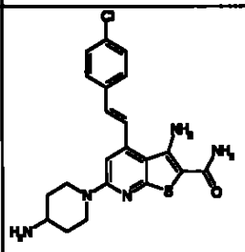
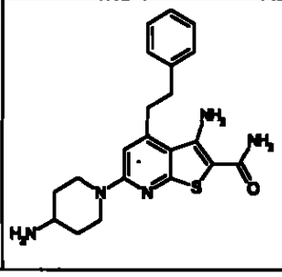
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	Amida de ácido 3-Amino-6-[4-(2-amino-etanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-oxo-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-carbamoil-piperazin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-((S)-3-amino-pirrolidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-((R)-3-amino-pirrolidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-4-ciano-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	

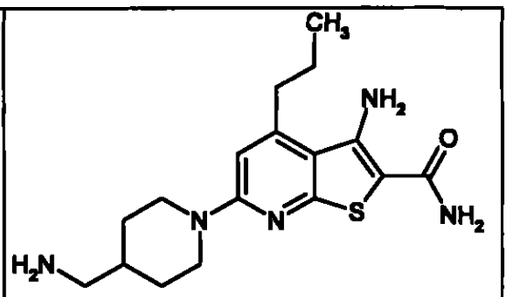
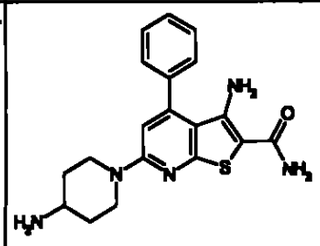
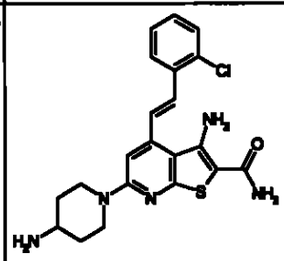
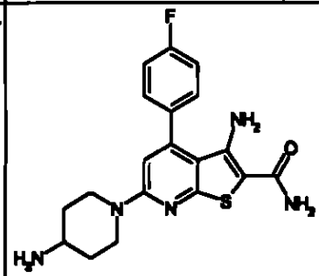
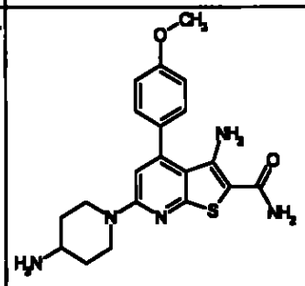
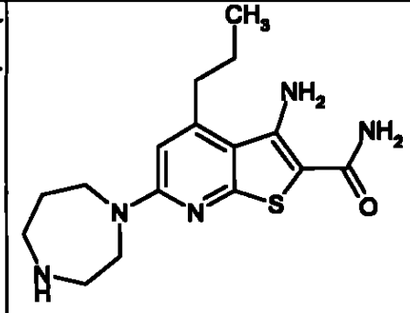
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	Éster metílico de ácido 4-(3-Amino-2-carbamoil-4-propil-tieno[2,3-b]piridin-6-il)-piperazin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-(4-amino-butanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-((R)-2-amino-propanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-((S)-2-amino-propanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-hidroxi-4-metil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-metilamino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	

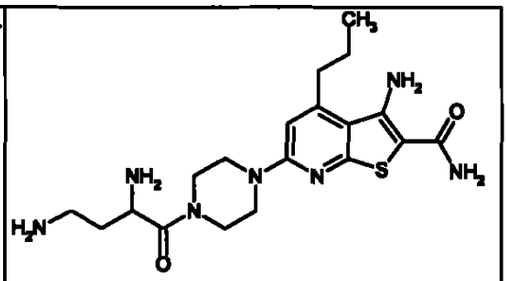
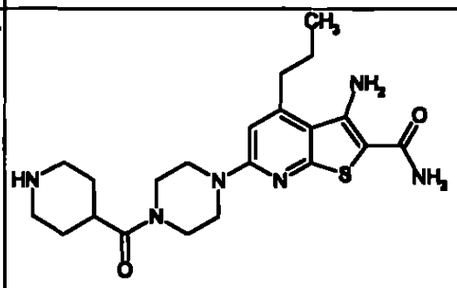
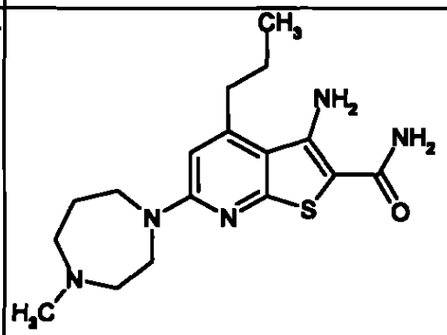
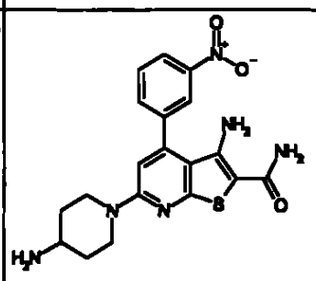
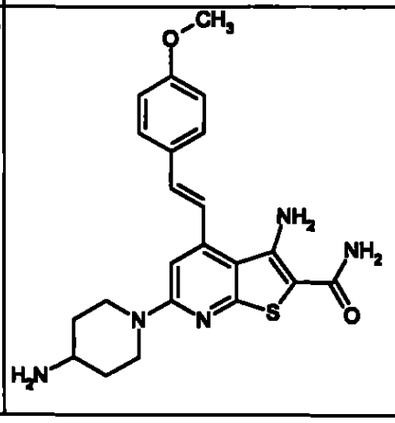
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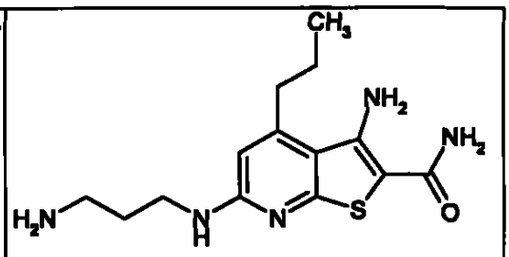
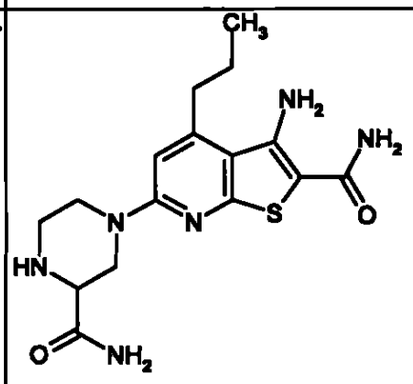
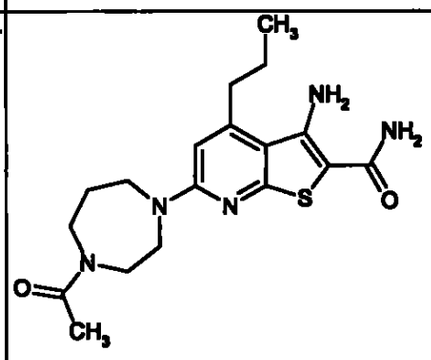
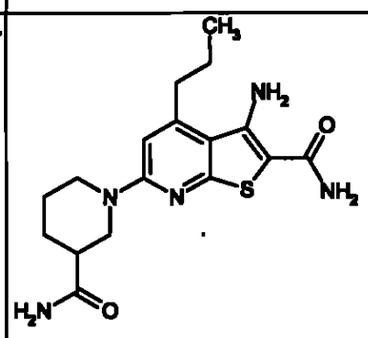
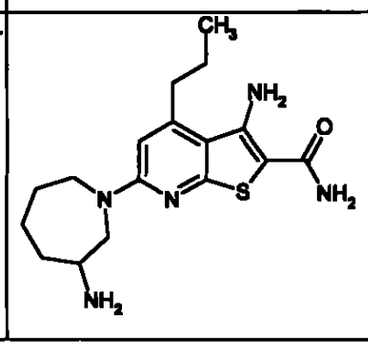
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	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-((E)-estiril)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-nitro-fenil)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-[(E)-2-(4-cloro-fenil)-vinil]-tieno[2,3-b]piridin-2-carboxílico	
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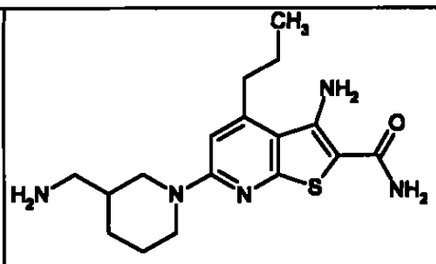
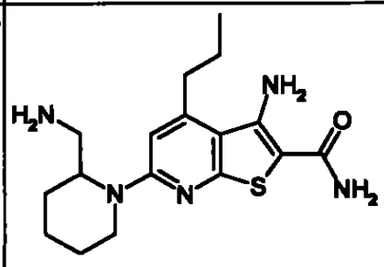
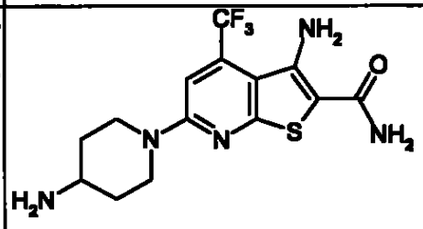
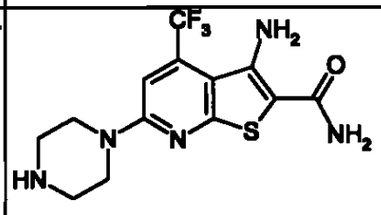
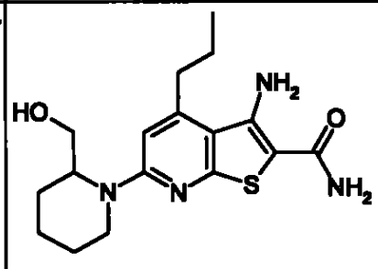
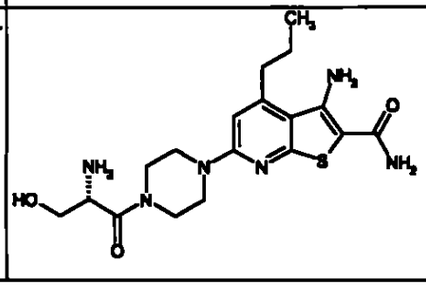
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	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-[(E)-2-(2-cloro-fenil)-vinil]-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-fluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-metoxi-fenil)-tieno[2,3-b]piridin-2-carboxílico	
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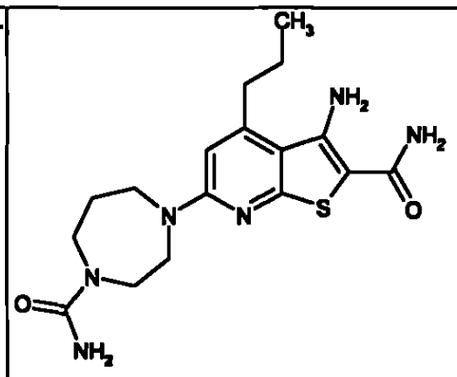
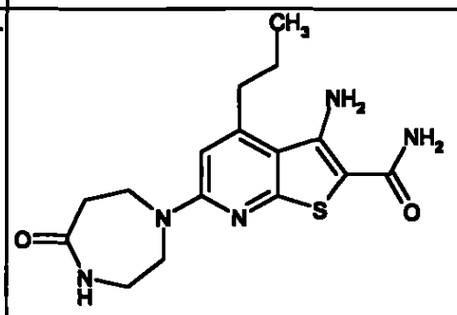
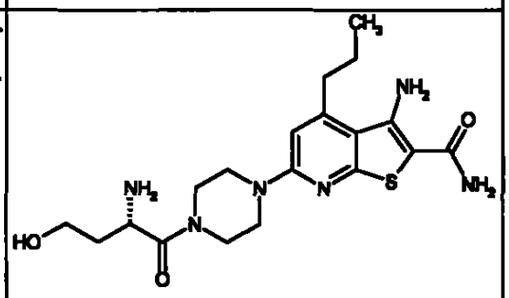
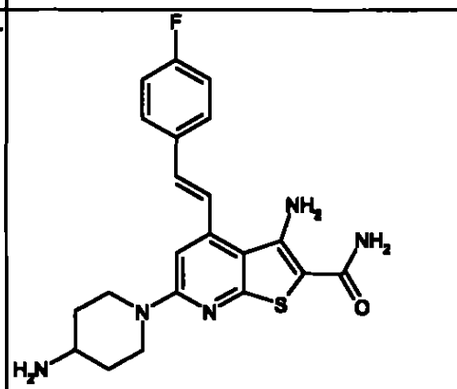
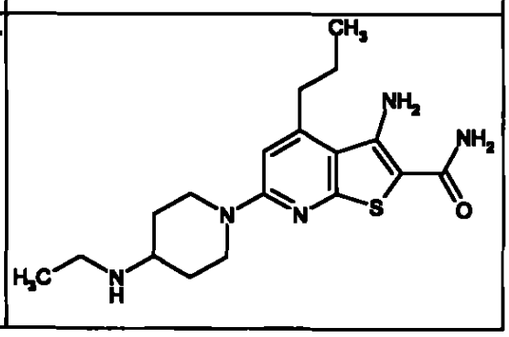
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	Amida de ácido 3-amino-6-[4-(1-piperidin-4-il-metanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-metil-[1,4]diazepan-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(3-nitro-fenil)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-[(E)-2-(4-metoxi-fenil)-vinil]-tieno[2,3-b]piridin-2-carboxílico	

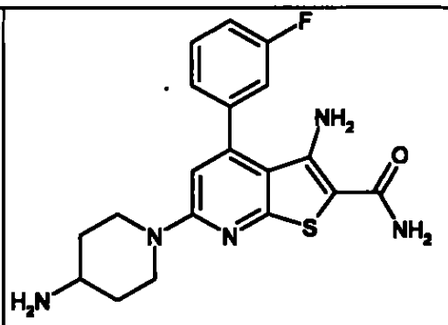
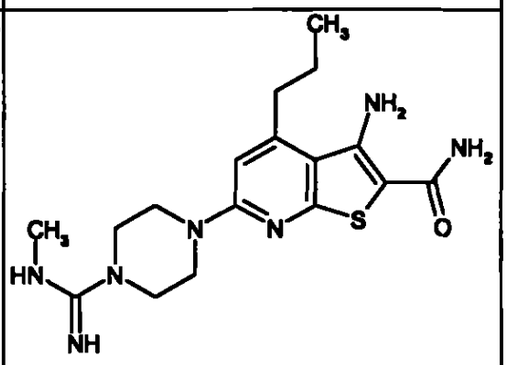
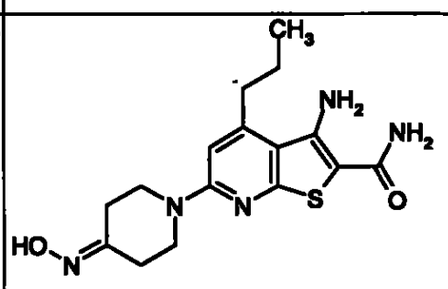
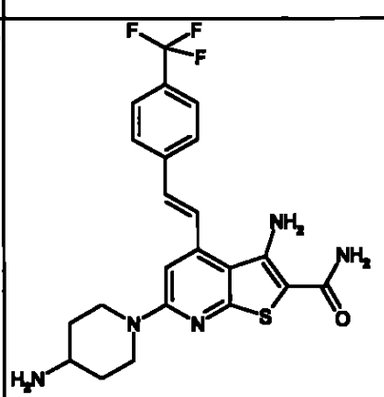
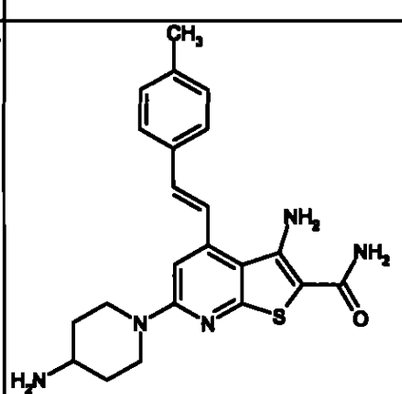
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	Amida de ácido 6-(4-acetil-[1,4]diazepan-1-il)-3-amino-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(3-carbamoil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
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	Amida de ácido 3-amino-6-(3-aminometil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(2-aminometil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-trifluorometil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-piperazin-1-il-4-trifluorometil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(2-hidroximetil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-((S)-2-amino-3-hidroxi-propionil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	

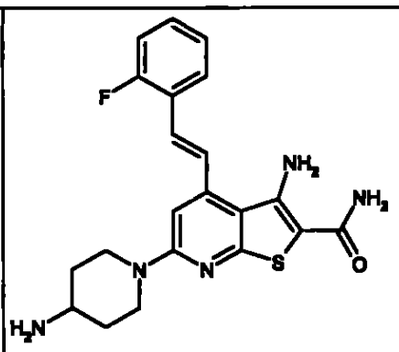
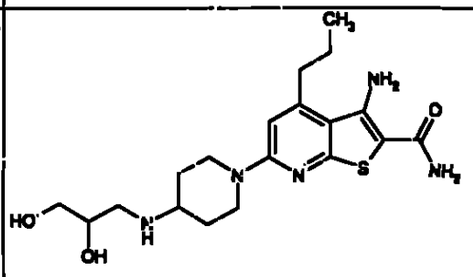
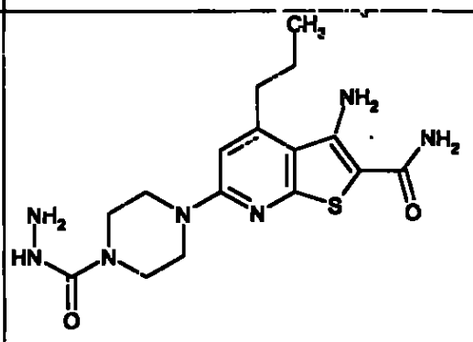
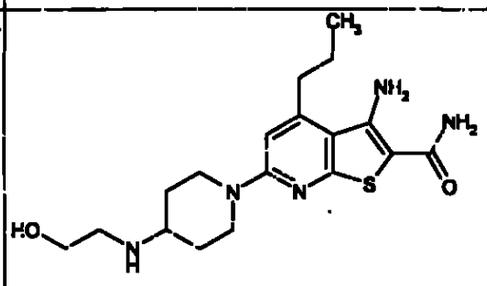
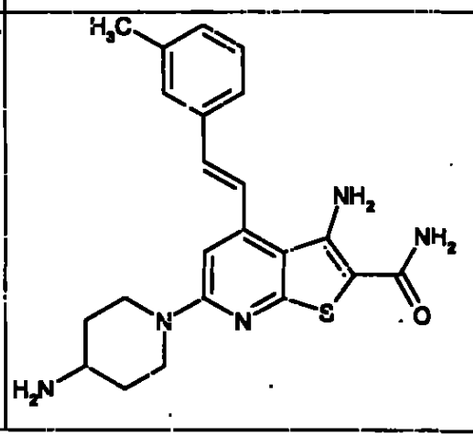
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	Amida de ácido 3-amino-6-(4-carbamoil-[1,4]diazepan-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(5-oxo-[1,4]diazepan-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-((S)-2-amino-4-hidroxi-butyril)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-[(E)-2-(4-fluoro-fenil)-vinil]-tieno[2,3-b]piridin-2-carboxílico	
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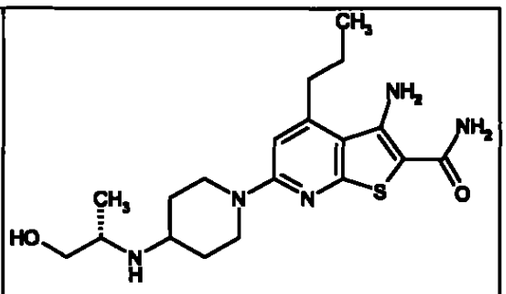
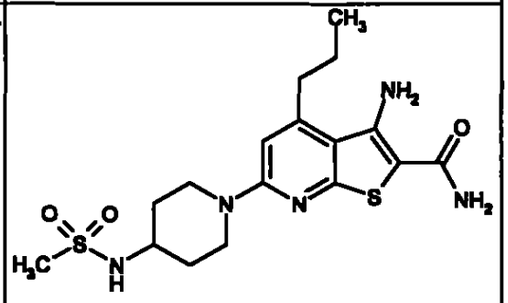
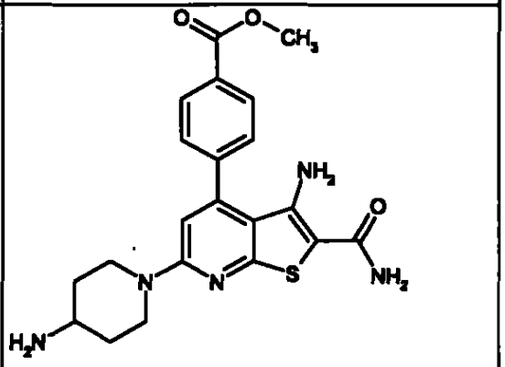
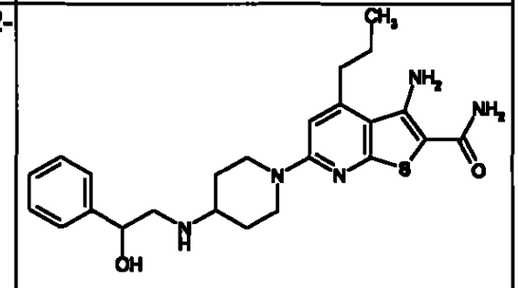
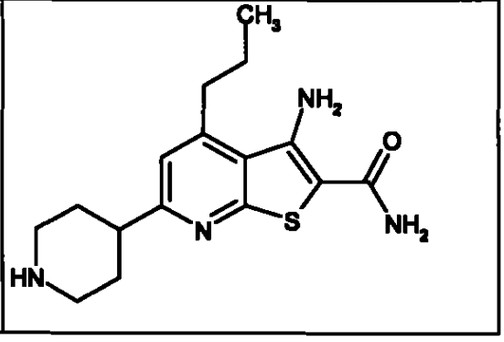
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	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(3-fluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-(N-metilcarbamidoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
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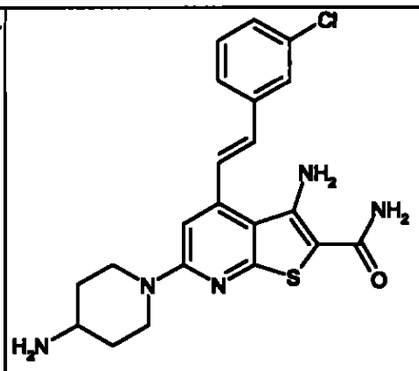
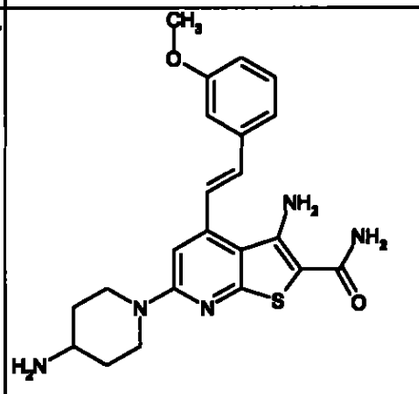
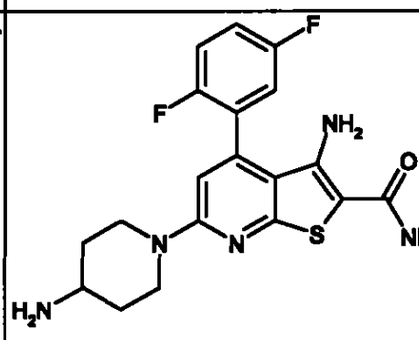
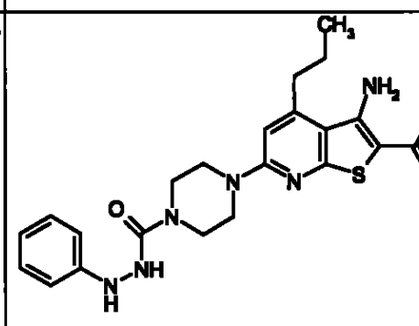
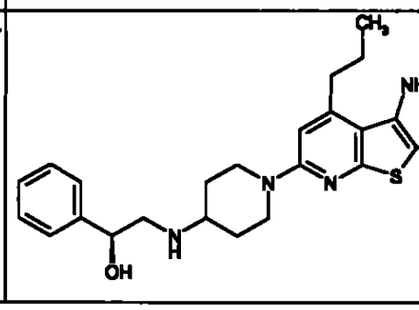
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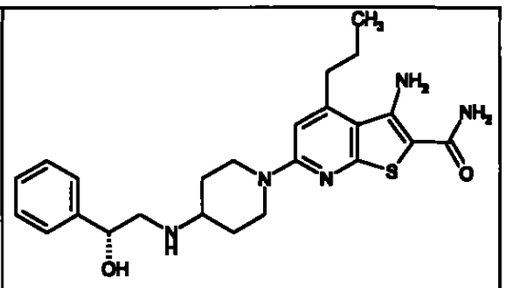
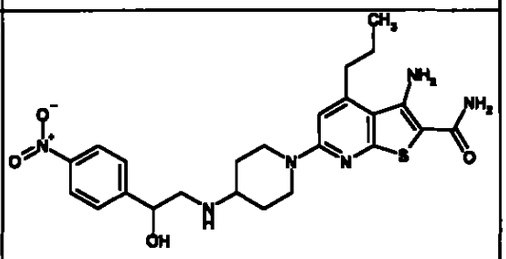
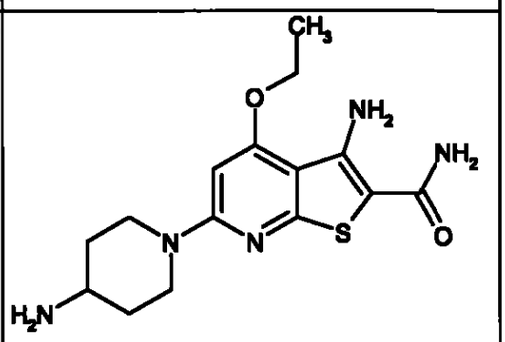
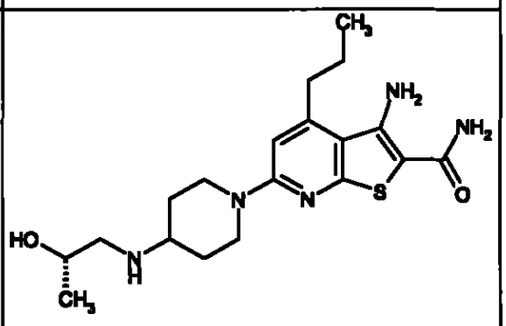
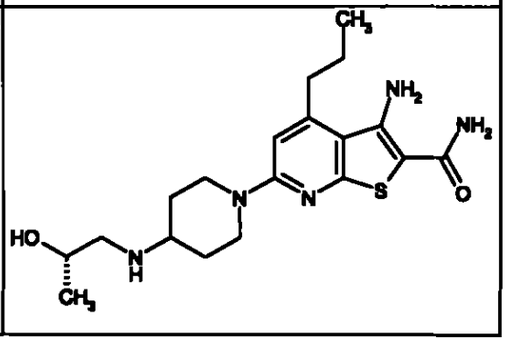
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	Amida de ácido 3-amino-6-[4-((S)-2-hidroxi-1-metil-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-metanosulfonilamino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Éster metílico de ácido 4-[3-Amino-6-(4-amino-piperidin-1-il)-2-carbamoil-tieno[2,3-b]piridin-4-il]-benzoico	
	Amida de ácido 3-amino-6-[4-(2-hidroxi-2-fenil-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-piperidin-4-il-4-propil-tieno[2,3-b]piridin-2-carboxílico	

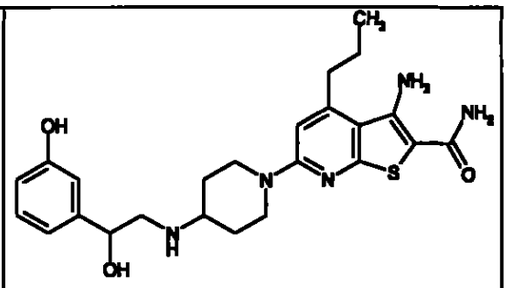
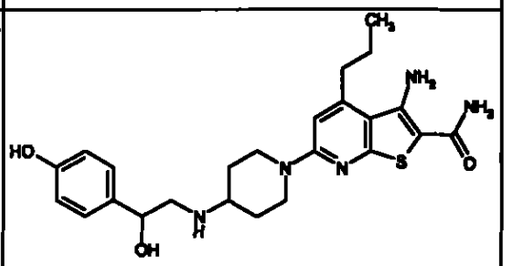
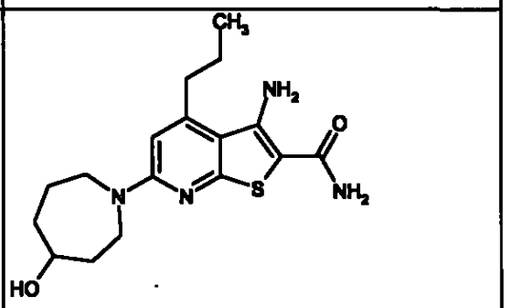
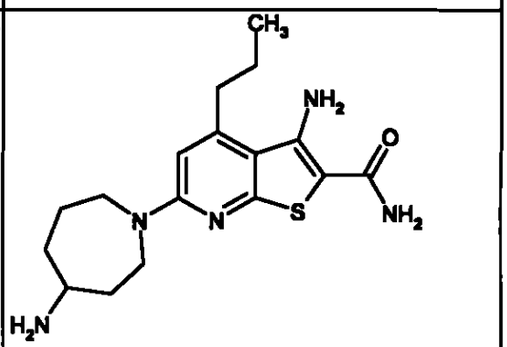
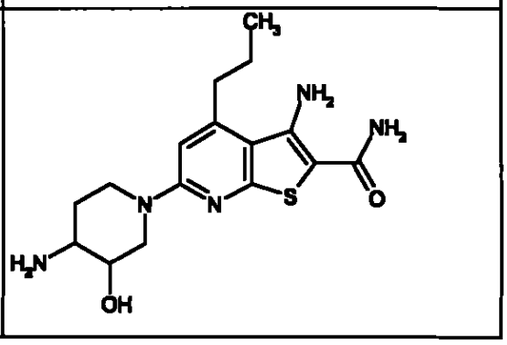
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	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-[(E)-2-(3-cloro-fenil)-vinil]-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-[(E)-2-(3-metoxi-fenil)-vinil]-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(2,5-difluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-(N'-fenil-hidrazinocarbonil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-((S)-2-hidroxi-2-fenil-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	

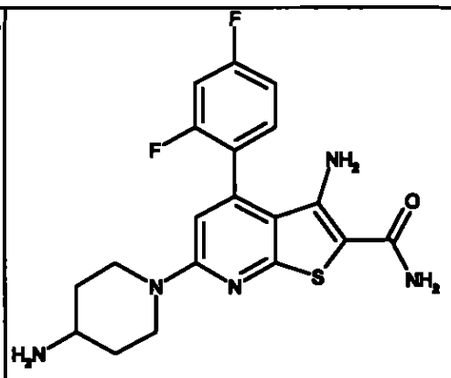
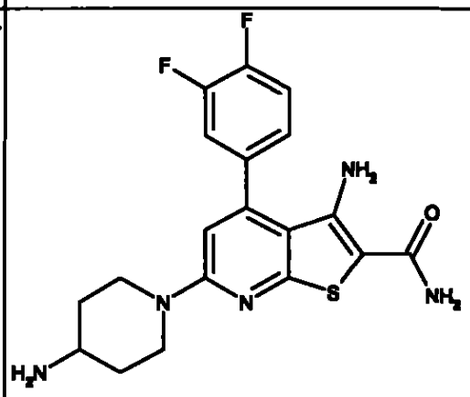
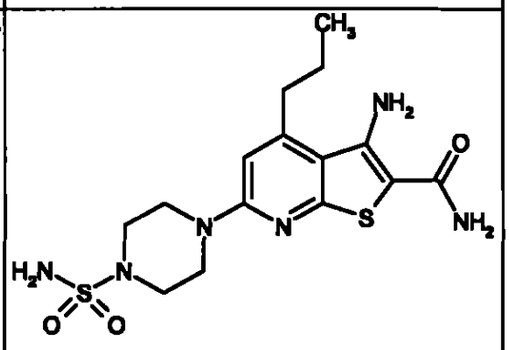
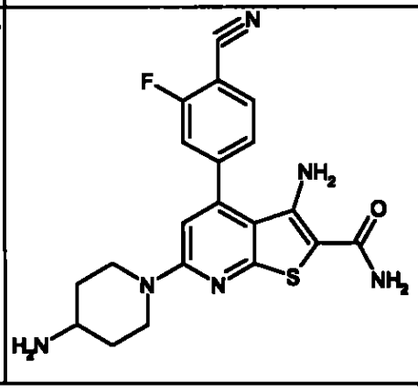
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	Amida de ácido 3-amino-6-[4-((R)-2-hidroxi-2-fenil-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(4-nitro-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-etoxi-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-((R)-2-hidroxi-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-((S)-2-hidroxi-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	

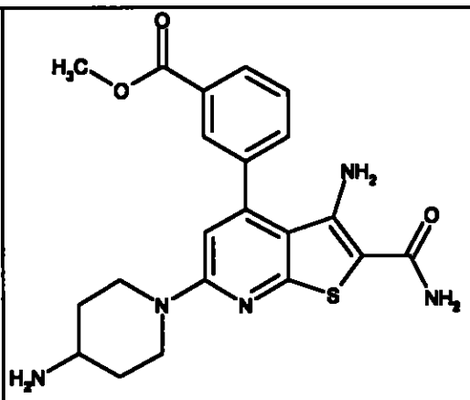
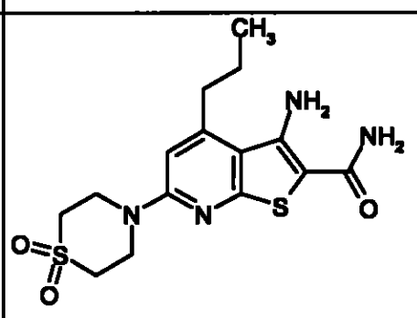
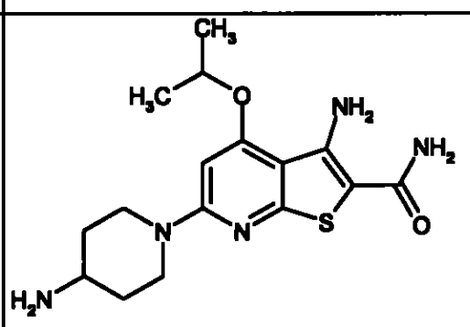
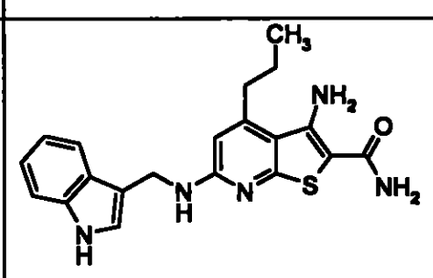
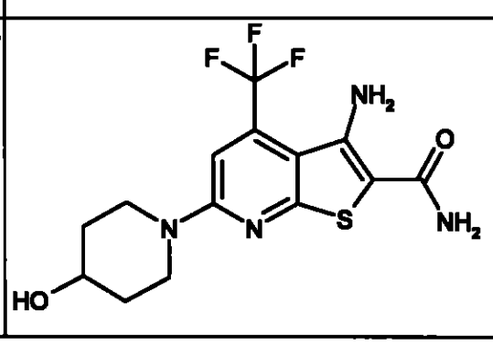
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	Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(3-hidroxi-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(4-hidroxi-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-hidroxi-azepan-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-azepan-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
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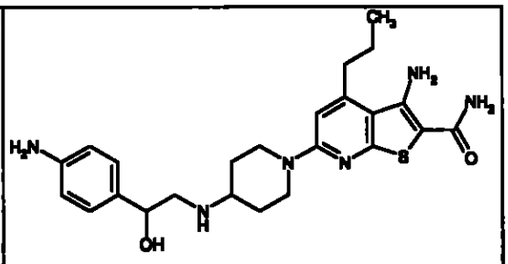
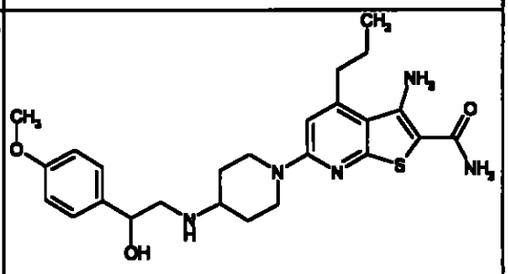
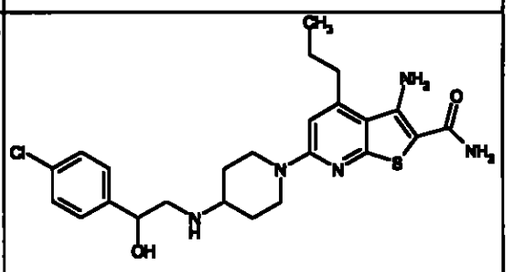
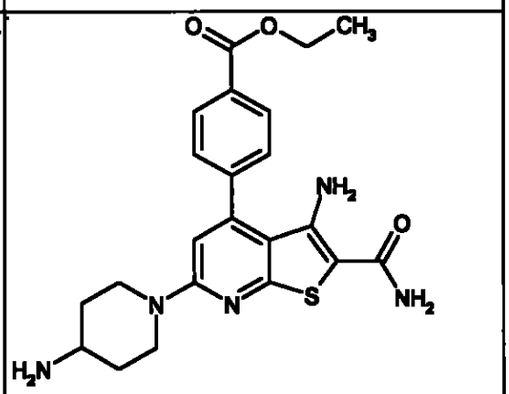
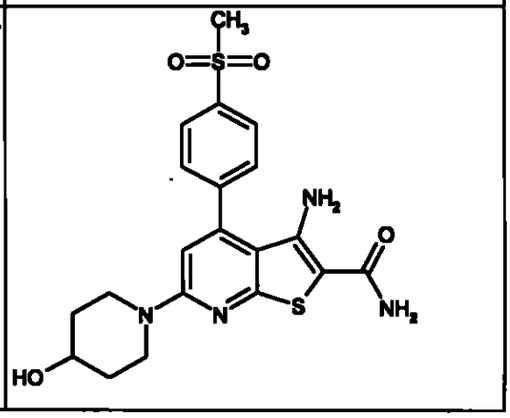
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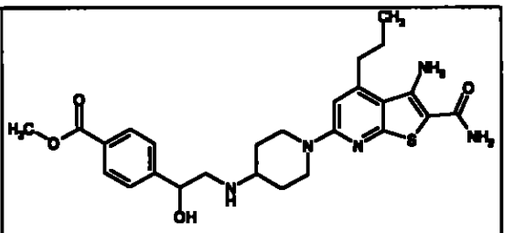
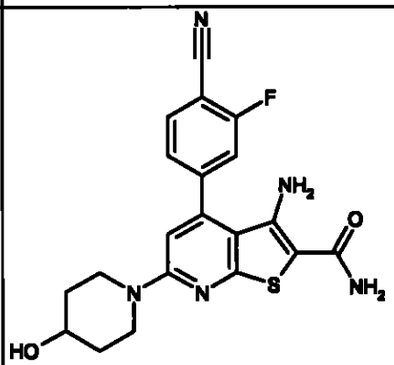
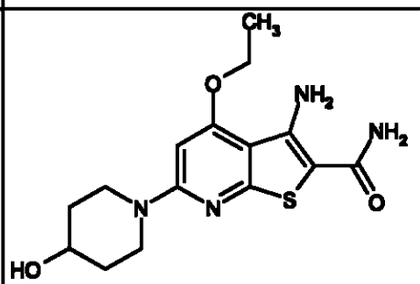
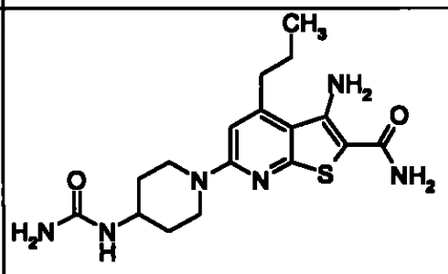
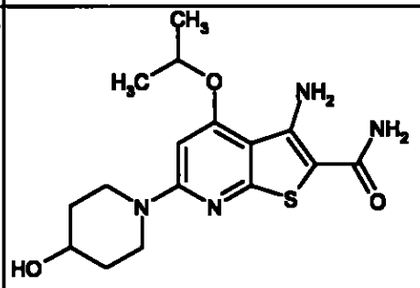
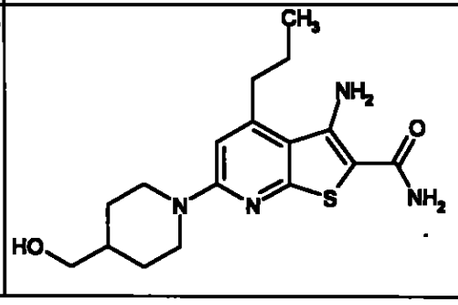
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(2,4-difluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(3,4-difluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-4-propil-6-(4-sulfamoil-piperazin-1-il)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-ciano-3-fluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico	

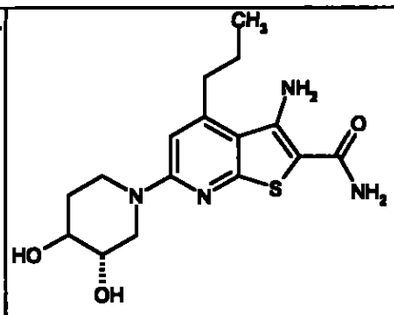
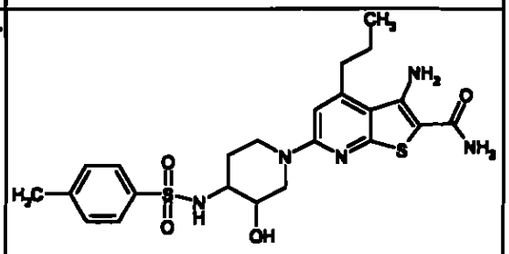
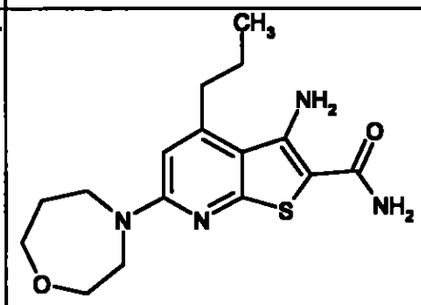
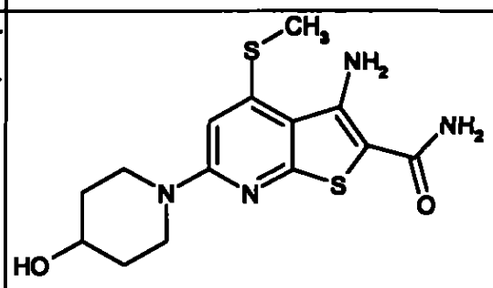
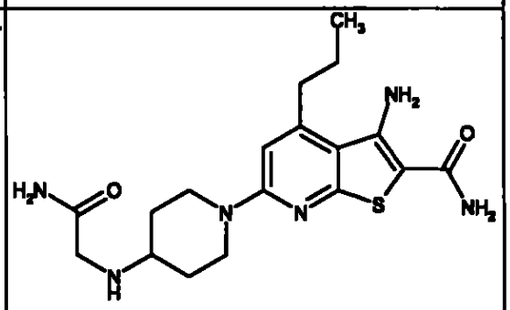
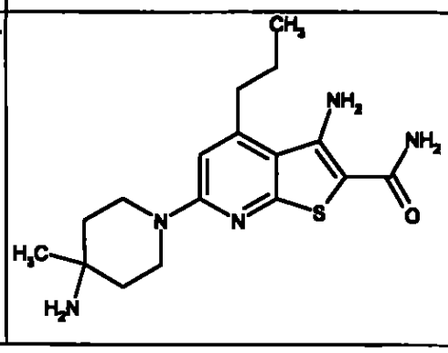
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	Éster metílico de ácido 3-[3-Amino-6-(4-amino-piperidin-1-il)-2-carbamoil-tieno[2,3-b]piridin-4-il]-benzoico	
	Amida de ácido 3-amino-6-(1,1-dioxo-tiomorfolin-4-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-isopropoxi-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[(1H-indol-3-ilmetil)-amino]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
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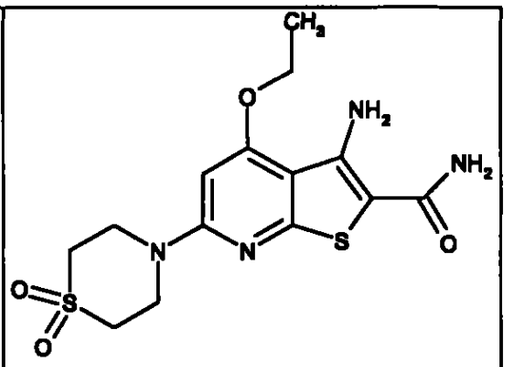
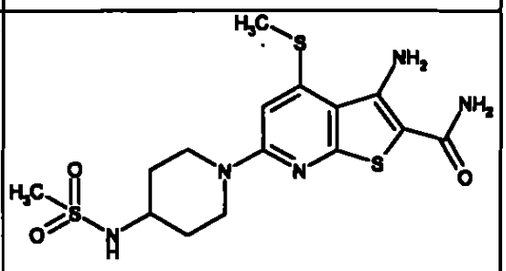
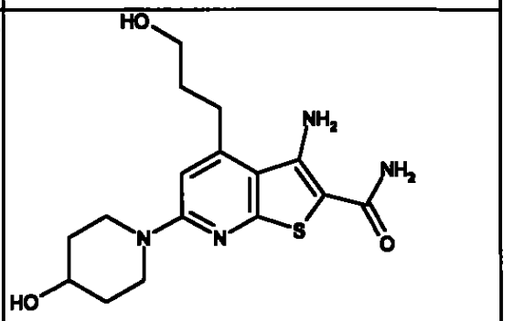
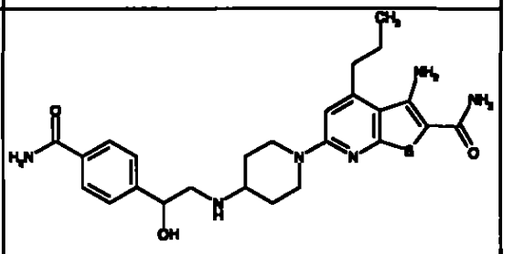
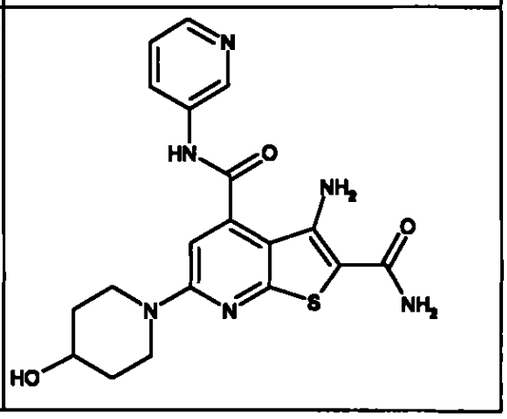
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	Amida de ácido 3-amino-6-{4-[2-(4-amino-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(4-metoxi-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-{4-[2-(4-cloro-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Éster etílico de ácido 4-[3-Amino-6-(4-amino-piperidin-1-il)-2-carbamoil-tieno[2,3-b]piridin-4-il]-benzoico	
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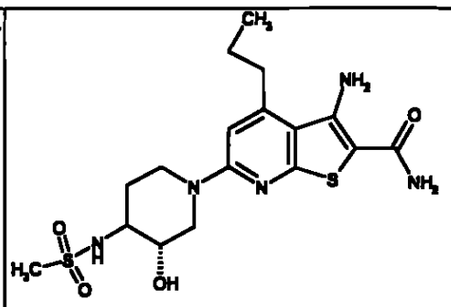
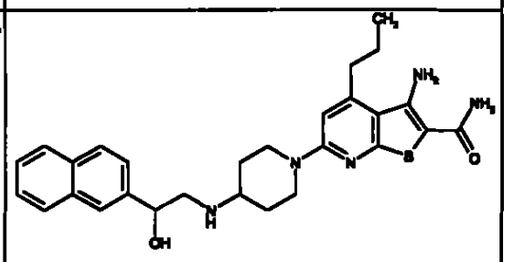
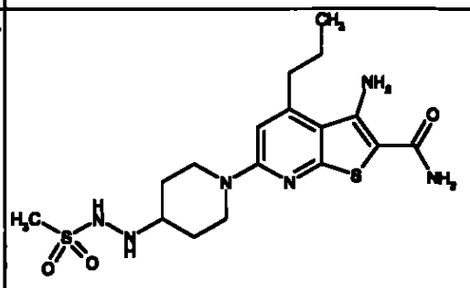
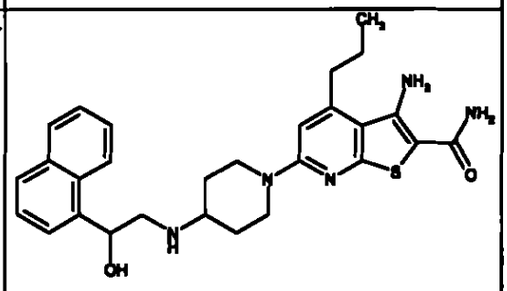
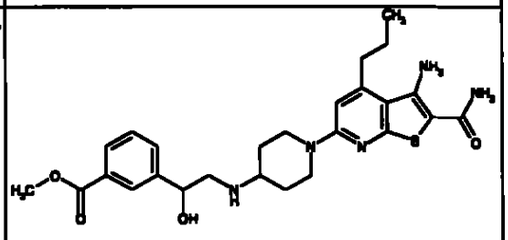
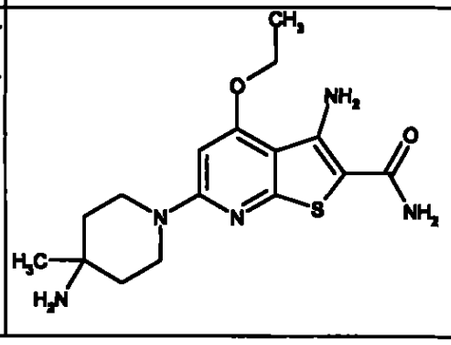
	Éster metílico de ácido 4-{2-[1-(3-amino-2-carbamoil-4-propil-tieno[2,3-b]piridin-6-il)-piperidin-4-ilamino]-1-hidroxi-etil}-benzoico	
	Amida de ácido 3-amino-4-(4-ciano-3-fluoro-fenil)-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-4-etoxi-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-4-propil-6-(4-ureido-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-isopropoxi-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-hidroximetil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	

	Amida de ácido 3-amino-6-((S)-3,4-dihidroxi-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[3-hidroxi-4-(tolueno-4-sulfonilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[1,4]oxazepan-4-il-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-metilsulfanil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-(carbamoilmetil-amino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-amino-4-metil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	

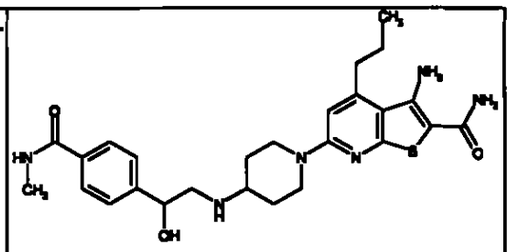
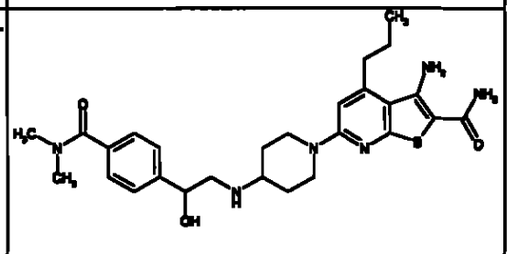
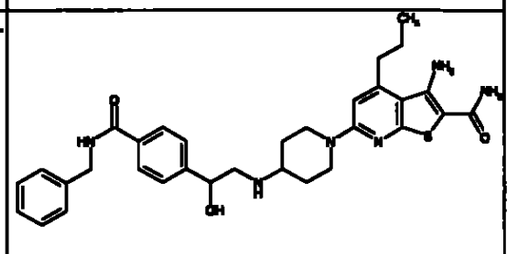
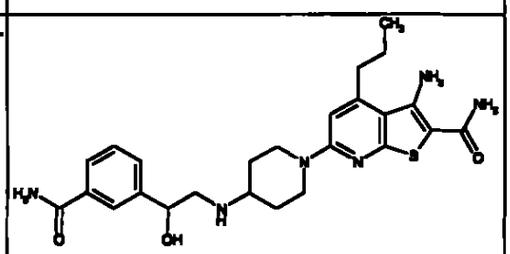
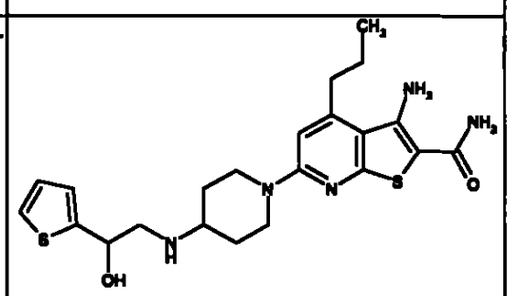
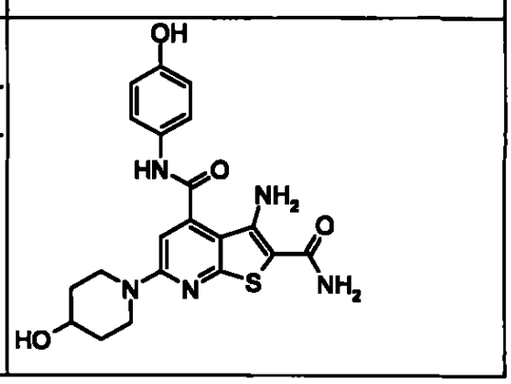
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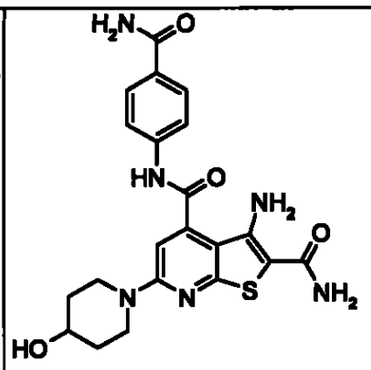
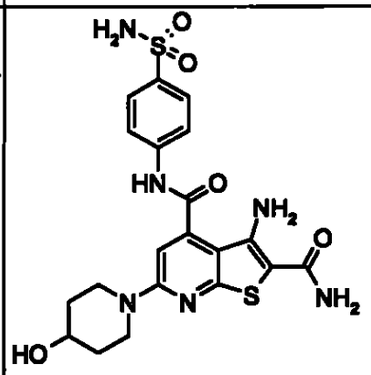
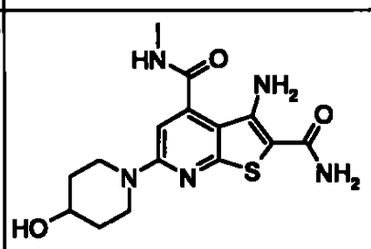
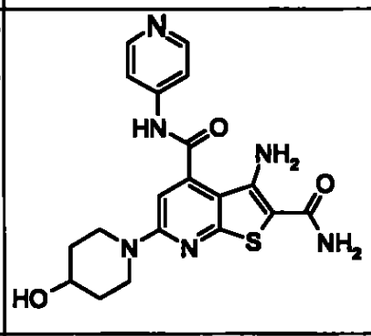
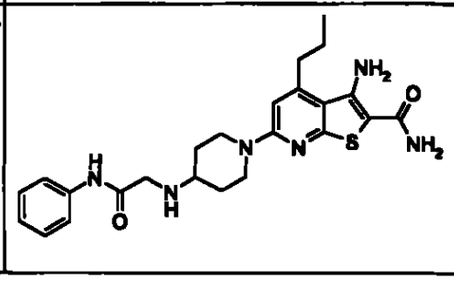
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	Amida de ácido 3-amino-6-(4-metanosulfonilamino-piperidin-1-il)-4-metilsulfanil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-(3-hidroxi-propil)-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-{4-[2-(4-carbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	2-amida-4-piridin-3-ilamida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico	

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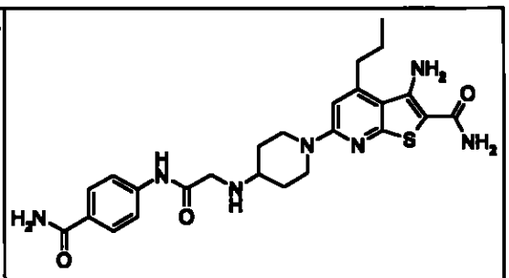
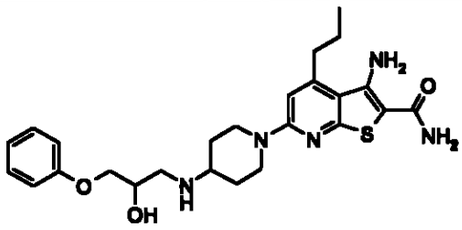
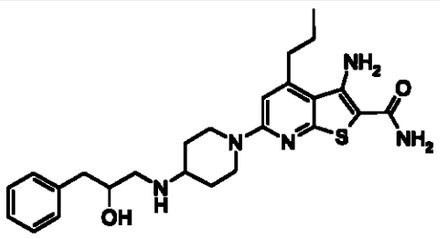
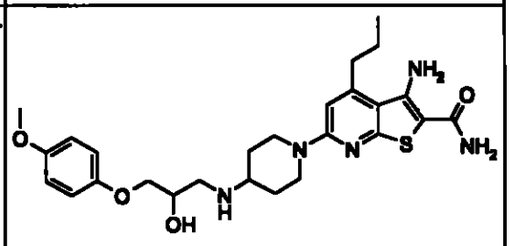
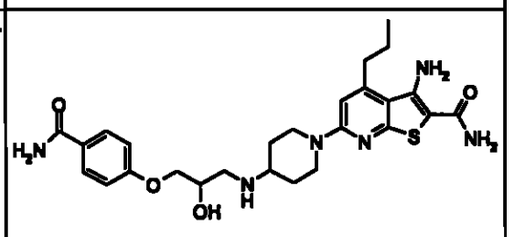
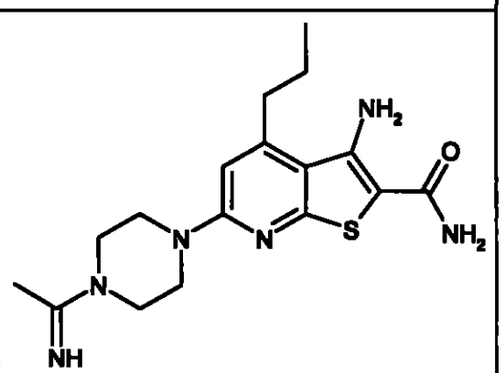
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	Amida de ácido 3-amino-6-[4-(2-hidroxi-2-naftalen-2-il-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-(N'-metilsulfonil-hidrazino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-(2-hidroxi-2-naftalen-1-il-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Éster metílico de ácido 3-{2-[1-(3-amino-2-carbamoil-4-propil-tieno[2,3-b]piridin-6-il)-piperidin-4-ilamino]-1-hidroxi-etil}-benzoico	
	Amida de ácido 3-amino-6-(4-amino-4-metil-piperidin-1-il)-4-etoxi-tieno[2,3-b]piridin-2-carboxílico	

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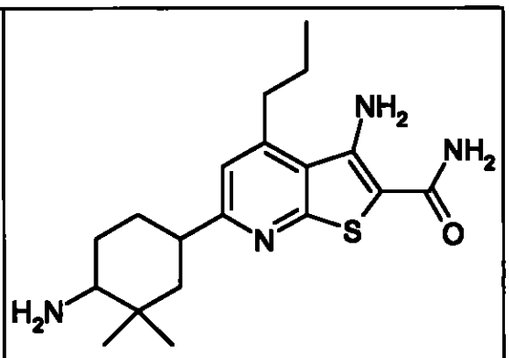
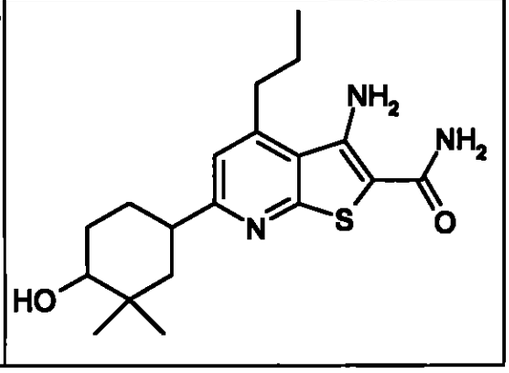
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	Amida de ácido 3-amino-6-{4-[2-(4-dimetilcarbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-{4-[2-(4-bencilcarbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-{4-[2-(3-carbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-(2-hidroxi-2-tiofen-2-il-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	2-Amida-4-[(4-hidroxi-fenil)-amida] de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico	

	2-Amida-4-[(4-carbamoil-fenil)-amida] de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico	
	2-Amida-4-[(4-sulfamoil-fenil)-amida] de ácido 3-amino-6-(4-hidroxi-piperidin-1-ilo)-tieno[2,3-b]piridin-2,4-dicarboxílico	
	2-Amida-4-metilamida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico	
	2-amida-4-piridin-4-ilamida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico	
	Amida de ácido 3-amino-6-[4-(fenilcarbamoilmetil-amino)-piperidin-1-il]-4-propil-tieno[2,3-*b*]piridin-2-carboxílico	

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	Amida de ácido 3-amino-6-(4-{[(4-carbamoil-fenilcarbamoil)-metil]-amino}-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-(2-hidroxi-3-fenoxi-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-*b*]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-(2-hidroxi-3-fenil-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-*b*]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-{4-[2-hidroxi-3-(4-metoxi-fenoxi)-propilamino]-piperidin-1-il}-4-propil-tieno[2,3-*b*]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-{4-[3-(4-carbamoil-fenoxi)-2-hidroxi-propilamino]-piperidin-1-il}-4-propil-tieno[2,3-*b*]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-[4-(1-imino-etil)-piperazin-1-il]-4-propil-tieno[2,3-*b*]piridin-2-carboxílico	

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	Amida de ácido 3-amino-6-(4-amino-3,3-dimetil-ciclohexil)-4-propil-tieno[2,3-b]piridin-2-carboxílico	
	Amida de ácido 3-amino-6-(4-hidroxi-3,3-dimetil-ciclohexil)-4-propil-tieno[2,3-b]piridin-2-carboxílico	

y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables.

Para todos los compuestos descritos en esta solicitud, en el caso de que la nomenclatura esté en conflicto con la estructura, debe entenderse que el compuesto está definido por la estructura.

En otra realización de la invención, se proporcionan los siguientes compuestos:

Amida de ácido 3-amino-6-(4-oxo-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-4-ciano-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-metanosulfonil-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-metilsulfanil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-((E)-estiril)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-nitro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[1,4]diazepan-1-il-4-propil-tieno[2,3-b]piridin-2-carboxílico;

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Amida de ácido 3-amino-6-[4-(2,4-diamino-butanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-[(E)-2-(4-metoxi-fenil)-vinil]-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(2-aminometil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-trifluorometil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-piperazin-1-il-4-trifluorometil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-((E)-2-p-tolil-vinil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2,3-dihidroxi-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-((E)-2-m-tolil-vinil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-metanosulfonilamino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Éster metílico de ácido 4-[3-amino-6-(4-amino-piperidin-1-il)-2-carbamoil-tieno[2,3-b]piridin-4-il]-benzoico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-2-fenil-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-piperidin-4-il-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(2,5-difluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(N'-fenil-hidrazinocarbonil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-((S)-2-hidroxi-2-fenil-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-((R)-2-hidroxi-2-fenil-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(4-nitro-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-etoxi-tieno[2,3-b]piridin-2-carboxílico;

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Amida de ácido 3-amino-6-[4-((S)-2-hidroxi-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-((S)-2-hidroxi-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(3-hidroxi-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(4-hidroxi-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-azepan-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-3-hidroxi-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(2,4-difluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-ciano-3-fluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-isopropoxi-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[(1H-indol-3-ilmetil)-amino]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-trifluorometil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(4-amino-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(4-metoxi-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(4-cloro-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-(4-metanosulfonil-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Éster metílico de ácido 4-{2-[1-(3-Amino-2-carbamoil-4-propil-tieno[2,3-b]piridin-6-il)-piperidin-4-ilamino]-1-hidroxi-etil}-benzoico;

Amida de ácido 3-amino-4-(4-ciano-3-fluoro-fenil)-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-4-etoxi-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-4-propil-6-(4-ureido-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico;

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Amida de ácido 3-amino-6-((S)-3,4-dihidroxi-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-metilsulfanil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-(3-hidroxi-propil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(4-carbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

2-Amida-4-piridin-3-ilamida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico;

Amida de ácido 3-amino-6-((S)-3-hidroxi-4-metanosulfonilamino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-2-naftalen-2-il-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(N'-metilsulfonil-hidrazino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-2-naftalen-1-il-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Éster metílico de ácido 3-{2-[1-(3-amino-2-carbamoil-4-propil-tieno[2,3-b]piridin-6-il)-piperidin-4-ilamino]-1-hidroxi-etil}-benzoico;

Amida de ácido 3-amino-6-(4-amino-4-metil-piperidin-1-il)-4-etoxi-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(4-metilcarbamoil-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(4-dimetilcarbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(4-bencilcarbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(3-carbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

2-Amida-4-[(4-hidroxi-fenil)-amida] de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico;

2-Amida-4-[(4-carbamoil-fenil)-amida] de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico;

2-Amida-4-[(4-sulfamoil-fenil)-amida] de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico;

2-Amida-4-piridin-4-ilamida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-3-fenoxi-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-*b*]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-3-fenil-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-*b*]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-hidroxi-3-(4-metoxi-fenoxi)-propilamino]-piperidin-1-il}-4-propil-tieno[2,3-*b*]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[3-(4-carbamoil-fenoxi)-2-hidroxi-propilamino]-piperidin-1-il}-4-propil-tieno[2,3-*b*]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-3,3-dimetil-cyclohexil)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables.

La invención incluye los derivados farmacéuticamente aceptables de los compuestos de fórmula (I). Un "derivado farmacéuticamente aceptable" se refiere a cualquier ácido, sal o éster farmacéuticamente aceptable de un compuesto de esta invención, y cualquier otro compuesto que, tras ser administrado a un paciente, sea capaz de proporcionar (directa o indirectamente) un compuesto de esta invención o un metabolito farmacológicamente activo o residuo farmacológicamente activo del mismo.

Las sales farmacéuticamente aceptables de los compuestos de esta invención incluyen las derivadas de ácidos y bases inorgánicos y orgánicos farmacéuticamente aceptables. Ejemplos de ácidos adecuados incluyen los ácidos clorhídrico, bromhídrico, sulfúrico, nítrico, perclórico, fumárico, maleico, fosfórico, glicólico, láctico, salicílico, succínico, tolueno-p-sulfónico, tartárico, acético, cítrico, metanosulfónico, fórmico, benzoico, malónico, naftaleno-2-sulfónico y bencenosulfónico. Otros ácidos, como el ácido oxálico, aunque no son en sí farmacéuticamente aceptables, pueden ser empleados en la preparación de sales útiles como intermedios para obtener los compuestos de esta invención y sus sales por adición de ácidos farmacéuticamente aceptables. Las sales derivadas de bases apropiadas incluyen sales de metales alcalinos (por ejemplo, sodio), metales alcalino-térreos (por ejemplo, magnesio), amonio y N-(alquilo C_1-C_4)$_4^+$.

Además, los compuestos de esta invención incluyen profármacos de compuestos de fórmula (I). Los profármacos incluyen los compuestos que, tras una transformación sencilla, son modificados para producir los compuestos de la invención. Las transformaciones químicas sencillas incluyen hidrólisis, oxidación y reducción que se producen de forma enzimática, metabólica o de alguna otra forma. Específicamente, cuando un profármaco de esta invención es administrado a un paciente, el profármaco puede ser transformado en un compuesto de fórmula

(I), confiriendo así el efecto farmacológico deseado.

Cualquiera de los compuestos de esta invención que contenga uno o más átomos de carbono asimétricos se puede producir en forma de racematos y mezclas racémicas, enantiómeros individuales, mezclas diastereómeras y diastereómeros individuales. Todas estas formas isométricas de estos compuestos están expresamente incluidas en la presente invención. Cada átomo de carbono estereogénico puede estar en la configuración R o S, o una combinación de las configuraciones.

Algunos de los compuestos de la invención puede existir en más de una forma tautómera. La invención incluye todos estos tautómeros.

Los compuestos de la invención son solamente los que están contemplado que sean "químicamente estables" como se apreciará por los expertos en la técnica. Por ejemplo, un compuesto que tenga una "valencia cambiante" o un "carbanión" no son compuestos contemplados por la invención.

En la presente memoria descriptiva se usan las siguientes abreviaturas:

DMF es dimetilformamida;

DMSO es dimetil-sulfóxido;

EtOAc es acetato de etilo;

EtOH es etanol;

HPLC es cromatografía líquida de alta resolución;

MeOH es metanol;

THF es tetrahidrofurano;

TLC es cromatografía de capa fina.

Los términos que no estén específicamente definidos en la presente memoria descriptiva deben adoptar los significados que se les daría por un experto en la técnica teniendo en cuenta la descripción y el contexto. Por ejemplo, "alcoxi C_{1-6}" es un alquilo C_{1-6} con un oxígeno terminal, como metoxi, etoxi, propoxi, pentoxi y hexoxi. Todos los grupos alquilo, alquileno o alquilino debe entenderse que están ramificados o sin ramificar salvo que se especifique otra cosa. Otras definiciones más específicas son como sigue:

El término "alquilo" se refiere a un radical alifático saturado que contiene de uno a diez átomos de carbono o un radical hidrocarbonado alifático monò- o poli-insaturado que contiene de dos a doce átomos de carbono salvo que se establezca otra cosa. El radical alifático monò- o poli-insaturado contiene al menos un enlace doble o triple, respectivamente. "Alquilo" se refiere a grupos alquilo tanto ramificados como sin ramificar. Ejemplos de "alquilo" incluyen grupos alquilo que son grupos alquilo de cadena lineal que contienen de uno a ocho átomos de carbono y grupos alquilo ramificados que contienen de tres a diez átomos de carbo-

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no. Otros ejemplos incluyen grupos alquilo inferior que son grupos alquilo de cadena lineal que contienen de uno a seis átomos de carbono y grupos alquilo ramificados que contienen de tres a seis átomos de carbono. Debe entenderse que cualquier término de combinación que use los prefijos "alk" o "alquilo" se refiere a análogos según la definición anterior de "alquilo". Por ejemplo, los términos como "alcoxi", "alquiltio" se refieren a grupos alquilo unidos a un segundo grupo a través de un átomo de oxígeno o azufre. "Alcanoilo" se refiere a un grupo alquilo unido a un grupo carbonilo (C=O). Cad alquilo o análogo de alquilo descrito en la presente memoria descriptiva debe entenderse que está de forma opcional parcial o completamente halogenado.

El término "cicloalquilo" se refiere al análogo cíclico de un grupo alquilo, como se definió anteriormente. Ejemplos de grupos cicloalquilo son grupos cicloalquilo no aromáticos saturados o insaturados que contienen de tres a ocho átomos de carbono, y otros ejemplos incluyen grupos cicloalquilo que tienen tres a seis átomos de carbono.

El término "heterocicloalquilo" se refiere a un radical heterocíclico monocíclico de 4-8 miembros (pero preferentemente de 5 ó 6 miembros) o bicíclico de 8-11 miembros, que puede estar saturado o insaturado, y que es no aromático. Cada heterociclo consiste en átomos de carbono y de 1 a 4 heteroátomos escogidos entre nitrógeno, oxígeno y azufre. El heterociclo puede estar unido por cualquier átomo del ciclo, que de lugar a la creación de una estructura estable. Ejemplos de "heterocicloalquilo" incluyen radicales como pirrolinilo, pirrolidinilo, pirazolinilo, pirazolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, azetidinilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrofuranilo, hexahidropirimidinilo, hexahidropiridazinilo, dihidro-oxazolilo, 1,2-tiazinanil-1,1-dióxido, 1,2,6-tiadiazinanil-1,1-dióxido, isotiazolidinil-1,1-dióxido e imidazolidinil-2,4-diona.

El término "halógeno" se refiere a bromo, cloro, flúor o yodo.

El término "arilo" debe entenderse que significa un carbociclo aromático de 6-12 miembros, que puede ser un anillo único o puede ser de múltiples anillos conjuntamente condensados o unidos covalentemente. El término "arilo" incluye, por ejemplo, fenilo y naftilo; y otros términos que comprenden "arilo" tendrán la misma definición para el componente de arilo, y ejemplos de estos restos incluyen: arilalquilo, ariloxi o ariltio.

El término "heteroarilo" se refiere a un radical heterocíclico aromático estable monocíclico de 5-8 miembros (pero preferentemente de 5 ó 6 miembros) o bicíclico de 8-11 miembros. Cada heterociclo consiste en átomos de carbono y de 1 a 4 heteroátomos escogidos entre nitrógeno, oxígeno y azufre. El grupo heteroarilo puede estar unido por cualquier átomo del anillo que dé lugar a la creación de una

estructura estable. Ejemplos de "heteroarilo" incluyen radicales como furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, isoxazolilo, isotiazolilo, oxadiazolilo, triazolilo, tetrazolilo, tiadiazolilo, piridinilo, piridazinilo, pirimidinilo, pirazinilo, indolizinilo, indolilo, isoindolilo, benzofuranilo, benzotienilo, indazolilo, bencimidazolilo, benztiazolilo, benzoxazolilo, purinilo, quinolizinilo, quinolinilo, isoquinolinilo, cinolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, naftiridinilo, pteridinilo, carbazolilo, acridinilo, fenazinilo, fenotiazinilo y fenoxazinilo.

Los términos "opcional" u "opcionalmente" significan que el acontecimiento o circunstancias posteriormente descritos pueden ocurrir o no ocurrir, y que la descripción incluye los casos en que el acontecimiento o circunstancia se produce y los casos en que no se produce. Por ejemplo, "arilo opcionalmente sustituido" significa que el radical arilo puede estar o no estar sustituido y que la descripción incluye tanto los radicales arilo sustituidos como los radicales arilo que no tienen ninguna sustitución.

El término "sustituido" significa que uno o más átomos de hidrógeno o un átomo de un grupo o resto, tanto si se designa específicamente como si no, está sustituido con una selección del grupo de sustituyentes indicado, con la condición de que la valencia normal de los átomos no se sobrepasa y que la sustitución dé lugar a un compuesto estable. Si un enlace a un sustituyente es mostrado de forma que cruza el enlace que conecta dos átomos en un anillo, entonces cada sustituyente puede estar unido a cualquier átomo en el anillo. Cuando un sustituyente es citado sin indicar el átomo a través del cual este sustituyente está unido al resto del compuesto, entonces este sustituyente puede estar unido a través de cualquier átomo en este sustituyente. Por ejemplo, cuando el sustituyente es piperazinilo, piperidinilo o tetrazolilo, salvo que se especifique otra cosa, este grupo piperazinilo, piperidinilo o tetrazolilo puede estar unido al resto del compuesto de la invención a través de cualquier átomo en este grupo piperazinilo, piperidinilo o tetrazolilo. Generalmente, cuando cualquier sustituyente o grupo se produce más de una vez en cualquier constituyente o compuesto, su definición en cada aparición es independiente de su definición en cualquier otra aparición. Por tanto, por ejemplo, si un grupo se muestra que está sustituido con 0 a 2 R, entonces este grupo está opcionalmente sustituido con hasta dos grupos R y R en cada aparición se selecciona independientemente entre la lista definida de posibles R. Estas combinaciones de sustituyentes y/o variables, sin embargo, es permisible solo si estas combinaciones dan lugar a compuestos estables.

Como se usan en la presente memoria descriptiva con anterioridad y en toda esta solicitud, "nitrógeno" y "azufre" incluyen cualquier forma oxidada de nitrógeno y azufre y la forma cuaternizada de cualquier nitrógeno básico.

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Métodos de uso terapéutico

De acuerdo con la invención, se proporcionan nuevos métodos para usar los compuestos de fórmula (I). Los compuestos de la invención son eficaces para inhibir la actividad de IKKβ y/o IKKα. En particular, estos compuestos son útiles para bloquear procesos de enfermedades exacerbados por la activación de NF-κB mediada por IKKβ y la activación de IKKα de la actividad de células B o el gen regulador del ciclo celular Ciclina D1. En el bloqueo de la activación deNF-κB, los compuestos de la invención bloquean eficazmente la transcripción de genes que codifican citoquinas inflamatorias que incluyen IL-1, IL-2, IL-6, IL-8, TNFα, quimioquinas que incluyen IL-8 y RANTES así como otras moléculas pro-inflamatorias que incluyen COX-2 y moléculas de adhesión celular como ICAM-1, VCAM-1 y E-selectina. Estos mediadores desempeñan una función clave en la etiología de trastornos inflamatorios, autoinmunes y cardiovasculares y del cáncer. La prevención de la producción de estos mediadores es un medio deseable para tratar estos trastornos. Por tanto, se proporcionan métodos para tratar estos estados usando los compuestos de la invención. Estos estados inflamatorios y autoinmunes incluyen, pero sin limitación, osteoartritis, herida de reperfusión, asma, enfermedad de obstrucción pulmonar crónica (COPD), esclerosis múltiple, síndrome de Guillain-Barre, enfermedad de Crohn, colitis ulcerativa, psoriasis, enfermedad de injerto frente a hospedante, lupus sistémico eritematoso, artritis reumatoide, enfermedad de Alzheimer, síndrome de choque tóxico, diabetes mellitus dependiente de insulina, dolor agudo y crónico, herida térmica, síndrome de angustia respiratoria en adultos (ARDS), herida múltiple de órganos secundaria por trauma, glomerulonefritis aguda, dermatosis con componentes inflamatorios agudos, meningitis purulenta aguda y otros trastornos del sistema nervioso central, enfermedad de Grave, miastenia grave, esclerodema y dermatitis atópica. Estos trastornos cardiovasculares incluyen, pero sin limitación, aterosclerosis, infarto de miocardio y apoplejía. Estos cánceres incluyen, pero sin limitación, enfermedades malignas de derivación linfoide, mieloide y epitelial que incluyen leucemia, linfomas y cánceres de mamas, gástrico, de colorrectal, de pulmón y pancreático. Los compuestos de la invención pueden ser usados también para tratar otros trastornos asociados con la activación de IKK de NF-κB o relacionados con los anteriormente citados o expuestos en el apartado de antecedentes de la invención. Por ejemplo, los compuestos de la invención pueden ser útiles también en el tratamiento del cáncer aumentando la eficacia de los agentes quimioterapéuticos. Por lo tanto, la invención proporciona también métodos para tratar enfermedades inflamatorias y autoinmunes, y otras enfermedades que incluyen cáncer, que comprende administrar a un paciente que

necesita este tratamiento una cantidad farmacéuticamente eficaz de un compuesto según la invención.

Para un uso terapéutico, los compuestos de la invención pueden ser administrados en cualquier forma de dosificación convencional y de cualquier manera convencional. Las vías de administración incluyen, pero sin limitación, las vías intravenosa, intramuscular, subcutánea, intrasinovial, por infusión, sublingual, transdermal, oral, tópica o por inhalación. Los modos preferidos de administración son el oral e intravenoso. Las composiciones que comprenden los compuestos de la invención para cada una de las vías de administración anteriormente mencionadas serán evidentes para el experto en la técnica. La invención proporciona también composiciones farmacéuticas que incluyen una cantidad terapéuticamente eficaz de los compuestos según la invención. Estas composiciones farmacéuticas incluirán los vehículos y adyuvantes farmacéuticamente aceptables como se describe en detalle con posterioridad.

Los compuestos de esta invención pueden ser administrados solos o en combinación con adyuvantes que aumenten la estabilidad de los inhibidores, faciliten la administración de las composiciones farmacéuticas que los contienen en ciertas realizaciones, proporcionen una disolución o dispersión aumentada, aumenten la actividad inhibidora, proporcionen una terapia auxiliar y similares, que incluyen otros ingredientes activos. Ventajosamente, estas terapias de combinación utilizan dosificaciones inferiores de los agentes terapéuticos convencionales, evitando así la posible toxicidad y efectos secundarios adversos que se producen cuando los agentes se usan en forma de monoterapias. Los compuestos de la invención se pueden combinar físicamente con los agentes terapéuticos convencionales u otros adyuvantes en forma de una única composición farmacéutica. Ventajosamente, los compuestos pueden ser seguidamente administrados conjuntamente en una única forma de dosificación. En algunas realizaciones, las composiciones farmacéuticas que comprenden estas combinaciones de compuestos contienen al menos aproximadamente 15%, pero más preferentemente al menos aproximadamente 20% de un compuesto de la invención (p/p) o una combinación de los mismos. Alternativamente, los compuestos pueden ser administrados separadamente (en serie o en paralelo). Las dosificaciones separadas permiten una mayor flexibilidad en el régimen de dosificación.

Como se mencionó anteriormente, las formas de dosificación de los compuestos de esta invención incluyen vehículos y adyuvantes farmacéuticamente aceptables conocidos por los expertos ordinarios en la técnica. Estos vehículos y adyuvantes incluyen, por ejemplo, intercambiadores iónicos, alúmina, estearato de aluminio, lecitina, proteínas de suero, sustancias tamponantes, agua, sales o elec-

trolitos y sustancias basadas en celulosa. Las formas de dosificación preferidas incluyen comprimidos, cápsulas, grageas, líquidos, soluciones, suspensiones, emulsiones, pastillas, jarabes, polvos reconstituibles, gránulos, supositorios y parches transdermales. Los métodos para preparar estas formas dosificación son conocidos (véase, por ejemplo, H.C. Ansel y N. G. Popovish, Pharmaceutical Dosage Forms and Drug Delivery Systems, 5 th ed., Lea and Febiger (1990)). Los niveles de dosificación y los requisitos están bien reconocidos en la técnica y pueden sër seleccionados por un experto ordinario en la técnica a partir de métodos y técnicas disponibles adecuados para un paciente particular. En algunos casos, los niveles de dosificación varían en el intervalo de aproximadamente 10-1000 mg/dosis para un paciente de 70 kg. aunque una dosis por día puede ser suficiente, se pueden proporcionar hasta 5 dosis por día. Para dosis orales, pueden ser requeridos hasta 2000 mg/día. Como apreciará el experto en la técnica, pueden ser necesarias dosis inferiores o superiores dependiendo de los factores particulares. Por ejemplo, los régimenes específicos de dosificación y tratamiento dependerán de factores como el perfil sanitario general del paciente, la gravedad y transcurso del trastorno del paciente o su disposición respecto al mismo, y el criterio del facultativo encargado.

MÉTODOS SINTÉTICOS

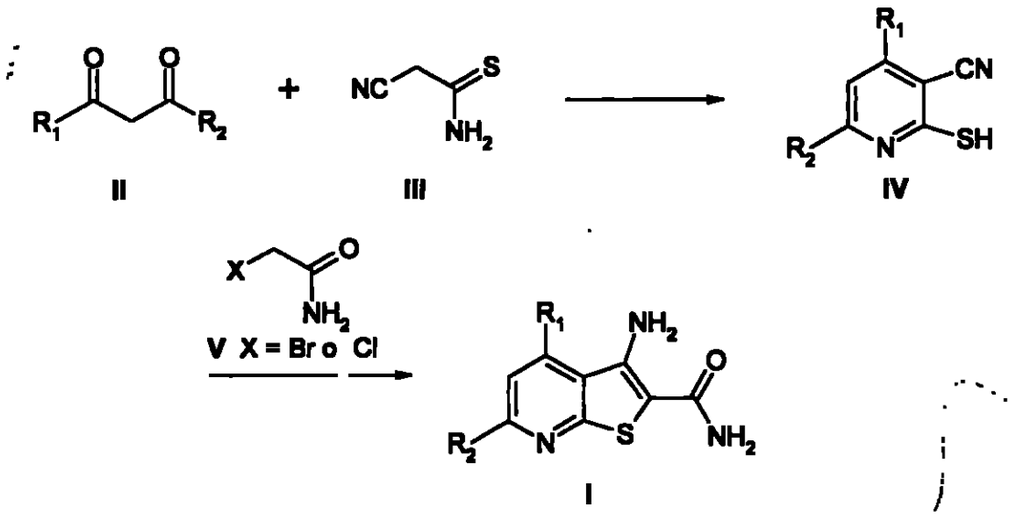
La invención proporciona adicionalmente métodos para preparar los compuestos de fórmula (I). Los compuestos de la invención pueden ser preparados mediante los métodos y ejemplos generales presentados a continuación, y los métodos conocidos por un experto ordinario en la técnica. Las condiciones de la reacción y los tiempos de reacción óptimos pueden variar dependiendo de los reactantes particulares usados. Salvo que se especifique otra cosa, los disolventes, temperaturas, presiones y otras condiciones de la reacción se pueden seleccionar fácilmente por un experto ordinario en la técnica. Los procedimientos específicos se proporcionan en la sección de Ejemplos Sintéticos. El progreso de la reacción puede ser verificado por métodos convencionales como cromatografía de capa fina (TLC). Los intermedios y productos pueden ser purificados por métodos conocidos en la técnica que incluyen cromatografía de columna, HPLC o recristalización.

Como se ilustra en el Esquema I, los compuestos de fórmula (I) pueden ser preparados partiendo de una 1,3-diona que porta los sustituyentes R_1 y R_2 (II). La reacción de (II) con cianotioacetamida (III) en un disolvente adecuado como EtOH, en presencia de una base adecuada como trietilamina, proporciona el 2-mercaptonicotinonitrilo sustituido IV. La reacción de IV con cloro- o bromoacetamida (V) en un disolvente adecuado como DMF, THF o EtOH en presencia

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de una base adecuada como carbonato de sodio, hidróxido de sodio o etóxido de sodio, proporciona el compuesto deseado de fórmula (I). Los sustituyentes R_1 y R_2 pueden ser adicionalmente modificados por métodos conocidos en la técnica para producir compuestos adicionales de la invención.

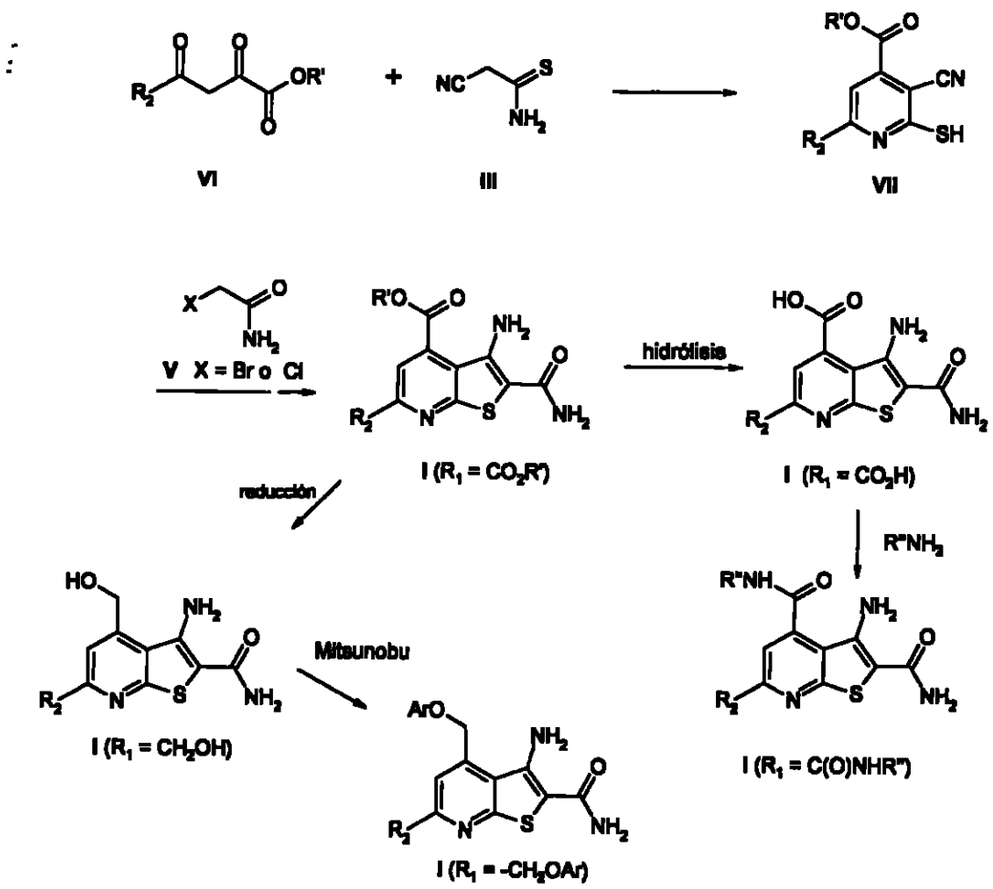
Esquema I



Por ejemplo, como se ilustra en el Esquema II, partiendo de un diceto-éster VI y usando el procedimiento anteriormente indicado, se obtiene el éster I (R_1 = CO_2R', en donde R' es un grupo alquilo como metilo o etilo). Usando métodos conocidos en la técnica, R_1 puede ser modificado para preparar otro R_1 deseado. Por ejemplo, la hidrólisis proporciona el ácido carboxílico I (R_1 = CO_2H) y la reacción del ácido carboxílico con una amina $R"NH_2$ bajo condiciones estándar de acoplamiento proporciona la amida I (R_1 = C(O)NHR"). Alternativamente, la reducción del éster a través de un agente reductor adecuado como hidruro de litio-aluminio proporciona un alcohol I (R_1 = CH_2OH). La reacción del alcohol con un fenol ArOH bajo condiciones de Mitsunobu proporciona el aril-éter I (R_1 = CH_2OAr). Estas y otras modificaciones se describen en la sección de Ejemplos Sintéticos.

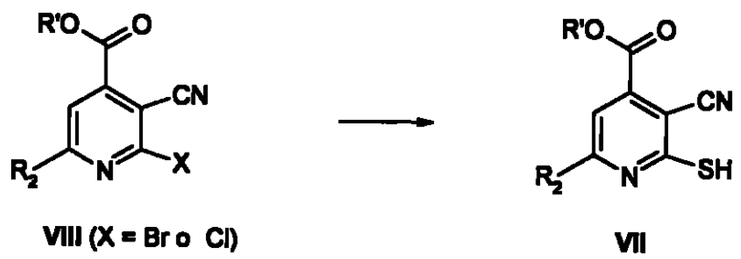
263

Esquema II



En una modificación del procedimiento anterior para preparar VII, se parte de un éster de ácido 2-cloro o 2-bromo-3-ciano-isonicotínico (VIII, Esquema III). El grupo 2-halo puede ser seguidamente convertido en un grupo 2-mercapto por métodos conocidos en la técnica, por ejemplo, por reacción con tiourea en un disolvente adecuado como EtOH que proporcione el intermedio de éster VII.

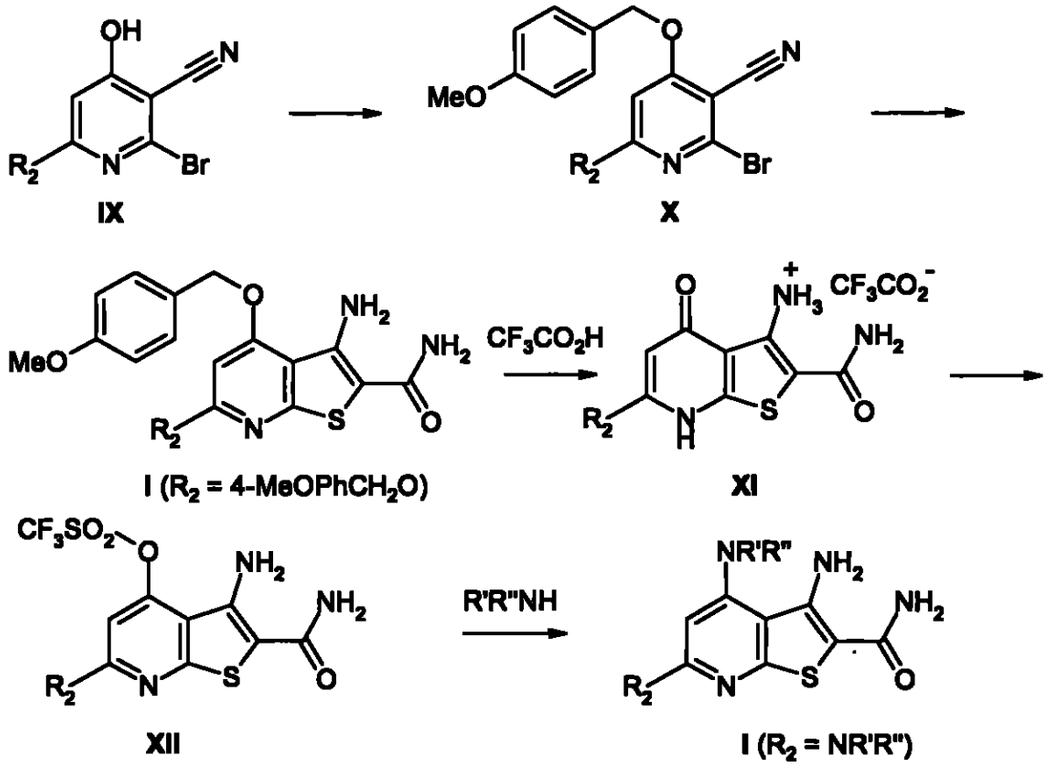
Esquema III



El Esquema IV ilustra un procedimiento mediante el que se pueden obtener compuestos de fórmula (I) que tengan una amina en R_1. El 2-bromo-4-hidroxi-nicotinotrilo (IX) es tratado con cloruro de 4-metoxibencilo en presencia de una base adecuada como hidruro de sodio en un disolvente adecuado como DMF para proporcionar el 4-metoxibencil-éter X. Este puede ser seguidamente convertido en

el compuesto de 2-mercapto como se describió anteriormente en el Esquema III. El compuesto de mercapto resultante se puede hacer reaccionar seguidamente con una haloacetamida como se describe en los Esquemas I y II para proporcionar I (R_1 = 4-metoxibencil-éter). Alternativamente, se puede hacer reaccionar X con mercaptoacetamida en presencia de una base adecuada como hidruro de sodio en un disolvente adecuado como DMF para proporcionar I (R_1 = 4-metoxibencil-éter) directamente. El tratamiento del éter con ácido trifluoroacético proporciona la sal XI. La reacción de XI con N-feniltrifluorometanosulfinimida en presencia de una base adecuada como diisopropiletilamina en un disolvente adecuado como dioxano proporciona el trifluorometanosulfonato XII. La reacción de XII con una amina R'R"NH en un disolvente adecuado como dioxano proporciona I (R_1 = NR'R"). La reacción puede ser opcionalmente calentada para obtener aminas menos reactivas como aril-aminas.

Esquema IV



IX X

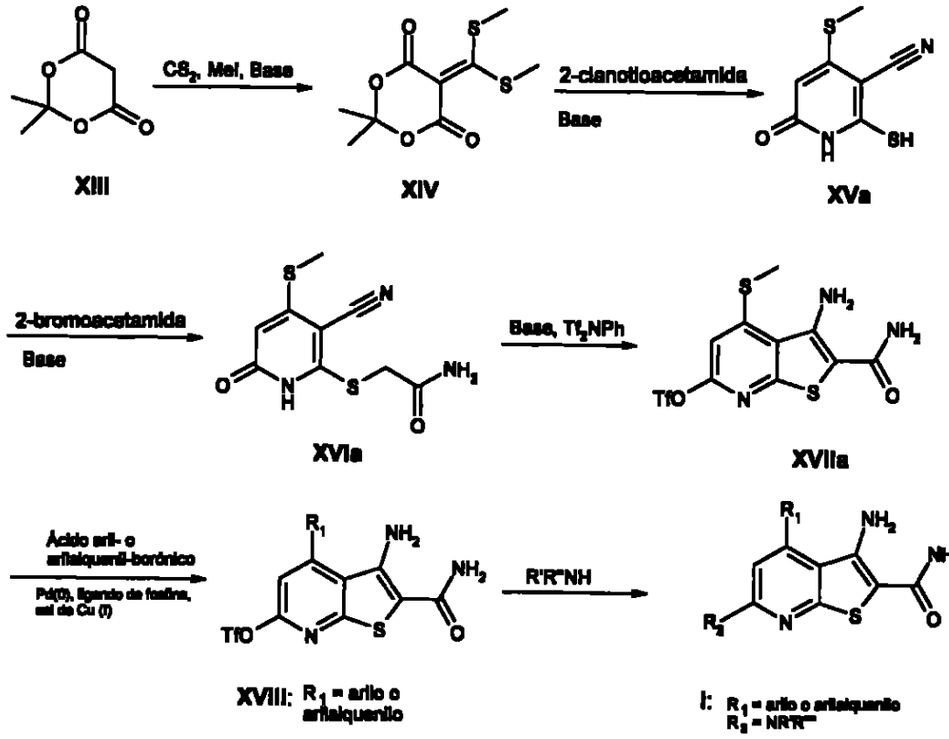
I (R_2 = 4-MeOPhCH$_2$O) XI

XII I (R_2 = NR'R")

En el Esquema V se ilustra un procedimiento que puede ser usado para introducir una diversidad de grupos arilo o arilalquenilo en R_1 y grupos nucleófilos como aminas en R_2. El ácido de Meldrum (XIII) es tratado con disulfuro de carbono, yoduro de metilo y una base adecuada como trietilamina, en un disolvente adecuado como DMSO, para proporcionar la bis-metilsulfanilmetileno-diona (XIV). El tratamiento de XIV con 2-cianotioacetamida bajo condiciones alcalinas adecuadas como con étoxido de sodio en etanol proporciona el nitrilo XVa. La reacción de XVa con 2-cloro- o 2-bromo-acetamida en presencia de una base adecuada como

hidruro de sodio en un disolvente adecuado como DMF proporciona XVIa. La ciclación del intermedio de triflato XVIIa se puede conseguir haciendo reaccionar XVI con N-feniltrifluorometano-sulfonimida en presencia de una base adecuada como hidruro de sodio en un disolvente adecuado como DMF. La reacción de XVIIa con el ácido aril-borónico o ácido arilalquenil-borónico deseado en presencia de un catalizador de paladio adecuado, preferentemente un aducto de tris(dibencilidenoacetona)dipaladio(0)-cloroformo, un ligando de fosfina, preferentemente tri-2-furilfosfina y una sal de cobre, preferentemente tiofeno-2-carboxilato de cobre (I), en un disolvente adecuado como THF, proporciona el intermedio de arilo o arilalquenilo XVIII deseado. La reacción de XVIII con el nucleófilo deseado como una amina R'R"NH como se muestra, en un disolvente adecuado como dioxano, proporciona el compuesto deseado de fórmula (I). Los alcoholes (R'OH) o tioles (R'SH) en presencia de una base adecuada podrían ser usados en lugar de una amina para obtener éteres o tioéteres, respectivamente, en R_2.

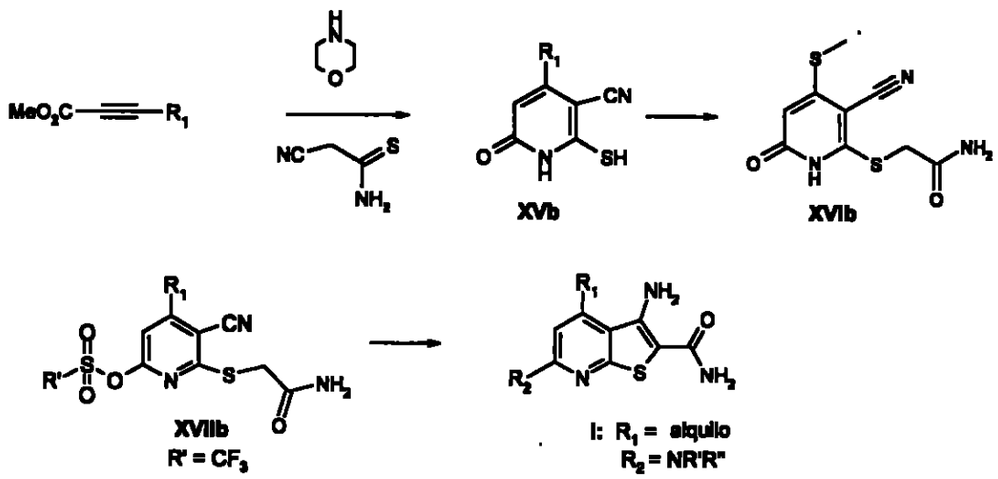
Esquema V



En el Esquema VI se ilustra una modificación del procedimiento anterior que proporcionará un grupo alquilo en R_1. Un éster de alquinoato, como el éster metílico mostrado, se hace reaccionar con 2-cianotioacetamida en presencia de una base adecuada como morfolina en un disolvente adecuado como etanol, para proporcionar XVb. El tratamiento de XVb como se describe para la conversión de XVa en XVIa en el Esquema V anterior proporciona XVIb. La reacción de XVIb con un reactivo de sulfonación adecuado como N-feniltrifluorometano-sulfonimida en pre-

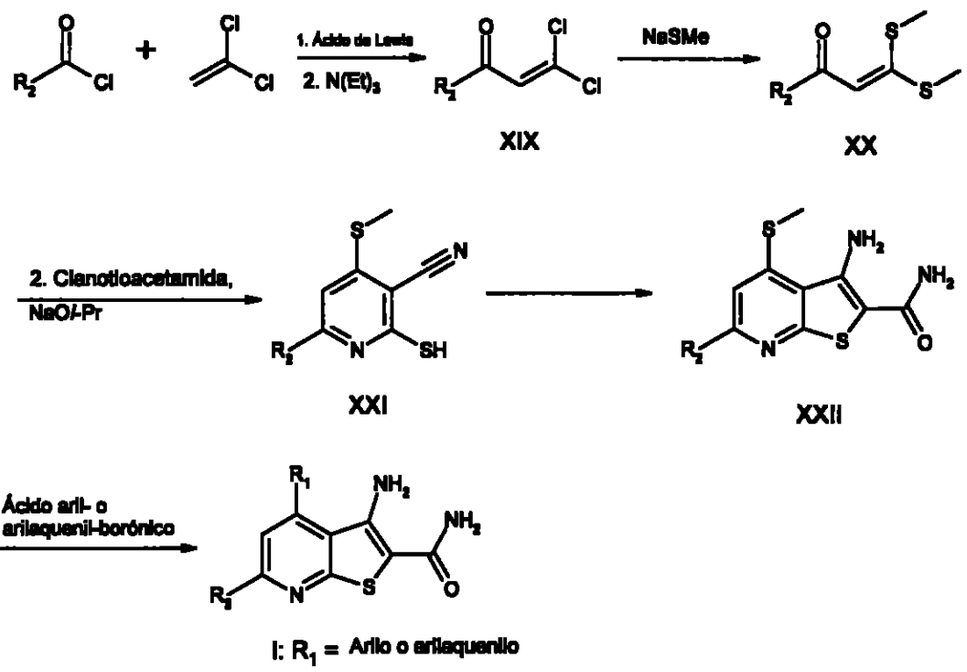
sencia de una base adecuada como diisopropiletilamina en un disolvente adecuado como dioxano proporciona el éster de sulfonilo XVIIb (R' = CF_3 en este caso). La reacción de XVIIb con el nucleófilo deseado, como una amina en presencia de una base adecuada como trietilamina, mientras se calienta opcionalmente de 50°C a 100°C, da lugar al desplazamiento del éster de sulfonilo por el nucleófilo. La ciclación in situ se puede conseguir añadiendo una segunda base adecuada como carbonato de sodio acuoso seguido de calentamiento continuado para proporcionar el compuesto deseado de fórmula (I).

Esquema VI



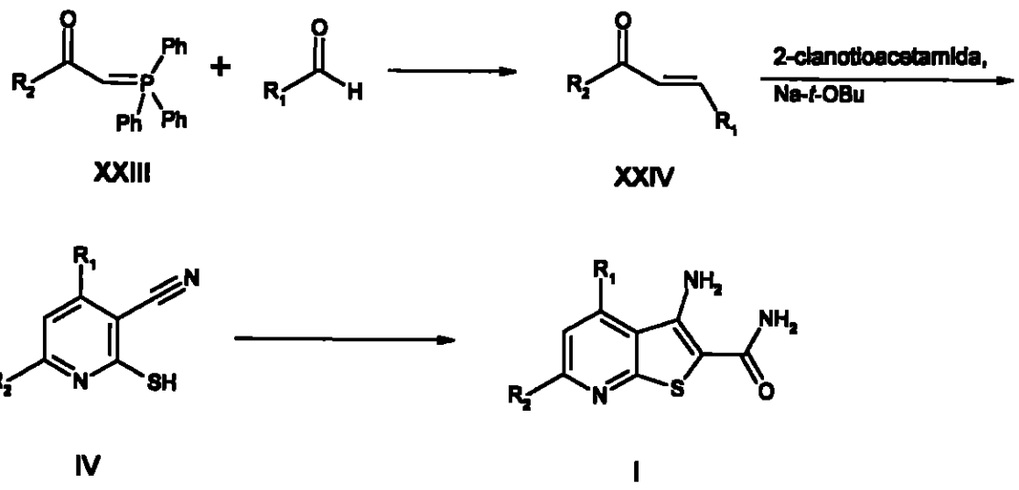
Otro procedimiento que proporcionará grupos arilo o arilalquenilo en R_1 y una diversidad de grupos como arilo y alquilo en R_2 se ilustra en el Esquema VII. Como se ilustran en el Esquema VII, un cloruro de ácido que porta R_2 se hace reaccionar con cloruro de vinilideno en presencia de un ácido de Lewis como $AlCl_3$, en un disolvente adecuado como cloruro de metileno, seguido de tratamiento con una base adecuada como trietilamina para proporcionar XIX. La reacción de XIX con tiometóxido de sodio proporciona XX. El tratamiento de XX con 2-cianotioacetamida en presencia de una base adecuada como isopropóxido de sodio proporciona XXI. La reacción de XXI con 2-bromo o 2-cloro-acetamida como se describe en el Esquema I proporciona XXII. El tratamiento de XXII con un ácido arilborónico o un ácido arilalquenilborónico como se describe en el Esquema V proporciona el compuesto deseado de fórmula (I).

Esquema VII



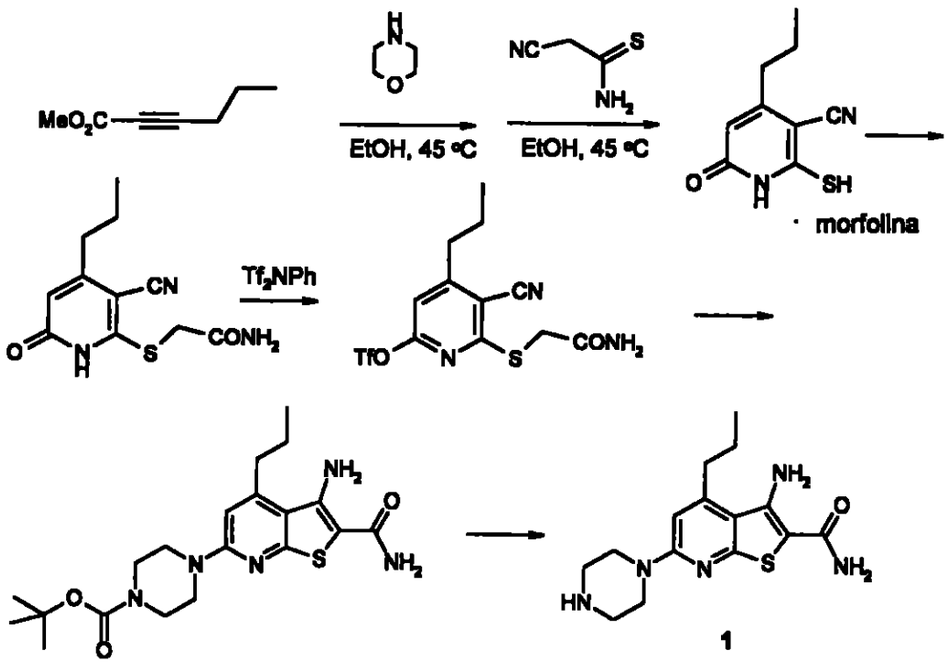
Un procedimiento adicional que puede ser usado para preparar compuestos de fórmula (I) se ilustra en el Esquema VIII. Un aldehído que porta R_1 se hace reaccionar con un trifenilfosforanilideno que porta R_2 (XXIII) en presencia de un ácido adecuado como ácido acético, en un disolvente adecuado como tolueno, para proporcionar la cetona XXIV alfa,beta-insaturada. El tratamiento de XXIV con 2-cianotioacetamida en presencia de una base adecuada como t-butóxido de sodio proporciona IV. Este se convierte en I como se describió en el Esquema I.

Esquema VIII



EJEMPLOS SINTÉTIC S

Ejemplo 1: Síntesis de 3-amino-6-piperazin-1-il-4-propil-tien [2,3-b]piridin-2-carboxílico



A una solución de 2-hexinoato de metilo (15 g, 0,119 moles) en EtOH (40 ml) se añadió morfolina (10,5 g, 0,120 moles) gota a gota a temperatura ambiente. La solución se calentó seguidamente a 45°C durante 4 h bajo nitrógeno. Seguidamente se añadió $NCFH_2C(S)NH_2$ sólido (12,1 g, 0,120 moles) en pequeñas porciones. Después de agitar a 45°C durante 30 minutos, la mezcla se agitó a temperatura ambiente durante una noche. El precipitado amarillo se recogió por filtración, proporcionando 10,9 g de la mercaptopiridona deseada en forma de un complejo con 1 molécula de morfolina.

Una mezcla de la mercaptopiridona anterior (5,25 g, 18,68 mmoles), 2-bromoacetamida (2,58 g, 18,68 mmol) y K_2CO_3 (2,58 g, 18,68 mmol) en DMF seca (50 ml) se calentó bajo Ar a 70°C durante 4 h. La mezcla se enfrió seguidamente a 0°C y se acidificó a pH ~ 2 con HCl 6 N (~ 3 ml). La mezcla se mantuvo a 0°C durante 2 h y el precipitado blanco resultante se recogió por filtración. El producto se lavó con agua fría para proporcionar 5,5 g de la mercaptoacetamida deseada.

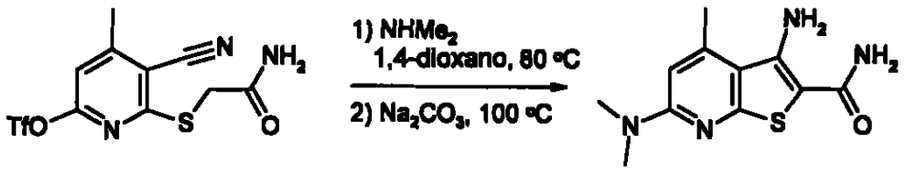
A una mezcla de la mercaptoacetamida anterior (4,15 g, 16,54 mmol) y iPr_2NEt (4,6 ml, 32,82 mmol) en dioxano seco (40 ml) se añadió en pequeñas porciones N-feniltrifluorometano-sulfonimida (5,91 g, 16,54 mmol). La mezcla se agitó bajo nitrógeno durante 16 h, se concentró y se purificó por cromatografía en columna de gel de sílice eluyendo con 50-80% de EtOAc-hexano (gradiente) para

proporcionar 4,7 g de la 2-(3-ciano-4-n-propil-6-trifluorometanosulfonilpiridin-2-ilmercapto)acetamida deseada.

A una solución de 600 mg (1,57 mmol) de la acetamida anterior se añadieron 542,4 mg (2,86 mmol) de 1-Boc-piperazina y 379,8 microlitros (2,72 mmol) de trietilamina. La mezcla resultante se agitó durante 2 h a 100°C. Seguidamente se añadió una solución 2 M (4 ml) de carbonato de sodio. La agitación se continuó durante una noche a 100°C. La mezcla de reacción se diluyó seguidamente con EtOAc, se secó con sulfato de sodio y se concentró. El producto en bruto se cromatografió (TLC preparativa sobre gel de sílice eluyendo con 10% de MeOH/diclorometano, rf = 0,75) para proporcionar 408,4 mg (62,2%) del intermedio de N-Boc-piperazina deseado.

A una suspensión de 408,4 mg (0,97 mmol) del intermedio de N-Boc anterior en 9 ml de EtOAc se añadieron 6 ml de una solución 6 M de HCl en MeOH. La mezcla resultante se agitó durante 4 h a temperatura ambiente. El disolvente se separó seguidamente a vacío, el residuo se puso en suspensión en diclorometano, se agitó durante 10 minutos y se filtró. El producto se lavó con cloruro de metileno dos veces. El sólido se secó a vacío para proporcionar 295 mg del compuesto del título.

Ejemplo 2: Síntesis de amida de ácido 3-amino-6-dimetilamino-4-metiltieno[2,3-b]piridin-2-carboxílico

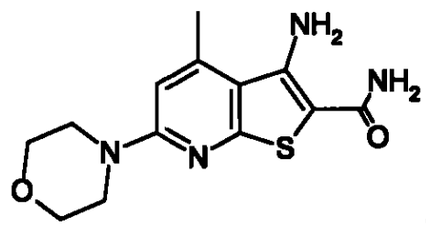


Se mezclaron 2-(3-ciano-4-metil-6-trifluorometano-sulfonilpiridin-2-ilmercapto)acetamida (30,0 mg, 0,08 mmol) (preparado como se describió en el Ejemplo 1 para el análogo de n-propilo pero usando 2-butinoato de metilo) y dimetilamina (170,0 microlitros, 0,34 mmol) en 1,4-dioxano (0,5 ml) en un tubo a presión y se calentó a 80°C durante 1 h. Se añadió carbonato de sodio acuoso (520 µl, 1,04 mmol) y la reacción se calentó a 100°C durante 6 h y seguidamente se enfrió a temperatura ambiente durante una noche. La mezcla se vertió en cloruro de amonio acuoso saturado y se extrajo con EtOAc. El extracto orgánico se lavó con salmuera, se secó (Na_2SO_4), se filtró y se concentró a vacío para proporcionar 23,0 mg del producto en bruto. Este se purificó por medio de cromatografía de sílice rápida automatizada (columna de gel de sílice de 4 g, 30-100% de EtOAc/hexanos) para proporcionar 9,0 mg (0,02 mmol, 45% de rendimiento) del compuesto del título.

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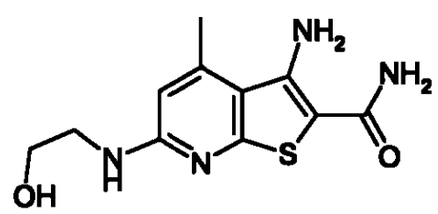
Los siguientes compuestos se prepararon también usando el procedimiento descrito en el Ejemplo 2 y la amina apropiada:

Amida de ácido 3-amino-4-metil-6-morfolin-4-il-tieno[2,3-b]piridin-2-carboxílico



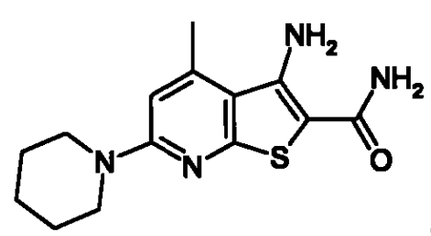
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Amida de ácido 3-amino-6-(2-hidroxi-etilamino)-4-metil-tieno[2,3-b]piridin-2-carboxílico



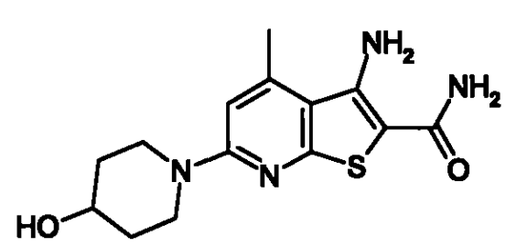
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Amida de ácido 3-amino-4-metil-6-piperidin-1-il-tieno[2,3-b]piridin-2-carboxílico



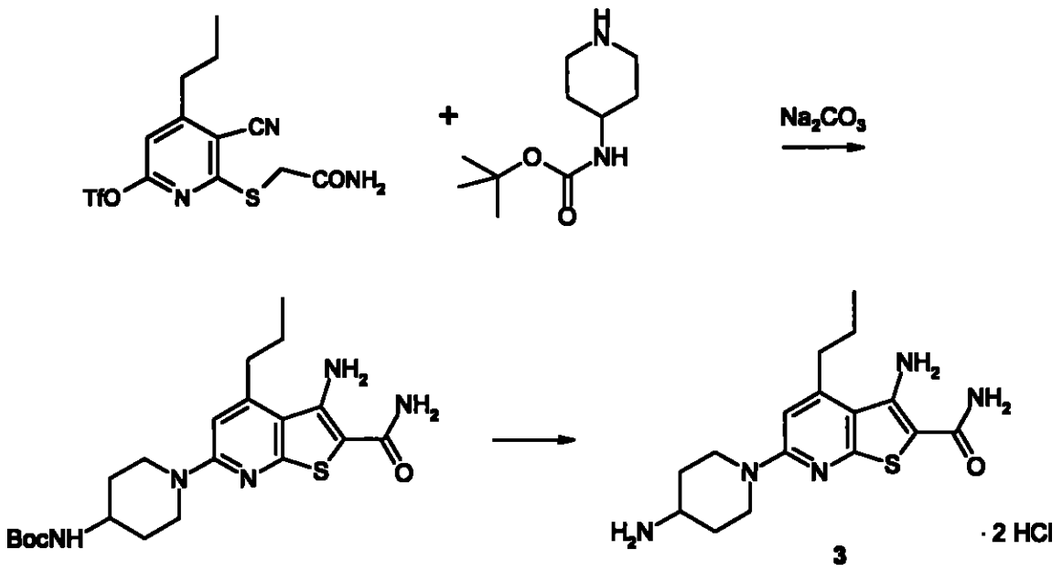
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Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-metil-tieno[2,3-b]piridin-2-carboxílico



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Ejemplo 3: Síntesis de amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico



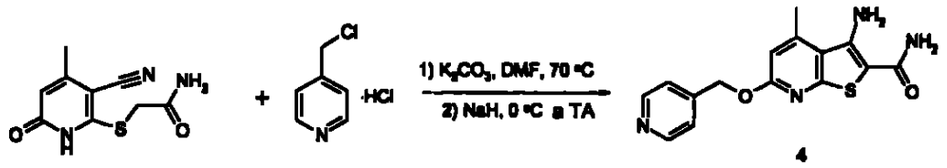
Se disolvieron 400 mg (1,04 mmol) de intermedio de piridina-triflato (véase el Ejemplo 1) en 1,4-dioxano (10 ml) y se colocaron en un tubo seco a presión con una barra agitadora magnética y bajo atmósfera de Ar. Se añadió 4-N-Boc-aminopiperidina (640 mg, 3,13 mmol) y el tubo se selló. La reacción se agitó mientras se calentaba a 80°C durante 35 minutos. Una TLC indicó la desaparición completa del triflato de partida. La reacción se enfrió a temperatura ambiente y se añadió una solución acuosa 2,0 M de carbonato de sodio (4,0 ml, 8,00 mmol). La reacción se calentó a 100°C, se agitó durante 20 h y después de esto se enfrió a temperatura ambiente.

La mezcla de reacción se concentró a vacío y el residuo se recogió en acetona/MeOH (aproximadamente 50:50). La mezcla resultante se filtró y el filtrado se concentró a vacío. El material fue pre-absorbido en tierra de diatomeas y se purificó primero a través de cromatografía de gel de sílice rápida automatizada (columna de 10 g de gel de sílice, gradiente de 30-70% de EtOAc/hexanos con barrido de EtOAc) para proporcionar 274 mg de producto ligeramente en bruto. Este se purificó adicionalmente a través de cromatografía rápida regular sobre gel de sílice (columna de 30 mm de diámetro por 10,16 cm de altura) eluyendo con un gradiente por etapas de 33%-50% de EtOAC/hexanos, seguidamente un barrido con EtOAc, para proporcionar 249,3 mg (55% de rendimiento) de éster terc-butílico de ácido 3-amino-2-carbamoil-4-propil-tieno[2,3-b]piridin-6-il)-piperidin-4-il]-carbámico.

Se pusieron en suspensión 249,3 mg (0,57 mmol) del compuesto anterior en 10,0 ml de EtOAc. El material se disolvió completamente mediante la adición de metanol (2,0 ml) y diclorometano (2,0 ml). A esto se añadieron 5,0 ml (30,0

mmol) de una solución 6 M de ácido clorhídrico en metanol. Esta mezcla de reacción se agitó durante 4 h a temperatura ambiente mientras un sólido amarillo se separó lentamente por precipitación de la solución. Una TLC mostró la desaparición completa del material de partida, por lo que la reacción se concentró a vacío. El residuos e separó por lavado de las paredes del matraz con una pequeña cantidad de metanol y seguidamente se trituró con acetato de etilo. El sólido amarillo se recogió por medio de filtración con succión y se lavó sucesivamente con acetato de etilo, diclorometano y acetona. El sólido se secó a vacío para proporcionar 191,4 mg del compuesto del título (83% de rendimiento).

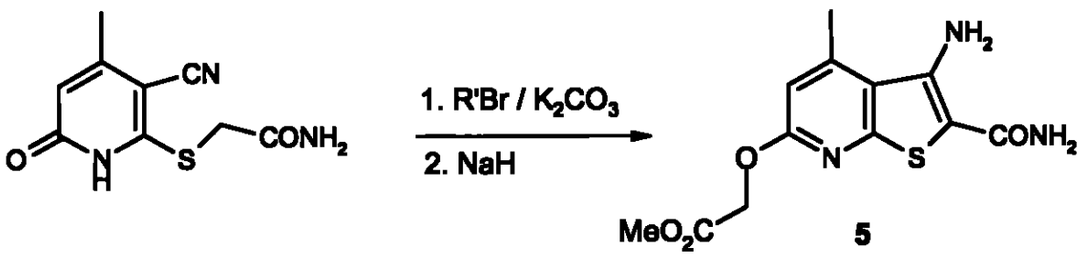
Ejemplo 4: Síntesis de amida de ácido 3-amino-4-metil-6-(piridin-4-ilmetoxi)-tieno[2,3-b]piridin-2-carboxílico



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Se combinó hidrocloruro de 4-clorometilpiridina (57,0 mg, 0,34 mmol) con 50mg de intermedio de 4-metil-mercaptopiridona (preparado de forma análoga al Ejemplo 1) (0,22 mmol) y carbonato de potasio (95,0 mg, 0,68 mmol) en DMF (1,0 ml) en un tubo a presión secado a la llama) bajo Ar. El tubo se selló y se calentó a 70°C durante 45 minutos. Una TLC mostró la desaparición completa del material de partida y la formación de una nueva mancha. La reacción se enfrió a 0°C y se añadió hidruro de sodio (9,0 mg, 0,23 mmol). La mezcla se calentó a temperatura ambiente y se agitó durante 30 minutos, después de lo cual se enfrió en un baño con hielo y se inactivó con bicarbonato de sodio acuoso (saturado). La mezcla resultante se extrajo dos veces con EtOAc. Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron a vacío para proporcionar 65,8 mg del producto en bruto que se purificó por medio de sílice rápida automatizada para proporcionar 41,8 mg (0,13 mmol, 59% de rendimiento) del compuesto del título.

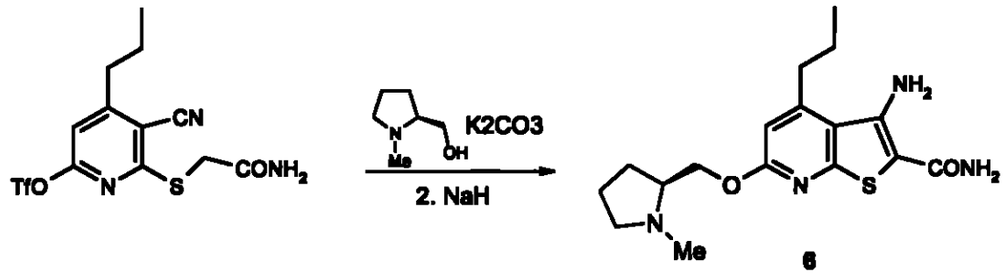
Ejemplo 5: Síntesis de éster metílico de ácido 3-amino-2-carbamoil-4-metil-tieno[2,3-b]piridin-6-iloxi)-acético



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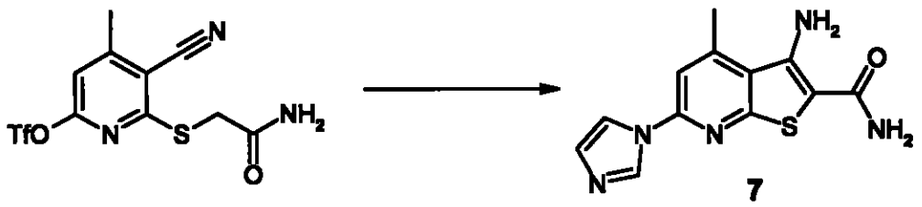
A una mezcla del intermedio de 4-metil-mercaptopiridona (preparado de forma análoga al Ejemplo 1) (62 mg) y K_2CO_3 (70 mg) en DMF (1 ml) se añadió bromoacetato de metilo (50 ml). La mezcla se calentó bajo Ar a 70°C durante 2 h. Después de enfriar a 0°C, la mezcla se trató con NaH (60%, 10 mg) y se agitó a temperatura ambiente durante 30 minutos. La mezcla se vertió seguidamente en una mezcla de hielo-NH_4Cl, se extrajo con EtOAc, se secó con Na SO_4 y se concentró. El residuo se purificó por TLC preparativa, proporcionando 5 mg del compuesto del título (sólido blanco).

Ejemplo 6: Síntesis de amida de ácido 3-amino-6-(1-metil-pirrolidin-2-ilmetoxi)-4-propil-tieno[2,3-b]piridin-2-carboxílico



Una mezcla de intermedio de piridina-triflato (véase el Ejemplo 1) (10 mg) y N-metil-L-prolinol (40 mg) en dioxano se calentó bajo Ar a 90°C durante 3 h. La mezcla se enfrió a temperatura ambiente y se añadió Na_2CO_3 (2 M, 0,2 ml). La mezcla se calentó a 100°C bajo Ar durante 10 h, se enfrió a temperatura ambiente y se diluyó con agua (1 ml). La mezcla se extrajo con EtOAc, se secó con Na_2SO_4 y se concentró. El residuo se purificó por cromatografía sobre gel de sílice preparativa para proporcionar 6 mg del compuesto del título en forma de un sólido blanco.

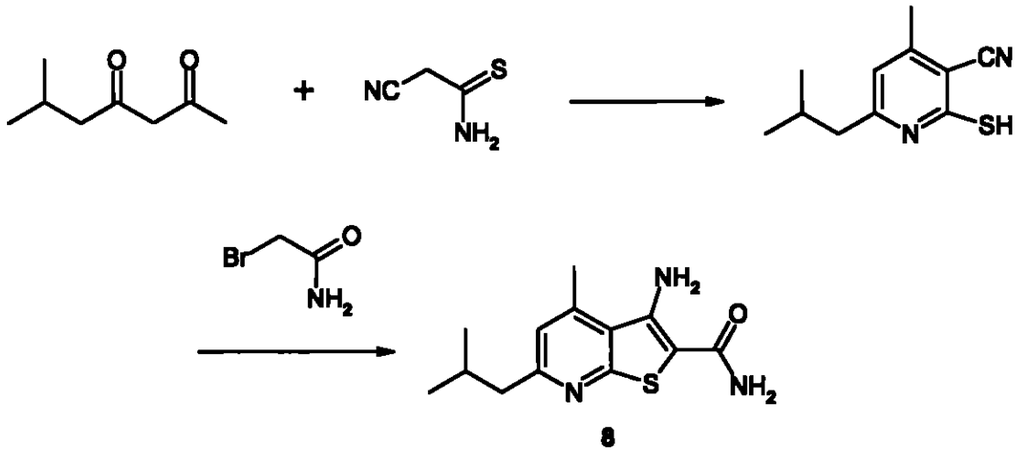
Ejemplo 7: Síntesis de amida de ácido 3-amino-6-imidazol-1-il-4-metil-tieno[2,3-b]piridin-2-carboxílico



7

A una solución de 20 mg (0,067 mmol) de intermedio de triflato de 4-metilpiridina de partida (véase el Ejemplo 2) en 1,2 ml de 1,4-dioxano se añadieron 9,2 mg de imidazol. La mezcla resultante se agitó durante 2 h a 80°C. Después de ese tiempo se añadieron 0,5 ml de solución 2 M de carbonato de sodio. La agitación se continuó durante una noche a 100°C. La mezcla de reacción se enfrió seguidamente a temperatura ambiente, se diluyó con EtOAc, se secó con sulfato de sodio y se concentró. El producto en bruto se cromatografió (TLC preparativa sobre gel de sílice eluyendo con 10% de MeOH/cloruro de metileno, rf = 0,56) para proporcionar 3,7 mg de producto, que se purificó adicionalmente por HPLC (fase inversa-sistema disolvente:isocrático 60% de agua/acetonitrilo) proporcionando 2,7 mg (14,7%) del compuesto del título.

Ejemplo 8: Síntesis de 3-amino-6-isobutil-4-metil-tieno[2,3-*b*]piridin-2-carboxílico



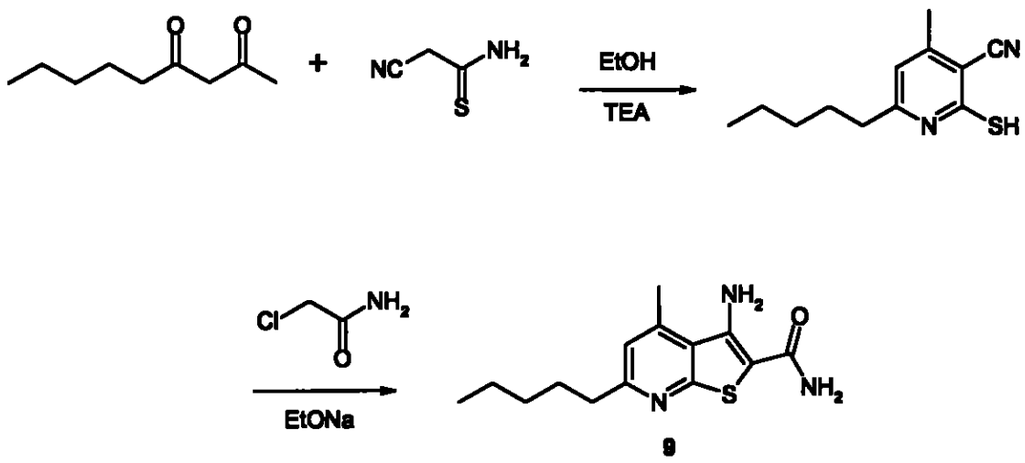
8

A una solución agitada de cianotioacetamida (2,20 g, 22 mmol) y 6-metil-2,4-heptanodiona (3,12 g, 22 mmol) en EtOAc anhidro (40 ml) se añadió trietilamina (0,4 ml) y la reacción se calentó a 50°C durante 1 h antes de que sejara enfriar a temperatura ambiente. Una filtración y lavado de los precipitados con EtOH proporcionó 6-isobutil-2-mercapto-4-metilnicotinonitrilo en forma de un sólido amarillo (2,8 g, 61%).

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Una mezcla del nitrilo anterior (1,00 g, 4,85 mmol), bromoacetatamida (0,67 g, 4,85 mmol) y etóxido de sodio (0,68 g, 10 mmol) en DMF (20 ml) se calentó a 70°C durante 1 h antes de que se dejara enfriar a temperatura ambiente. La mezcla resultante se diluyó con agua, se filtró y los precipitados se lavaron con EtOH proporcionando el compuesto del título (0,5 g, 39%).

Ejemplo 9: Síntesis de 3-amino-4-metil-6-pentil-tieno[2,3-*b*]piridin-2-carboxílico



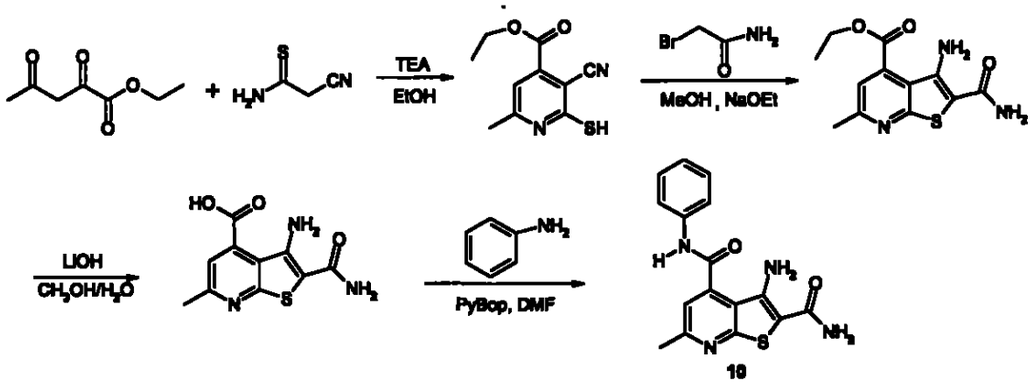
9

A una solución agitada de 2-cianotioacetamida (1,4 g, 14 mmol) y 2,4-nonanodiona (2,0 g, 13 mmol) en EtOH anhidro (40 ml) se añadió trietilamina (0,5 ml) y la reacción se calentó a 50°C durante 1 h y seguidamente se dejó enfriar a temperatura ambiente. Una filtración y lavado de los precipitados con EtOH proporcionó 6-pentil-2-mercapto-4-metil-nicotinotrilo en forma de un sólido amarillo (1,84 g, 62,1%).

Una mezcla del nicotinotrilo anterior (1,84 g, 6,7 mmol), 2-cloroacetamida (0,63 g, 6,7 mmol) y etóxido de sodio (0,91 g, 13,4 mmol) en MeOH (35 ml) se calentó a 75°C durante 2 h y seguidamente se dejó enfriar a temperatura ambiente. Una filtración y lavado de los precipitados con EtOH proporcionó el compuesto del título en forma de un sólido (1,31 g, 71,2 %).

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Ejempl 10: Síntesis de 2-amida-4-fenilamida de ácido 3-amino-6-metil-tieno[2,3-*b*]piridin-2,4-dicarboxílico

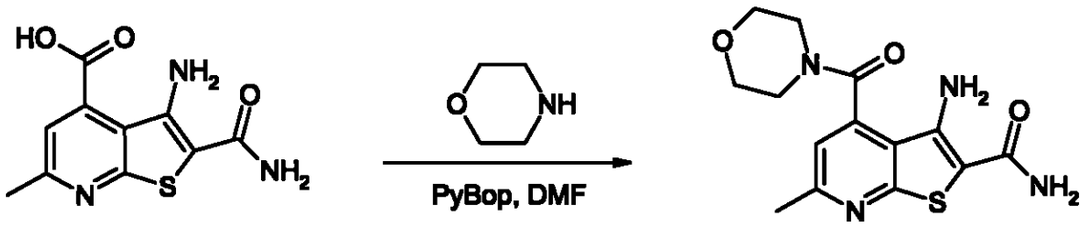


10

A una solución agitada de 2-cianotioacetamida (3,52 g, 35 mmol) y 2,4-dioxovalerato de etilo (5,0 g, 32 mmol) en EtOH anhidro (75 ml) a temperatura ambiente se añadió trietilamina (0,5 ml) y la reacción se agitó durante una noche. Una filtración y lavado de los precipitados con EtOH proporcionó éster etílico de ácido 3-ciano-2-mercapto-6-metil-isonicotínico en forma de un sólido amarillo (4,54 g, 64,5%). Una mezcla de este éster (3,54 g, 16 mmol), bromoacetamida (2,15 g, 16 mmol) y etóxido de sodio (2,18 g, 32 mmol) en MeOH se calentó a reflujo durante una noche. Seguidamente se dejó enfriar a temperatura ambiente. Una filtración y lavado de los precipitados con EtOH proporcionó éster etílico de ácido 3-amino-2-carbamoil-6-metil-tieno[2,3-*b*]piridin-4-carboxílico en forma de uns ólido (0,94 g, 21,1%).

Una mezcla del éster anterior (0,94 g, 3,4 mmol) e hidróxido de litio (0,11 g, 4,7 mmol) en MeOH/H_2O (100 ml, MeOH:H_2O = 3:1) se agitó durante 2 h a temperatura ambiente. La mezcla se neutralizó con HCl 2 M y se concentró a vacío para proporcionar ácido 3-amino-2-carbamoil-6-metil-tieno[2,3-b]piridino-2-carboxílico en forma de uns ólido color naranja (0,78 g, 63,2%). Una mezcla de este ácido (0,3 g, 1,2 mmol), anilina (0,56 f, 6,0 mmol) y PyBop (0,63 g, 1,4 mmol) en DMF (10 ml) se agitó a temperatura ambiente durante una noche. La reacción se diluyó seguidamente con agua, se filtró y el sólido resultante se lavó con EtOH proporcionando el compuesto del titulo en forma de un sólido (0,27 g, 73,6%).

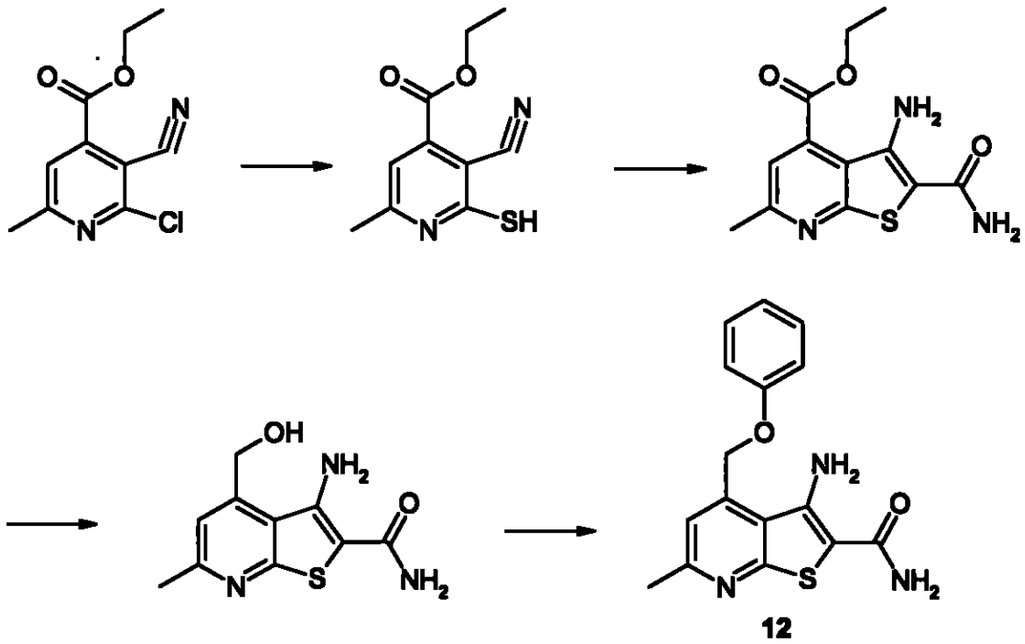
Ejemplo 11: Amida de ácido 3-amino-6-metil-4-(morfolin-4-carbonil)-tienó[2,3-*b*]piridin-2-carboxílico



11

Una mezcla de ácido 3-amino-2-carbamoil-6-metil-tieno[2,3-*b*]piridin-4-carboxílico a (véase el Ejemplo 10) (0,5 g, 2,0 mmol), morfolina (0,87 g, 10 mmol) y PyBop (0,88 g, 2,0 mmol) en DMF (10 ml) se agitó a temperatura ambiente durante una noche. Se diluyó con agua y se extrajo con cloruro de metileno (50 ml). Una concentración de la fase orgánica proporcionó el compuesto del título en forma de un sólido color naranja (0,45 g, 70,3%).

Ejemplo 12: Síntesis de amida de ácido 3-amino-6-metil-4-fenoximetil-tieno[2,3-*b*]piridin-2-carboxílico



12

Se añadió tiourea (339 mg, 4,46 mmol) a una solución de éster etílico de ácido 2-cloro-3-ciano-6-metil-isonicotínico (500 mg, 2,23 mmol) en EtOH (25 ml) a temperatura ambiente. La mezcla se calentó a reflujo durante 24 h. La mezcla se enfrió (la cristalización comenzó tras enfriar) a temperatura ambiente. El sólido se recogió por filtración a vacío proporcionando éster etílico de ácido 3-ciano-2-mercapto-6-metil-isonicotínico (250 mg, 50%) en forma de un sólido color amarillo-

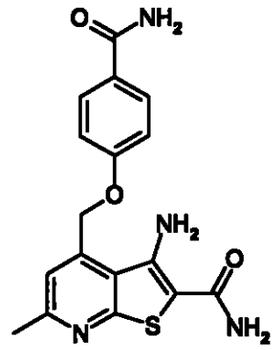
naranja.

Se añadió NaH (39 mg, 0,95 mmol) a una solución del éster anterior (210 mg, 0,95 mmol) en THF (15 ml) a temperatura ambiente. Después de agitar durante 5 minutos se añadieron α-bromoacetamida (134 mg, 0,97 mmol) y n-Bu_4NI (10 mg). La mezcla se agitó a temperatura ambiente durante 1 h y seguidamente se añadió NaH (39 mg, 0,95 mmol) y la mezcla se agitó durante 0,5 h adicional. La reacción se inactivó mediante la adición de NH_4Cl acuoso saturado, se diluyó con EtOAc, se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró para proporcionar un sólido color naranja. El residuo en bruto se recristalizó en MeOH proporcionando éster etílico de ácido 3-amino-2-carbamoil-6-metil-tieno[2,3-*b*]piridin-4-carboxílico (160 mg, 60%), p.f. 205-208°C.

Se añadió $LiBH_4$ (62 mg, 2,04 mmol) a una solución de éster etílico de ácido 3-amino-2-carbamoil-6-metil-tieno[2,3-b]piridino-4-carboxílico (205 mg, 0,73 mmol) en 10:1 de THF:MeOH (15 ml) a temperatura ambiente. Después de agitar durante 2 h, la reacción se inactivó mediante la adición de HCl 1 M. La mezcla se tamponó a pH ~ 7, se diluyó con EtOAc, se lavó secuencialmente con H_2O, salmuera, se secó sobre Na_2SO_4, se concentró y se trituró con 50% de EtOAc/hexano proporcionando amida de ácido 3-amino-4-hidroximetil-6-metil-tieno[2,3-*b*]piridin-2-carboxílico (123 mg, 71%) en forma de un sólido amarillo, p.f. >210°C.

Se añadió azodicarboxilato de diisopropilo (DIAD) (14 mg, 0,069 mmol) a una solución de amida de ácido 3-amino-4-hidroximetil-6-metil-tieno[2,3-*b*]piridin-2-carboxílico (15 mg, 0,063 mmol), fenol (6 mg, 0,069 mmol) y Ph_3P (18 mg, 0,069 mmol) en THF (1,5 ml) a 0°C. La mezcla se calentó a temperatura ambiente y se agitó durante 24 h. La mezcla de reacción se concentró y se fraccionó por TLC preparativa (10% de MeOH/CH_2Cl_2) proporcionando el compuesto del título (12 mg, 61%) en forma de un sólido color naranja, p.f. 194-196°C.

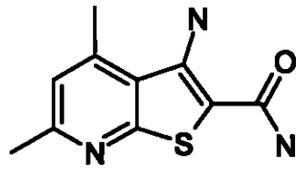
Ejemplo 13: Síntesis de amida de ácido amino-4-(4-carbamoil-fenoximetil)-6-metil-tieno[2,3-*b*]piridin-2-carboxílico



13

Se añadió DIAD (23 mg, 0,116 mmol) a una solución de amida de ácido 3-amino-4-hidroximetil-6-metil-tieno[2,3-*b*]piridin-2-carboxílico (véase el Ejemplo 12) (25 mg, 0,105 mmol), 4-hidroxi-benzamida (15 mg, 0,116 mmol) y Ph_3P (30 mg, 0,116 mmol) en THF (2,5 ml) a 0°C. La mezcla se calentó a temperatura ambiente y se agitó durante 24 h. La mezcla de reacción se concentró y se trituró con 2:1 de EtOAc:MeOH proporcionando el compuesto del título (7 mg, 19%) en forma de un sólido color naranja, p.f. >250°C.

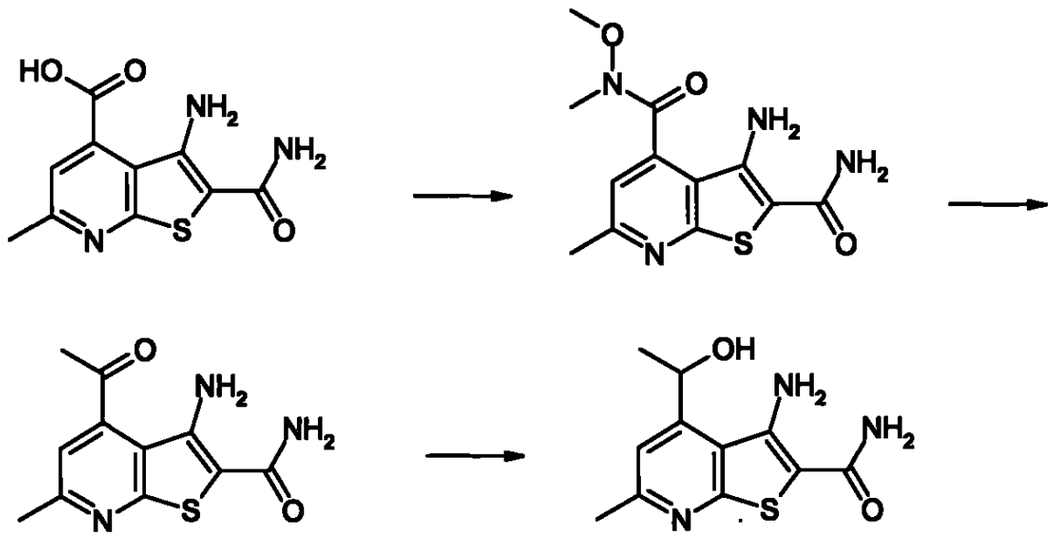
Ejemplo 14: Síntesis de amida de ácido 3-Amino-4,6-dimetil-tieno[2,3-*b*]piridin-2-carboxílico



Se añadió α-bromoacetamida (388 mg, 2,81 mmol) a una solución de 2-mercapto-4,6-dimetil-nicotinonitrilo (420 mg, 2,56 mmol) en MeOH (25 ml) a temperatura ambiente. Esto estuvo seguido de la adición de metóxido de sodio (1,76 ml, 25% de NaOMe en MeOH, 7,7 mmol). La mezcla de reacción se calentó a reflujo. El calentamiento a reflujo se continuó durante una noche, después de lo cual la mezcla de reacción se enfrió y se filtró. El producto se secó durante una noche proporcionando 450 mg (80%) del compuesto del título, p.f. 238-40°C.

280

Ejemplo 15: Síntesis de amida de ácido 3-amino-4-(1-hidroxi-etil)-6-metil-tieno[2,3-b]piridin-2-carboxílico



15

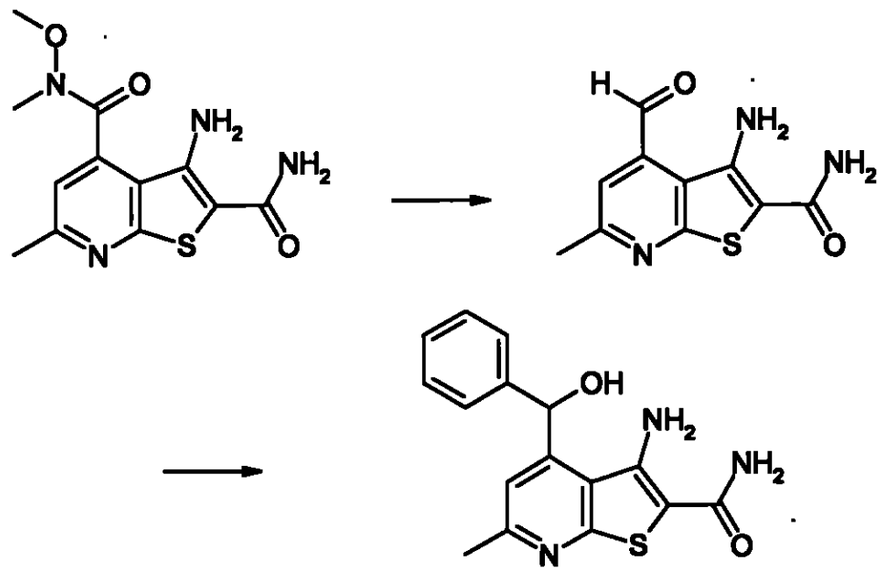
A una solución de 0,80 g de ácido 3-amino-2-carbamoil-6-metil-tieno[2,3-b]piridin-4-carboxílico y 0,37 g de hidroxloruro de N,O-dimetilhidroxilamina en DMF se añadieron 1,8 ml de diisopropiletilamina y 1,23 g de tetrafluoroborato de O-benzotriazol-1-il-N,N,N',N'-tetrametiluronio. La solución se agitó a temperatura ambiente durante una noche. La reacción se vertió en NH_4Cl acuoso, se extrajo 4 veces con EtOAc, se lavó 4 veces con agua y Na_2CO_3 acuoso, se secó y se concentró a vacío hasta 0,74 g. La fase acuosa se volivó a extraer 4 veces con n-butanol, se lavó con Na_2CO_3 acuoso, se concentró a vacío y se sometió 3 veces a destilación azeotrópica con tolueno para conseguir 0,71 g más de producto. La fase acuosa se hizo básica con Na_2CO_3, se volvió a extraer 4 veces con n-butanol, se lavó con agua, se concentró a vacío y se sometió 3 veces a destilación azeotrópica con tolueno para proporcionar un tercer cultivo de 0,52 g. Los tres cultivos se combinaron y se sometieron a cromatografía rápida sobre gel de sílice eluyendo con 5% de MeOH-CH_2Cl_2 para proporcionar 0,62 g de 2-amida-4-(metoxi-metil-amida) de ácido 3-amino-6-metil-tieno[2,3-b]piridin-2,4-dicarboxílico en forma de un sólido amarillo.

A 100 mg de 2-amida-4-(metoxi-metil-amida) de ácido 3-amino-6-metil-tieno[2,3-b]piridin-2,4-dicarboxílico en 3 ml de THF seco en un baño de hielo se añadieron 0,68 ml de bromuero de metil-magnesio 3 M y la reacción se agitó 1 h en el baño enfriado y a temperatura ambiente durante una noche bajo argón. Se añadió NH_4Cl acuoso y el producto se extrajo 4 veces con EtOAc, se secó y se concentró a vacío. Una purificación en una placa de preparación de gel de sílice

de 2 mm en 5% de MeOH-CH_2Cl_2 proporcionó 12,2 mg de amida de ácido 4-acetil-3-amino-6-metil-tieno[2,3-b]piridin-2-carboxílico.

Se añadió la punta de una espátula de $NaBH_4$ a una solución de 9,9 mg de amida de ácido 4-acetil-3-amino-6-metil-tieno[2,3-b]piridin-2-carboxílico en 1 ml de MeOH. Después de 0,5 h, la reacción se concentró a vacío, se inactivo con NH_4Cl acuoso, se extrajo 4 veces con EtOAc, se concentró a vacío, se disolvió en MeOH-CH_2Cl_2, se filtró, se concentró y se secó a vacío a 60°C para proporcionar 8,1 mg del compuesto del título en forma de un sólido color beige.

Ejemplo 16: Síntesis de amida de ácido 3-amino-4-(hidroxi-fenil-metil)-6-metil-tieno[2,3-b]piridin-2-carboxílico



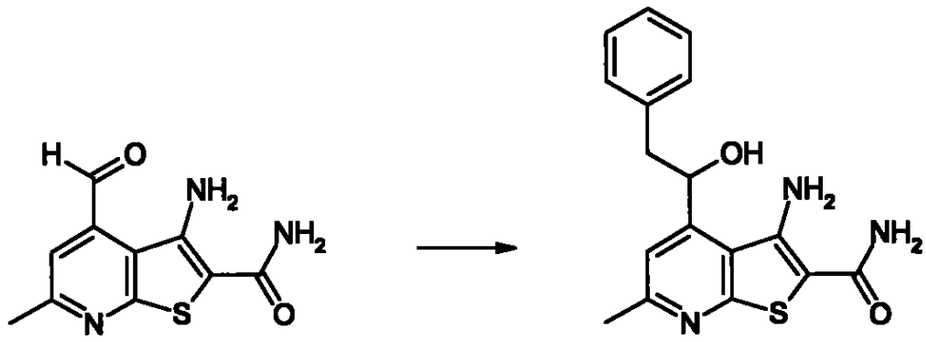
16

Se añadió $LiAlH_4$ (0,31 g) a una suspensión de 0,60 g de 2-amida-4-(metoxi-metil-amida) de ácido 3-amino-6-metil-tieno[2,3-b]piridin-2,4-dicarboxílico (véase el Ejemplo 15) en 15 ml de THF seco a -10°C y se agitó 1 h bajo Ar. Se añadió lentamente NH_4Cl acuoso y la mezcla se filtró a través de tierra de diatomeas, lavando con H_2O y EtOAc. La fase acuosa se separó y se extrajo 3 veces más con EtOAc y las partes orgánicas combinadas se concentraron a vacío hasta dar una resina que se sometió a cromatografía rápida eluyendo con 30% de acetona-éter de petróleo para proporcionar 163 mg de amida de ácido 3-amino-4-formil-6-metil-tieno[2,3-b]piridin-2-carboxílico en forma de una resina oscura.

A una suspensión de 314 mg de $CeCl_3$ en 3 ml de THF seco a -78°C se añadieron 0,425 ml de bromuro de fenilmagnesio 3 M y la reacción se agitó 1,5 h bajo Ar. Seguidamente se añadió amida de ácido 3-amino-4-formil-6-metil-tieno[2,3-b]piridin-2-carboxílico y la reacción se agitó 5 h en frío y seguidamente se

dejó calentar a temperatura ambiente durante 0,5 h. Se añadió NH_4Cl acuoso y la reacción se filtró a través de tierra de diatomeas, lavando con EtOAc, y la fase acuosa se separó y se extrajo 3 veces más con EtOAc. Las partes orgánicas combinadas se secaron y se concentraron a vacío, y el producto se purificó en una placa preparativa desarrollada con 5% de MeOH-CH_2Cl_2. La impureza del material de partida se separó disolviendo el producto en EtOAc con una traza de MeOH y lavando 3 veces con $NaHSO_3$ acuoso. Las partes orgánicas se secaron, se concentraron a vacío, se volvieron a disolver en MeOH-CH_2Cl_2, se filtraron, se concentraron y se secaron a vacío a 60°C para proporcionar 8,2 mg del compuesto del título en forma de un sólido amarillo.

Ejemplo 17: Síntesis de amida de ácido 3-amino-4-(1-hidroxi-2-fenil-etil)-6-metil-tieno[2,3-b]piridin-2-carboxílico

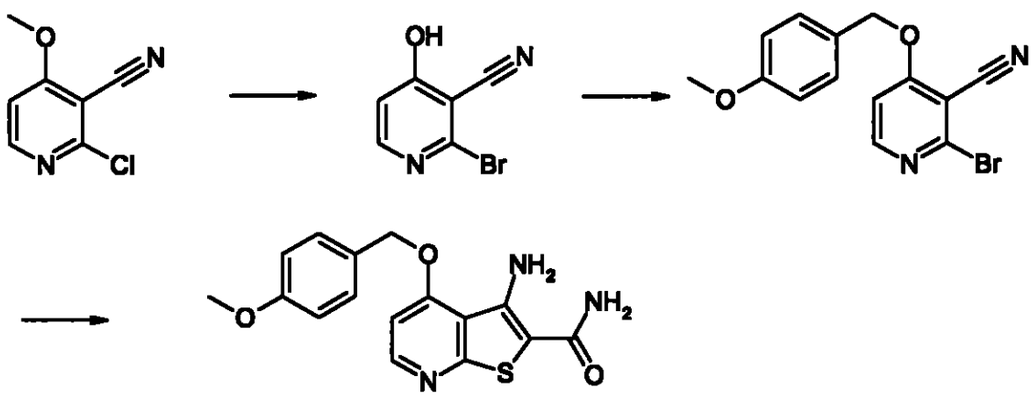


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A una suspensión de 344 mg de $CeCl_3$ en 3 ml de THF seco a -78°C se añadieron 0,70 ml de cloruro de bencilmagnesio 2 M y la reacción se agitó 1,5 h bajo Ar. Seguidamente se añadieron 41 mg de amida de ácido 3-amino-4-formil-6-metil-tieno[2,3-b]piridin-2-carboxílico (véase el Ejemplo 16) y la reacción se agitó 3,5 h en frío y seguidamente se dejó calentar a temperatura ambiente durante 0,5 h. Se añadió NH_4Cl acuoso y la reacción se filtró a través de tierra de diatomeas, lavando con EtOAc, y la fase acuosa se separó y se extrajo 3 veces más con EtOAc. Las partes orgánicas combinadas se secaron, se concentraron a vacío y se volvieron a disolver en EtOAc con una traza de MeOH y se lavaron 3 veces con $NaHSO_3$ acuoso. Esto se secó, se concentró a vacío y el producto se purificó en una placa preparatoria desarrollada con MeOH-CH_2Cl_2. El producto se volvió a disolver en MeOH-CH_2Cl_2, se filtró, se concentró y se secó a vacío a 60°C proporcionando 16,3 mg del compuesto del título en forma de un sólido color naranja.

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Ejemplo 18: Síntesis de amida de ácido 3-amino-4-(4-metoxi-benciloxi)-tieno[2,3-b]piridin-2-carboxílico



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Se puso en suspensión 2-cloro-4-metoxi-nicotinonitrilo (M. Mittelbach *et al.*, Arch.Pharm.(Weinheim Ger.); 1985, GE, 318, 6, 481-486) (6,92 g) en 70 ml de HBr al 30% en ácido acético en un recipiente a presión y se calentó con agitación a 100°C durante 2 h. La reacción se enfrió a temperatura ambiente y se filtró, lavando bien con H_2O y se secó a vacío durante una noche a 50°C proporcionando 4,85 g de 2-bromo-4-hidroxi-nicotinitrilo en forma de un sólido blanco. Una RMN protónica (DMSO) indicó que el producto era una mezcla de 69% de compuesto de bromo con 31% de análogo de cloro de partida.

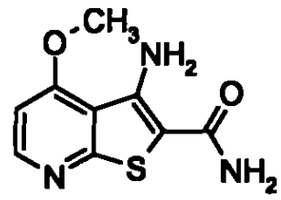
A una solución de 5,85 g de la mezcla anterior en 30 ml de DMF seca se añadieron 1,52 g de NaH al 60% en aceite mineral por partes y la reacción marrón se agitó 15 minutos a temperatura ambiente bajo Ar. Se añadió cloruro de 4-metoxibencilo (5,16 ml) y la reacción se calentó a 60°C durante 2,5 h y seguidamente se inactivó con NH_4Cl acuoso. Una extracción en EtOAc, seguida de lavado con H_2O proporcionó la precipitación de un producto secundario sólido blanco en un embudo separador que se separó por filtración. El filtrado se secó y se eliminó hasta dar 9,4 g de un semisólido que se trituró en CH_2Cl_2 y se filtró para proporcionar 730 mg de más producto secundario. El filtrado se concentró y se sometió a cromatografía rápida sobre gel de sílice eluyendo con CH_2Cl_2, proporcionando 4,80 g de un sólido céreo blanco. Una RMN protónica (DMSO) indicó que el producto era una mezcla 2:1 de 2-bromo-4-(4-metoxi-benciloxi)-nicotinotrilo con su análogo de 2-cloro.

Una solución de mercaptoacetamida de MeOH (6,80 ml) se concentró a vacío proporcionando 928 mg y 2,75 g de la mezcla 2:1 anterior y se añadió y disolvió en 14 ml de DMF bajo una purga de N_2. Se añadió una suspensión de NaH al 60% en aceite mineral (723 mg) y se agitó a 60°C durante una noche bajo Ar.

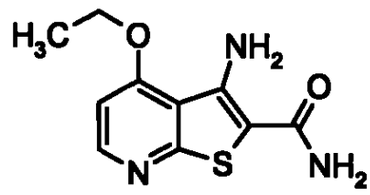
Se añadió NH_4Cl acuoso y el producto se filtró, se lavó con H_2O y se secó a vacío a 50°C proporcionando 1,97 g de producto en bruto que se recristalizó en MeOH para proporcionar 1,25 g del compuesto del título en forma de un sólido amarillo.

Los siguientes compuestos se prepararon de la manera anteriormente descrita a partir de 2-bromo-4-hidroxi-nicotinonitrilo y el halauro de alquilo apropiado. En el caso de los alquil-éteres, se usó bromuro o yoduro de alquilo. En el caso de bencil-éteres se usó cloruro o bromuro de bencilo.

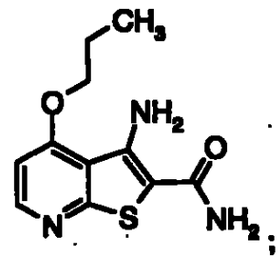
Amida de ácido 3-amino-4-metoxi-tieno[2,3-b]piridin-2-carboxílico



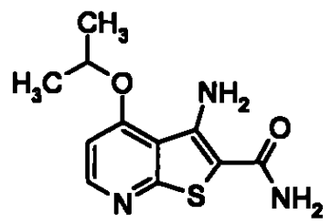
Amida de ácido 3-amino-4-etoxi-tieno[2,3-b]piridin-2-carboxílico



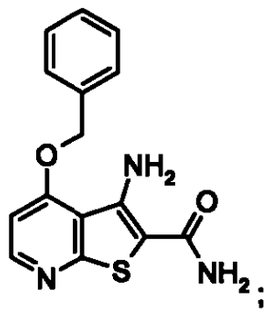
Amida de ácido 4-amino-4-propoxi-tieno[2,3-b]piridino-2-carboxílico;



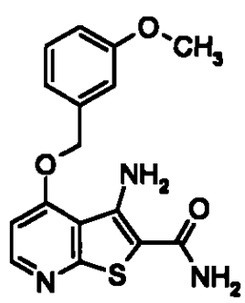
Amida de ácido 3-amino-4-isopropoxi-tieno[2,3-b]piridino-2-carboxílico



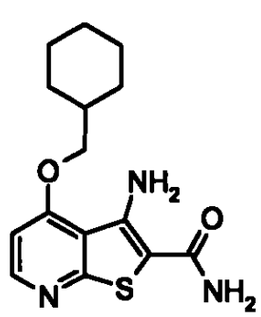
Amida de ácido 3-amino-4-benciloxi-tieno[2,3-b]piridin-2-carboxílico



Amida de ácido 3-Amino-4-(3-metoxibenciloxi)-tieno[2,3-b]piridin-2-carboxílico

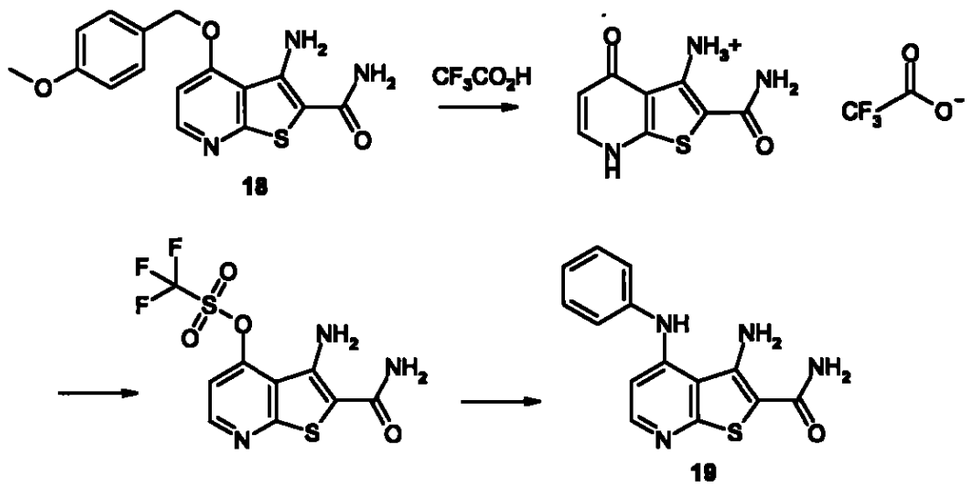


Amida de ácido 3-amino-4-(ciclohexilmetoxi)-tieno[2,3-b]piridin-2-carboxílico.



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Ejemplo 19: Síntesis de amida de ácid 3-amino-4-fenilamino-tieno[2,3-b]piridin-2-carboxílico



18

19

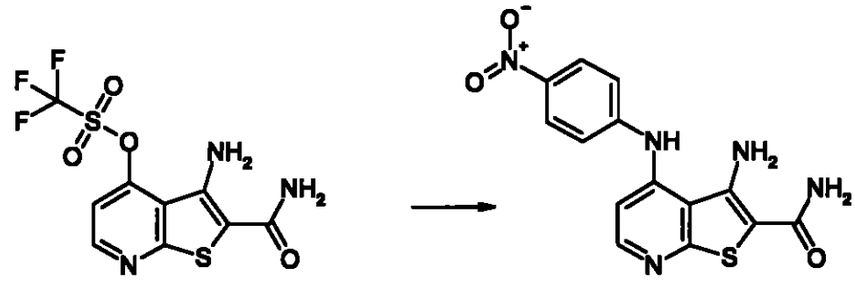
Una solución de 2,43 g de amida de ácido 3-amino-4-(4-metoxi-benciloxi)-tieno[2,3-b]piridin-2-carboxílico (Ejemplo 18) se agitó 6 h en 20 ml de ácido trifluoroacético con un tubo de secado. La reacción se concentró a vacío y seguidamente se evaporó conjuntamente 3 veces con tolueno y 2 veces con CH_2Cl_2 para proporcionar una resina amarilla. Esta se trituró en EtOAc y se filtró para proporcionar 1,88 g de sal de ácido trifluoroacético de amida de ácido 3-amino-4-oxo-4,7-dihidro-tieno[2,3-b]piridin-2-carboxílico en forma de un sólido amarillo.

Una mezcla de 1,0 g de sal de ácido trifluoroacético de amida de ácido 3-amino-4-oxo-4,7-dihidro-tieno[2,3-b]piridin-2-carboxílico y 2,76 g de N-feniltrifluorometanosulfonimida y 1,35 ml de diisopropiletilamina se agitó en 10 ml de dioxano a temperatura ambiente bajo Ar durante una noche. Se añadió EtOAc y la mezcla se lavó con H_2O, dos veces con NH_4Cl acuoso y una vez con Na_2CO_3 acuoso. La solución de EtOAc se secó y se concentró a vacío hasta dar 3,63 g de un sólido amarillo. Una cromatografía rápida, eluyendo con acetona-éter de petróleo, proporcionó 1,05 g de éster 3-amino-2-carbamoil-tieno[2,3-b]piridino-4-ílico de ácido trifluorometanosulfónico en forma de un sólido amarillo.

Una solución de 20 mg de éster 3-amino-2-carbamoil-tieno[2,3-b]piridin-4-ílico de ácido trifluorometanosulfónico y 27 microlitros de anilina en 1 ml de THF se calentó a 55°C durante una noche bajo Ar. La reacción se aplicó a una placa preparativa de gel de sílice de 2 mm que se desarrolló dos veces con 5% de MeOH-CH_2Cl_2. La banda se eluyó con 5% de MeOH-CH_2Cl_2 para proporcionar 18 mg. Estos se disolvieron en 5% de MeOH-CH_2Cl_2, se filtraron, se concentraron y se secaron a vacío a 60°C durante una noche para proporcionar 10,5 mg del compuesto del título en forma de un sólido amarillo-verde.

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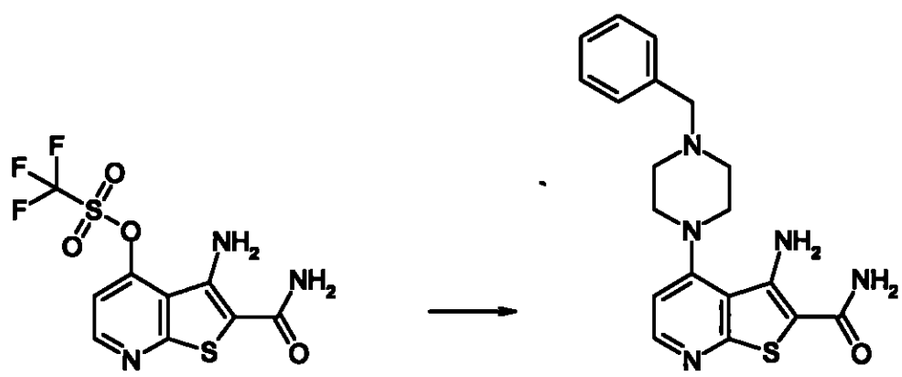
Ejemplo 20: Síntesis de amida de ácido 3-amino-4-(4-nitro-fenilamino)-tieno[2,3-b]piridin-2-carboxílico



20

Una solución de 20 mg de éster 3-amino-4-carbamoil-tieno[2,3-b]piridin-4-ílico de ácido trifluorometanosulfónico (véase el Ejemplo 19) y 40,5 mg de 4-nitroanilina en 1 ml de dioxano seco se calentó a 95°C durante una noche bajo N_2. La reacción se concentró y se aplicó a una placa preparativa de gel de sílice de 2 mm que se desarrolló dos veces con 7,5% de MeOH-CH_2Cl_2. La banda se eluyó con 20% de MeOH-CH_2Cl_2, se concentró a vacío, se volvió a disolver en 5% de MeOH-CH_2Cl_2, se filtró, se concentró y se secó a vacío a 60°C durante una noche para proporcionar 2,2 mg del compuesto del título en forma de un sólido color naranja.

Ejemplo 21: Síntesis de amida de ácido 3-amino-4-(4-bencil-piperazin-1-il)-tieno[2,3-b]piridin-2-carboxílico



21

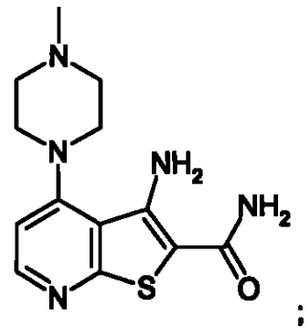
Una mezcla de 20 mg de éster 3-amino-2-carbamoil-tieno[2,3-b]piridin-4-ílico de ácido trifluorometanosulfónico y 50 microlitros de N-bencilpiperazina en 1 ml de dioxano seco se purgó con N_2 y se tapó y dejó a temperatura ambiente durante una noche. La reacción se diluyó con EtOAc, se lavó cuatro veces con agua, se secó y se concentró hasta sequedad a vacío. El producto se purificó en una placa preparativa de gel de sílice de 2 mm, desarrollando y eluyendo la banda con mezclas de MeOH-CH_2Cl_2 y concentrando seguidamente hasta sequedad. El producto se volvió a disolver en 5-10% de MeOH-CH_2Cl_2, se filtró para separar gel de sílice, se concentró y se secó a vacío a 60°C durante una noche para proporcionar

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7,9 mg del compuesto del título en forma de un sólido color beige.

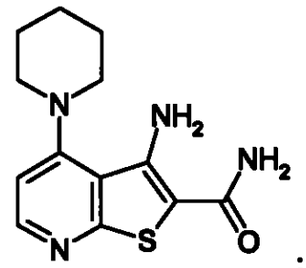
Los siguientes compuestos se prepararon usando el mismo procedimiento descrito en el ejemplo anterior. Si la amina secundaria intermedia era un sólido, se usaron 50 equivalentes molares en lugar de 50 microlitros. En algunos casos, si el producto se creía que tenía una solubilidad apreciable en agua, la mezcla de reacción se concentró sin extracción y el residuo se purificó por TLC preparativa como anteriormente. Se apreciaron otras ligeras modificaciones para compuestos particulares.

Amida de ácido 3-amino-4-(4-metil-piperazin-1-il)-tieno[2,3-b]piridin-2-carboxílico



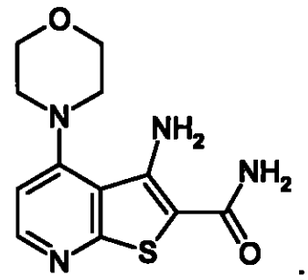
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Amida de ácido 3-amino-4-piperidin-1-il-tieno[2,3-b]piridin-2-carboxílico



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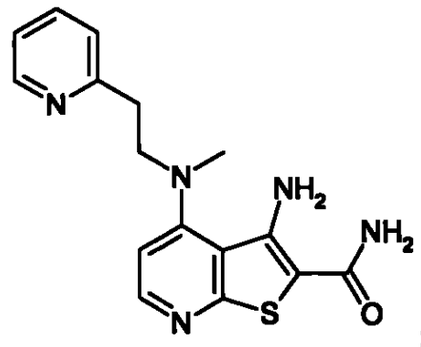
Amida de ácido 3-amino-4-morfolin-4-il-tieno[2,3-b]piridin-2-carboxílico



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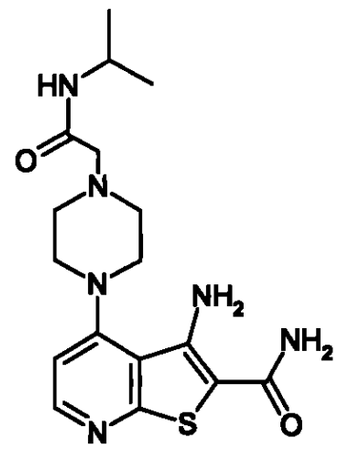
Amida de ácido 3-amino-4-[metil-(2-piridin-2-il-etil)-amino]-tieno[2,3-b]piridin-2-carboxílico

289



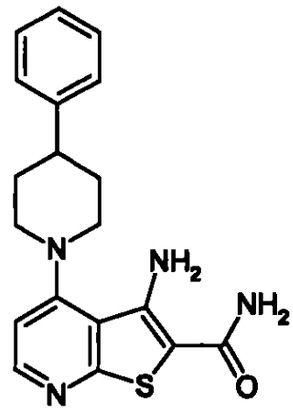
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Amida de ácido 3-amino-4-[4-(isopropilcarbamoil-metil)-piperazin-1-il]-tieno[2,3-b]piridin-2-carboxílico



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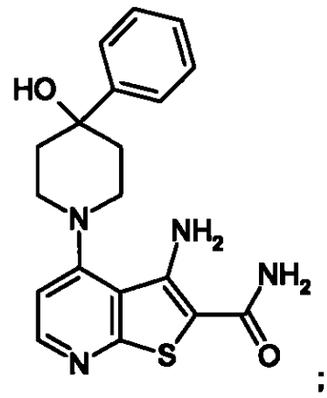
Amida de ácido 3-amino-4-(4-fenil-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico



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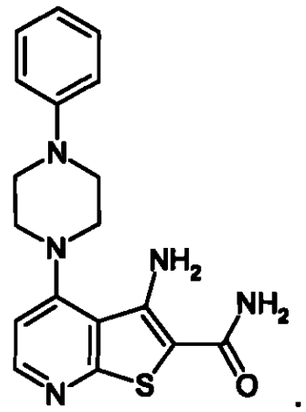
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Amida de ácido 3-amino-4-(4-hidroxi-4-fenil-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico



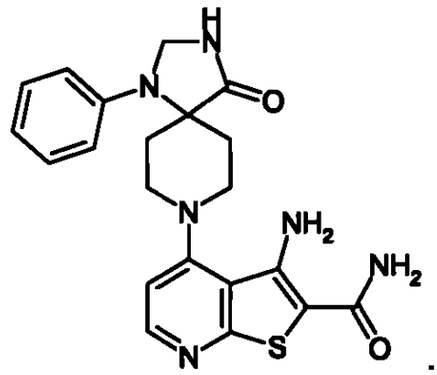
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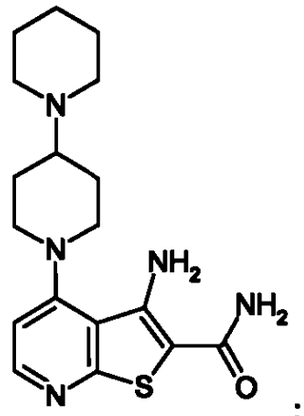
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Amida de ácido 3-amino-4-(4-oxo-1-fenil-1,3,8-triaza-spiro[4.5]dec-8-il)-tieno[2,3-b]piridin-2-carboxílico



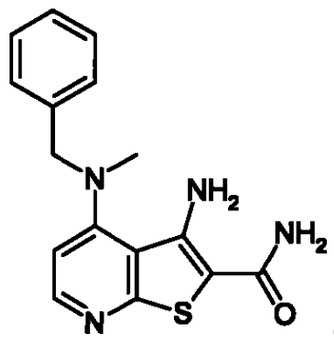
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Amida de ácido 3-amino-4-[1,4']bipiperidinil-1'-il-tieno[2,3-b]piridin-2-carboxílico



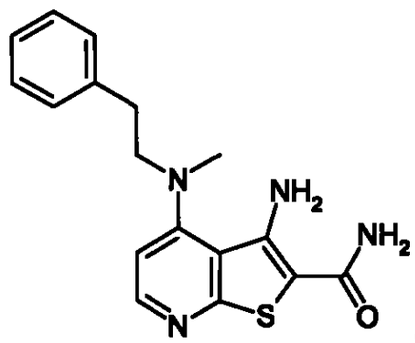
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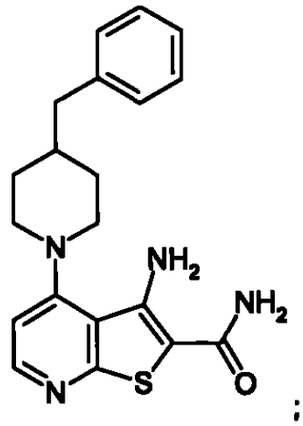
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Amida de ácido 3-amino-4-(metil-fenetil-amino)-tieno[2,3-b]piridin-2-carboxílico



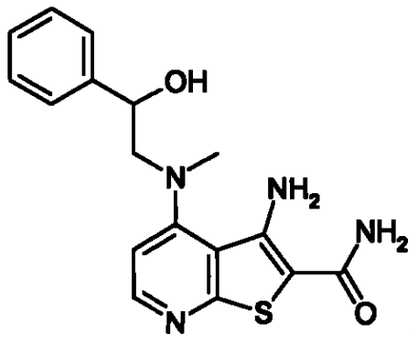
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Amida de ácido 3-amino-4-(4-bencil-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico



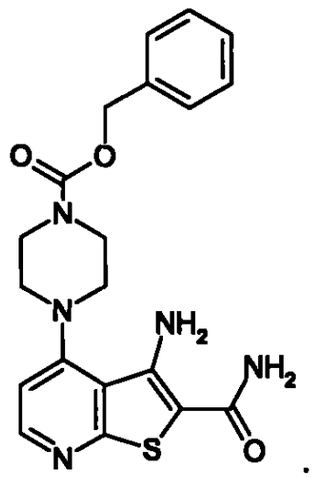
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Amida de ácido 3-amino-4-[(2-hidroxi-2-fenil-etil)-metil-amino]-tieno[2,3-b]piridin-2-carboxílico



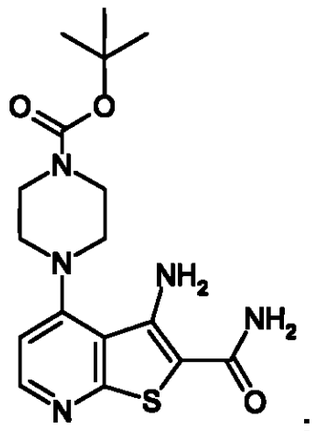
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Éster bencílico de ácido 4-(3-amino-2-carbamoil-tieno[2,3-b]piridin-4-il)-piperazin-1-carboxílico



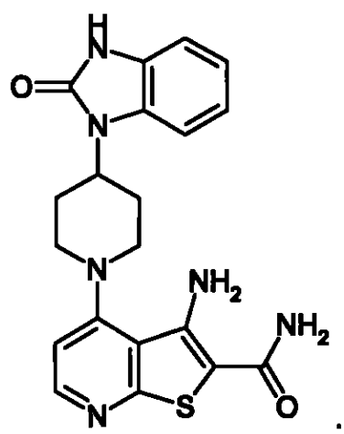
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Éster terc-butílico de ácido 4-(3-amino-2-carbamoil-tieno[2,3-b]piridin-4-il)-piperazin-1-carboxílico



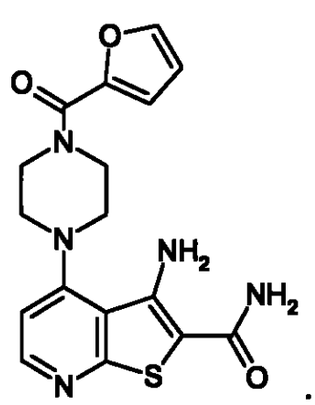
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Amida de ácido 3-amino-4-[4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-il]-tieno[2,3-b]piridin-2-carboxílico



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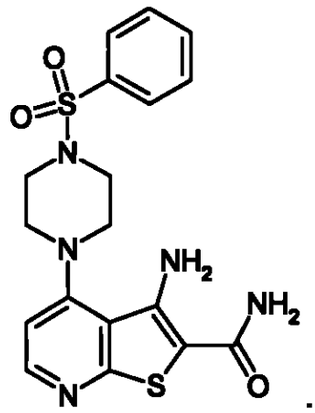
Amida de ácido 3-amino-4-[4-(furan-2-carbonil)-piperazin-1-il]-tieno[2,3-b]piridin-2-carboxílico



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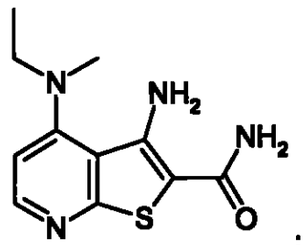
299

Amida de ácido 3-amino-4-(4-bencenosulfonil-piperazin-1-il)-tieno[2,3-b]piridin-2-carboxílico



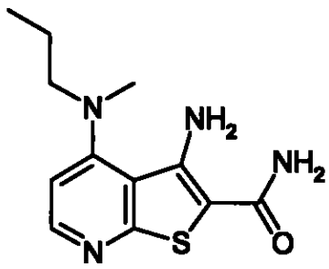
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Amida de ácido 3-amino-4-(etil-metil-amino)-tieno[2,3-b]piridin-2-carboxílico



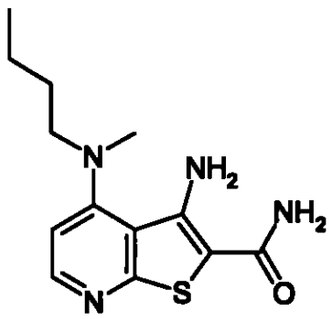
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Amida de ácido 3-amino-4-(metil-propil-amino)-tieno[2,3-b]piridin-2-carboxílico



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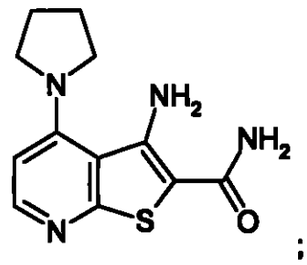
Amida de ácido 3-amino-4-(butil-metil-amino)-tieno[2,3-b]piridin-2-carboxílico



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Amida de ácido 3-amino-4-pirrolidin-1-il-tieno[2,3-b]piridin-2-carboxílico

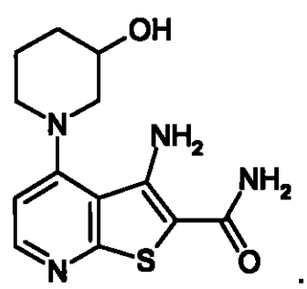
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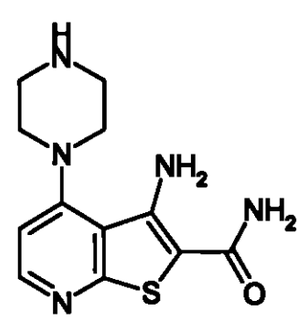
Amida de ácido 3-amino-4-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico

Este producto se purificó después de la placa preparativa por HPLC en una columna C8 eluyendo con 75% de H_2O-25% de acetonitrilo.



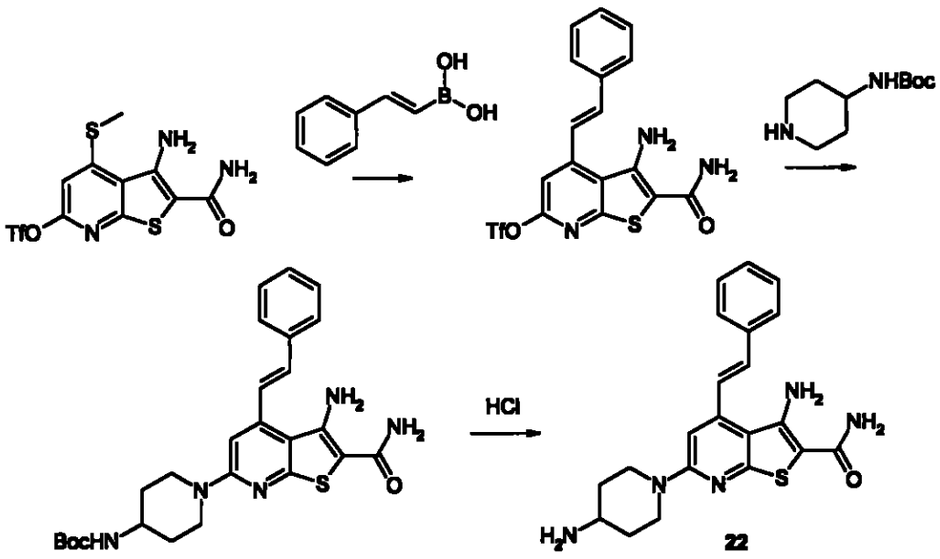
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Amida de ácido 3-amino-4-piperazin-1-il-tieno[2,3-b]piridin-2-carboxílico



Una solución de 18 mg de éster terc-butílico de ácido 4-(3-amino-2-carbamoil-tieno[2,3-b]piridin-4-il)-piperazin-1-carboxílico en 1 ml de CH_2Cl_2 + 1 ml de ácido trifluoroacético se agitó con un tubo de secado durante 4 h a temperatura ambiente. La reacción se concentró a vacío y se desarrolló en una placa preparativa en 25% de MeOH-CH_2Cl_2-2% de NH_4OH y la banda se eluyó con 50% de MeOH-CH_2Cl_2 para proporcionar un aceite que se volvió a disolver en 10% de MeOH-CH_2Cl_2, se filtró, se concentró y se secó a vacío a 60°C para proporcionar 4,6 mg del producto en forma de un sólido amarillo.

Ejemplo 22: Síntesis de amida de ácido 3-amino-6-(4-amin -piperidin-1-il)-4-((E)-estiril)-tieno[2,3-b]piridin-2-carboxílico



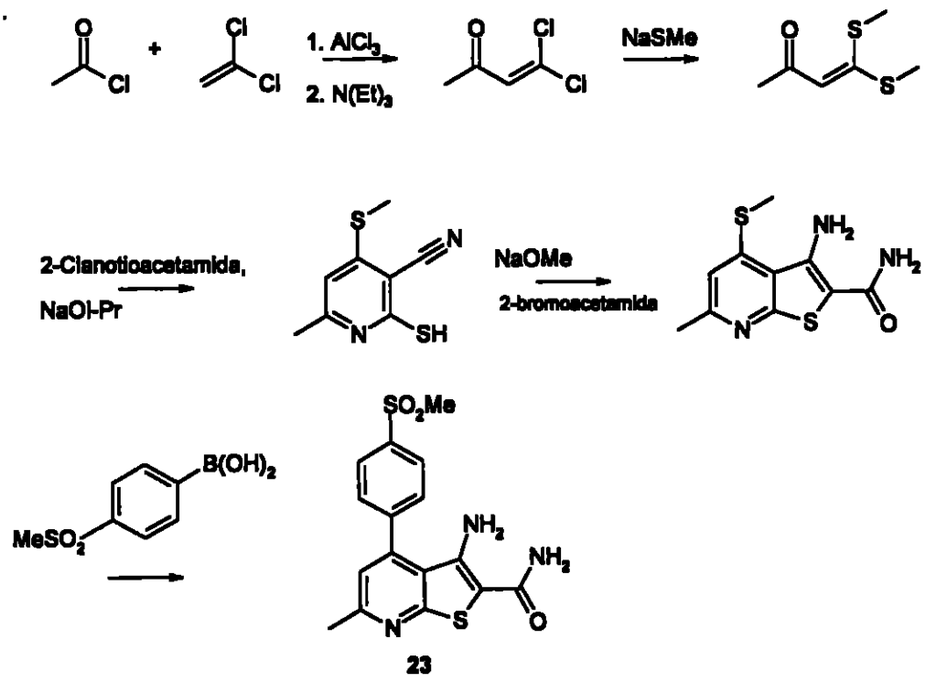
Se añadieron 30 ml de THF seco a un matraz sellable y se hizo burbuajer una corriente de Ar a través del disolvente durante 5 minutos. Se añadieron aducto de tris(dibencilidenoacetona)dipaladio (0)-cloroformo (76,1 mg, 73,5 µmol), tris-2-furilfosfina (121,9 mg, 0,5 mmol), tiofeno-2-carboxilato de cobre (1) (541,2 mg, 2,7 mmol), ácido trans-2-fenilvinilborónico (621,4 mg, 4,2 mmol) y amida de ácido 3-amino-4-metiltio-6-trifluorometilsulfonil-tieno[2,3-b]piridin-2-carboxílico (800,0 mg, 2,1 mmol) y el matraz sellado se calentó a 40°C durante 20 h. La solución se diluyó con CH_2Cl_2 y la fase orgánica se extrajo con solución saturada de $NaHCO_3$. La fase acuosa se extrajo dos veces con CH_2Cl_2 y las fases orgánicas combinadas se lavaron con salmuera. La solución se secó sobre $MgSO_4$, se filtró y se evaporó. El residuo se cromatografió sobre gel de sílice usando un gradiente (0-2,5% de MeOH/CH_2Cl_2 durante 50 minutos). Las fracciones que contenían el producto se combinaron, se evaporaron y se purificaron por TLC preparativa (10% de acetona/éter) para producir 415 mg (45%) del intermedio de 4-(E)-estirilo.

El intermedio anterior se disolvió en dioxano (20 ml), se añadió 4-N-Boc-aminopiperidina (382,6 mg, 1,9 mmol) y la mezcla se agitó durante 8 h a 100°C. La solución se enfrió a temperatura ambiente y se añadió solución saturada de NH_4Cl. La fase acuosa se extrajo con acetato de etilo y las fases orgánicas combinadas se secaron sobre $MgSO_4$. El compuesto se purificó adicionalmente por TLC preparativa (5% de MeOH/CH_2Cl_2) para producir 220 mg (48%) de producto.

El carbamato anterior se disolvió en dioxano (10 ml) y se añadió una solución 4 N de HCl-dioxano (5 ml). La suspensión se agitó durante 3 h después de lo cual se evaporó el disolvente. El residuo se purificó por TLC preparativa (10% de NH_4 4 N en MeOH/90% de CH_2Cl_2) para producir 115 mg (65%) del compuesto del

título.

Ejemplo 23: Síntesis de amida de ácido 3-amino-4-(4-metanosulfonil-fenil)-6-metil-tieno[2,3-b]piridin-2-carboxílico



Se puso en suspensión cloruro de aluminio (4,1 g, 32 mmol) en cloruro de metileno (5 ml) y se añadió gota a gota cloruro de acetilo (2,44 ml, 34 mmol) durante 30 minutos, mientras la temperatura interna se mantenía por debajo de 30°C. Se continuó la agitación durante 15 minutos, después de lo cual se añadió cloruro de vinilideno durante 10 minutos a 30°C. Después de agitar durante otros 90 minutos a temperatura ambiente la mezcla se vertió sobre hielo triturado. La mezcla se agitó durante 20 minutos y la fase acuosa se extrajo dos veces con cloruro de metileno. Las fases orgánicas combinadas se lavaron con agua. La solución de cloruro de metileno se enfrió seguidamente a 0°C y se añadió trietilamina (4,21 ml, 30 mmol) mientras se agitaba la solución. Después de 30 minutos se añadió HCl al 10% y la fase orgánica se lavó con HCl al 5%, agua y salmuera. Los componentes volátiles se evaporaron y el residuo se destiló sobre un aparato de destilación de trayectoria pequeña para producir 3,28 g (78%) de la diclorovinil-cetona deseada.

Se puso en suspensión tiometóxido de sodio (1,40 g, 20 mmol) en éter (20 ml) y se añadió gota a gota la diclorovinil-cetona anterior (10 mmol) disuelta en éter (10 ml). La solución resultante se llevó a reflujo durante 1 h, se filtró y el precipitado se lavó con agua. Los filtrados combinados se evaporaron para producir 1,4 g (87%) de la dimetiltiovinil-cetona deseada.

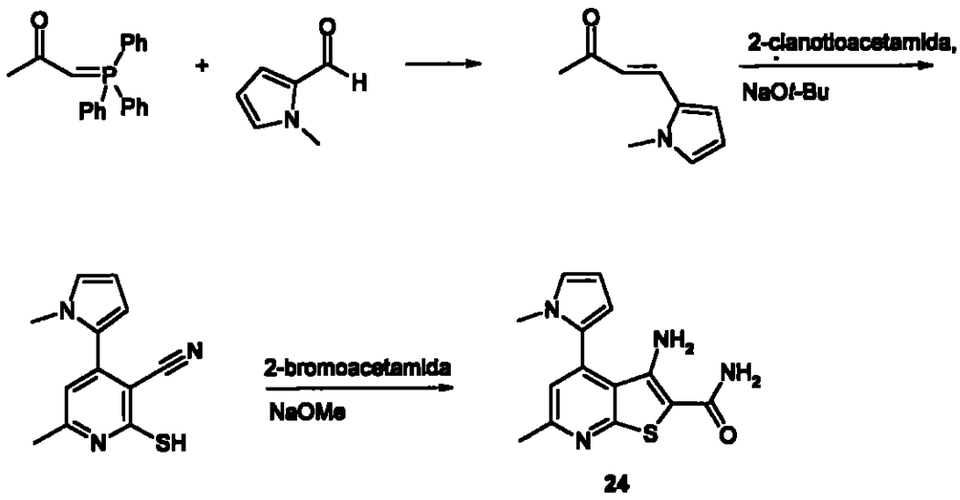
Se disolvió sodio (533 mg, 23,2 mmol) en isopropanol (50 ml) bajo calenta-

miento. Se añadió 2-cianotioacetamida (2,1 g, 21 mmol) y la solución se agitó durante 5 minutos a temperatura ambiente. Se añadió la dimetiltiovinil-cetona anterior (3,4 g, 21 mmol) a la mezcla de reacción y la solución se llevó a reflujo hasta que el material de partida desapareció (~ 30 h). El disolvente se evaporó y el residuo se disolvió en agua. La solución acuosa se filtró, se acidificó a pH 3 y el precipitado se separó por filtrción. El precipitado se lavó con éter y seguidamente con hexano para proporcionar 3,9 g (95%) de la tiopiridina deseada.

Se disolvió metóxido de sodio (2,16 g, 40 mmol) en MeOH (60 ml) y se añadió la tiopiridina anterior (3,9 g, 20 mmol). Después de 5 minutos se añadió 2-bromoacetamida (2,76 g, 20 mmol) y la solución se llevó a reflujo durante 2 h. El MeOH se evaporó parcialmente y el residuo se diluyó con solución acuosa de bicarbonato de sodio. La fase acuosa se extrajo varias veces con 10% de MeOH/cloruro de metileno y los extractos combinados se secaron sobre sulfato de magnesio. El disolvente se evaporó y el residuo se purificó por cromatografía de columna sobre gel de sílice para proporcionar 2,1 g (41%) del intermedio de tieno[2,3-b]piridina deseado.

Se añadió THF seco (3 ml) a un tubo sellable y se hizo burbujear una corriente de Ar a través del disolvente durante 5 minutos. Se añadieron el ácido 4-metanosulfonilfenilborónico anterior (48 mg, 0,24 mmol), aducto de tris(dibencilidenoacetona)dipaladio(0)-cloroformo (4 mg, 4 µmol), tri-2-furilfosfina (7,5 mg, 32 µmol) y tiofeno-2-carboxilato de cobre (I) (50 mg, 0,26 mmol). El tubo se selló y seguidamente se calentó a 65°C durante 24 h. La solución se diluyó con CH_2Cl_2 y la fase orgánica se extrajo con solución acuosa de bicarbonato de sodio. La fase acuosa se extrajo dos veces con CH_2Cl_2 y las fases orgánicas combinadas se lavaron con salmuera. La solución se secó sobre $MgSO_4$, se filtró y se evaporó. El residuo se purificó por cromatografía de columna. Todas las fracciones que contenían el producto se combinaron, se evaporaron y se volvieron a purificar por TLC preparativa para proporcionar 23 mg (32%) del compuesto del título.

Ejemplo 24: Síntesis de amida de ácido 3-amino-6-metil-4-(1-metil-1H-pirrol-2-il)-tieno[2,3-b]piridin-2-carboxílico



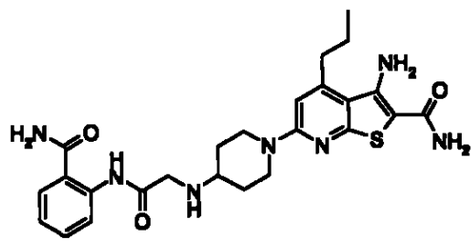
24

Se disolvió 1-metil-2-pirrolocarboxaldehído (500 mg, 4,58 mmol) en 10 ml de tolueno y seguidamente se añadió 1-trifenilfosforanilideno-2-propanona (1,53 g, 4,81 mmol) y 10 gotas de ácido acético. La mezcla de reacción se calentó a 120°C en un tubo sellado durante 16 h. La mezcla de reacción se enfrió a temperatura ambiente y el disolvente se evaporó. El residuo se disolvió en EtOAc y la fase orgánica se lavó con solución saturada de $NaHCO_3$ y salmuera. La fase orgánica se secó sobre Na_2SO_4 anhidro, se filtró y se concentró. El residuo se purificó por cromatografía de columna sobre gel de sílice para producir 565 mg (82,7%) de la vinil-cetona.

A un tubo sellado se añadió 2-cianotioacetamida (70,6 mg, 0,71 mmol) y t-butóxido de sodio (71 mg, 0,74 mmol) en 2-propanol (4 ml). La mezcla se agitó a temperatura ambiente durante 5 minutos y seguidamente se añadió la vinil-cetona anterior (100 mg, 0,67 mmol). La mezcla se calentó a 80°C durante 16 h. La solución se concentró y el residuo se disolvió en agua. Se añadió HCl diluido para ajustar el pH a 6. El sólido que se formó durante la acidificación se filtró y se lavó con agua. El sólido se secó bajo alto vacío para proporcionar 70 mg (45,5%) del intermedio de tiopiridina deseado.

El intermedio de tiopiridina anterior (70 mg, 0,31 mmol) se puso en suspensión en 2 ml de MeOH y seguidamente se añadieron 2-bromoacetamida (42 mg, 0,3 mmol) y 1,22 ml de solución 0,5 N de metóxido de sodio en MeOH. La mezcla se calentó en un tubo sellado a 70°C durante 2 h. La mezcla de reacción se concentró y el residuo se purificó por cromatografía de columna sobre gel de sílice para producir 36 mg (41%) del compuesto del título.

Ejemplo 25: Síntesis de amida de ácido 3-amino-6-(4-{[(2-carbamoil-fenilcarbamoil)-metil]-amino}-piperidin-1-il)-4-propil-tieno[2,3-*b*]piridin-2-carboxílico

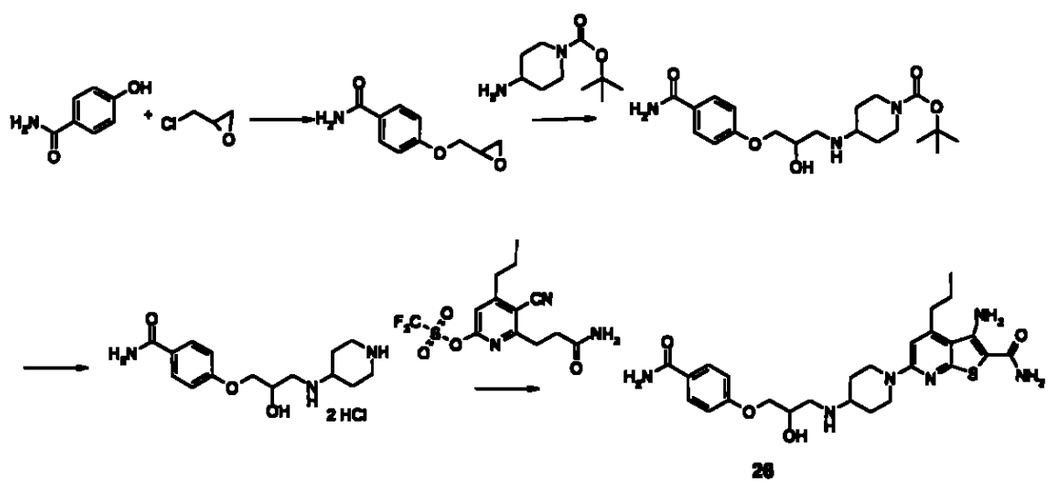


25

A una solución de 2-aminobenzamida (2,00 g, 14,4 mmol) y trietilamina (2,4 ml, 17 mmol) en dioxano seco (20 ml) se añadió bromuro de bromoacetilo (1,33 ml, 15,0 mmol). Esta mezcla de reacción se agitó a temperatura ambiente durante 1 h y seguidamente se vertió en agua. El sólido resultante se recogió por filtración y se recristalizó en MeOH para proporcionar el intermedio de diamida en forma de un sólido marrón (2,02 g).

El intermedio anterior (70 mg, 0,21 mmol) y la amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico (65 mg, 0,25 mmol), junto con trietilamina (0,05 ml, 0,36 mmol) se agitaron en 1 ml de DMF durante 2 h. El disolvente se separó a vacío. El residuo se trituró con agua. El sólido resultante se recogió por filtración y se recristalizó en acetonitrilo para proporcionar el compuesto del título (37 mg) en forma de un sólido color pálido.

Ejemplo 26: Síntesis de amida de ácido 3-amino-6-{4-[3-(4-carbamoil-fenoxi)-2-hidroxi-propilamino]-piperidin-1-il}-4-propil-tieno[2,3-*b*]piridin-2-carboxílico



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A un tubo sellado se añadieron 4-hidroxibenzamida (200 mg, 1,458 mmol), epiclorhidrina (135 mg, 1,458 mmol) y carbonato de potasio (403 mg, 2,916 mmol)

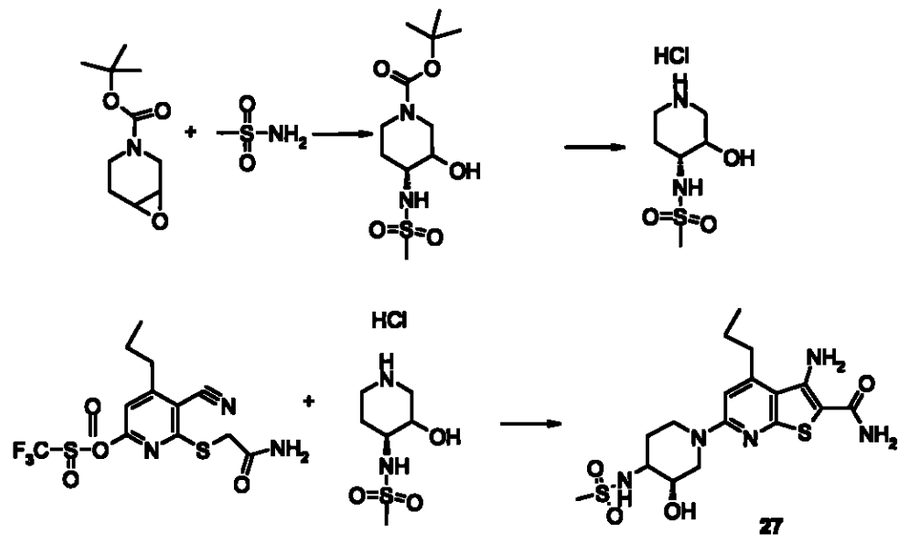
en 7 ml de DMF seca. La mezcla de reacción se agitó a 70°C durante 18 h. La mezcla de reacción se filtró y se concentró. El residuo se purificó por cromatografía rápida, eluyendo con 0-5% de NH_3 2 M en $MeOH/CH_2Cl_2$. Las fracciones de producto se recogieron ys e concentraron para suministrar 80 mg de 4-oxiranilmetoxi-benzamida en forma de un sólido blanco.

Se disolvió 4-oxiranilmetoxi-benzamida (76 mg, 0,393 mmol) en 8 ml de DMF seca y seguidamente se añadió 4-amino-1-N-Boc-piperidina (178 mg, 0,889 mmol). La mezcla de reacción se agitó a 80°C durante 48 h. La mezcla de reacción se concentró y el residuo se purificó por cromatografía rápida eluyendo con 0-5% de NH_3 2 M en $MeOH/CH_2Cl_2$. Las fracciones de producto se recogieron y se concentraron para proporcionar 62 mg de éster terc-butílico de ácido 4-[3-(4-carbamoil-fenoxi)-2-hidroxi-propilamino]-piperidin-1-carboxílico en forma de un aceite incoloro.

A un matraz de fondo redondo se añadió el éster anterior (62 mg, 0,158 mmol) en 5 ml de HCl 4,0 M en 1,4-dioxano y 2 ml de MeOH. La mezcla de reacción se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró por medio de una bomba de alto vacío para proporcionar 57 mg de la sal de cloruro de hidrógeno de 4-[2-hidroxi-3-(piperidin-4-ilamino)-propoxi]-benzamida, en forma de un producto sólido vítreo color blanco.

A un tubo sellado se añadió éster 6-(2-carbamoil-etil)-5-ciano-4-propil-piridin-2-ílico de ácido trifluoro-metanosulfónico (54,2 mg, 0,141 mmol) en 5 ml de DMF seca y seguidamente se añadió la sal de hidrocloruro anterior (57 mg, 0,156 mmol) y N,N-diisopropiletilamina (91,4 mg, 0,707 mmol). La mezcla de reacción se agitó a 70°C durante 2 h. La reacción se concentró y al residuo se añadió metóxido de sodio, solución 0,5 M en MeOH (1,41 ml, 0,707 mmol) y 2 ml de MeOH. La mezcla de reacción se calentó a 70°C durante 4 h. La mezcla de reacción se concentró y el residuo se purificó por cromatografía rápida eluyendo con 0-10% de NH_3 2 M en $MeOH/CH_2Cl_2$. Las fracciones de producto se recogieron y se concentraron para proporcionar 42 mg (56,4%) del compuesto del título en forma de un sólido cristalino color amarillo luminoso.

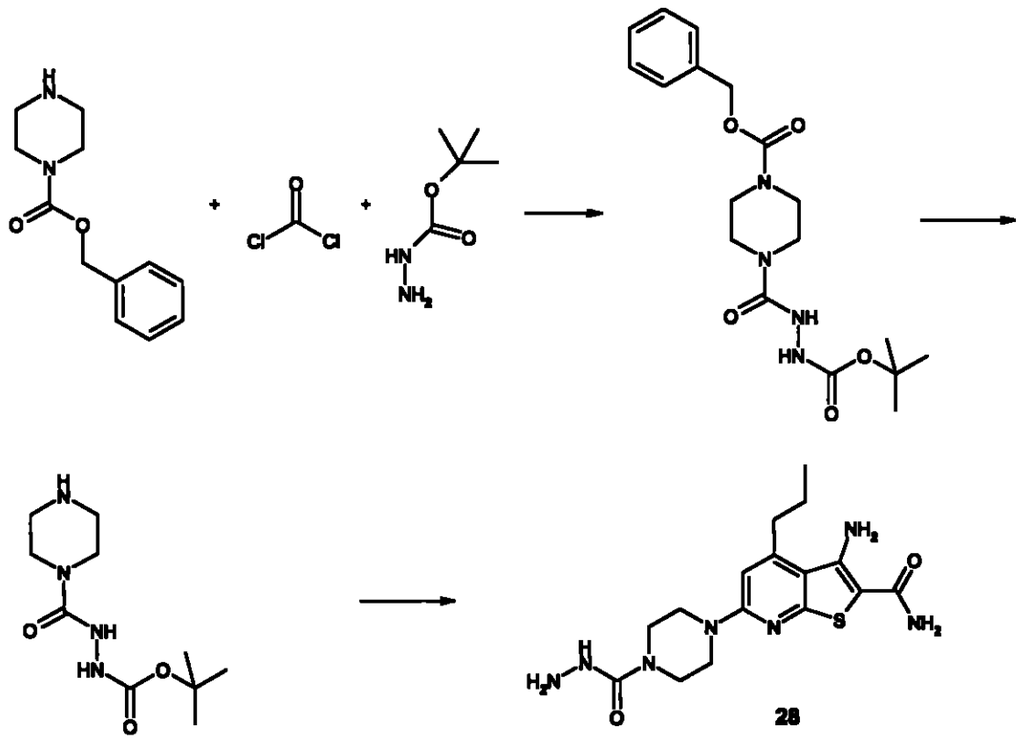
Ejemplo 27: Síntesis de amida de ácido 3-amino-6-((S)-3-hidroxi-4-metanosulfonilamino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico



Una mezcla de éster terc-butílico de ácido 7-oxa-3-aza-biciclo[4.1.0]heptane-3-carboxílico (830 mg, 4,2 mmol), metilsulfonamida (1,2 g, 12,5 mmol), carbonato de potasio (829 mg, 12,5 mmol), sulfato de magnesio (1,5 g, 12,5 mmol) en MeOH (15 ml) se calentó bajo Ar en un tubo a presión a 90ºC durante una noche. La mezcla se enfrió seguidamente a temperatura ambiente, se diluyó con CH_2Cl_2 (10 ml), se filtró a través de tierra de diatomeas y se concentró. El producto en bruto se purificó adicionalmente por cromatografía de columna sobre gel de sílice eluyendo con EtOAc como eluyente para proporcionar 504 mg del intermedio de hidroxipiperidina deseado.

El intermedio anterior (118 mg, 0,4 mmol) se disolvió en MeOH (1 ml). A esta solución se añadió HCl 4 M (0,2 ml en dioxano) gota a gota. La mezcla se agitó a temperatura ambiente durante una noche y se concentró. El producto así obtenido se disolvió en dioxano, se basificó con 300 microlitros de trietilamina y se hizo reaccionar con 144 mg (0,376 mmol) de 2-(3-ciano-4-*n*-propilo -6-trifluorometanosulfonilpiridin-2-ilmercapto)acetamida, mediante el procedimiento descrito en el Ejemplo 26, para proporcionar 73 mg del compuesto del título.

Ejemplo 28: Síntesis de amida de ácido 3-amino-6-(4-hidrazinocarbonil-piperazin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico



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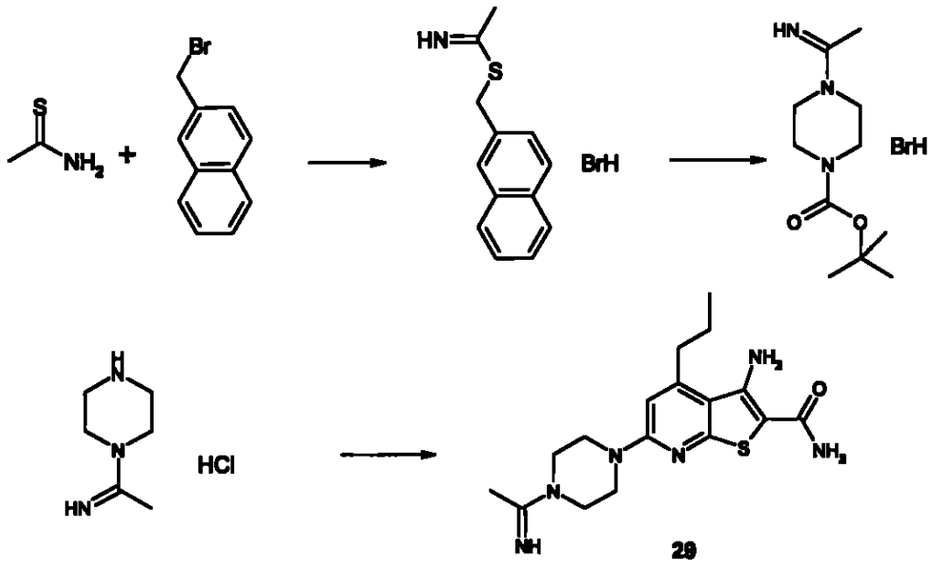
A una solución de fosgeno (solución al 20% en tolueno) a 0°C se añadió éster bencílico de ácido piperazino-1-carboxílico (0,385 ml, 1,996 mmol) y diisopropiletil-amina (0,383 ml, 4,397 mmol) en 5 ml de CH_2Cl_2 gota a gota. La mezcla amarilla pálida resultante se agitó 2 h calentando a temperatura ambiente bajo Ar. La solución de fosgeno se separó por destilación a vacío. Se añadieron 20 ml de CH_2Cl_2 anhidro. El recipiente de la reacción se enfrió a 0°C y se añadieron en una porción éster terc-butílico de ácido hidrazinocarboxílico y diisopropiletil-amina (0,383 ml, 4,397 mmol). La reacción se calentó a temperatura ambiente y se agitó durante 1 h. La reacción se inactivó con 10 ml de $NaHCO_3$ saturado, se diluyó con 30 ml de EtOAc y seguidamente se lavó con 2 x 30 ml de solución saturada de NH_4Cl y 30 ml de salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró para proporcionar 720 mg de éster bencílico de ácido 4-(*N-terc*-butoxicarbonil-hidrazinocarbonil)-piperazin-1-carboxílico en forma de un sólido blanco.

El éster bencílico anterior (720 mg, 1,913 mmol) se disolvió en 10 ml de EtOH y se colocó en un matraz de fondo redondo. Se añadió 10% de Pd/C (300 mg) y la reacción se colocó bajo 1 atm de H_2 en un balón. La reacción se dejó agitar durante una noche y sguidamente se filtró a través de un cartucho de tierra de diatomeas y se concentró para proporcionar 465 mg de 4-(N-terc-butoxicarbonil-

hidrazinocarbonil)-piperazina en forma de un sólido blanco pálido.

Se preparó éster terc-butílico de ácido *N'*-[4-(3-Amino-2-carbamoil-4-propil-tieno[2,3-*b*]piridin-6-il)-piperazin-1-carbonil]-hidrazinacarboxílico a partir del intermedio anterior como se describió en el Ejemplo 26. La separación del grupo protector t-Boc mediante disolución en EtOAc/CH_2Cl_2 y tratamiento en HCl 4 N en dioxano proporcionó el compuesto del título.

Ejemplo 29: Síntesis de amida de ácido 3-amino-6-[4-(1-imino-etil)-piperazin-1-il]-4-propil-tieno[2,3-*b*]piridin-2-carboxílico



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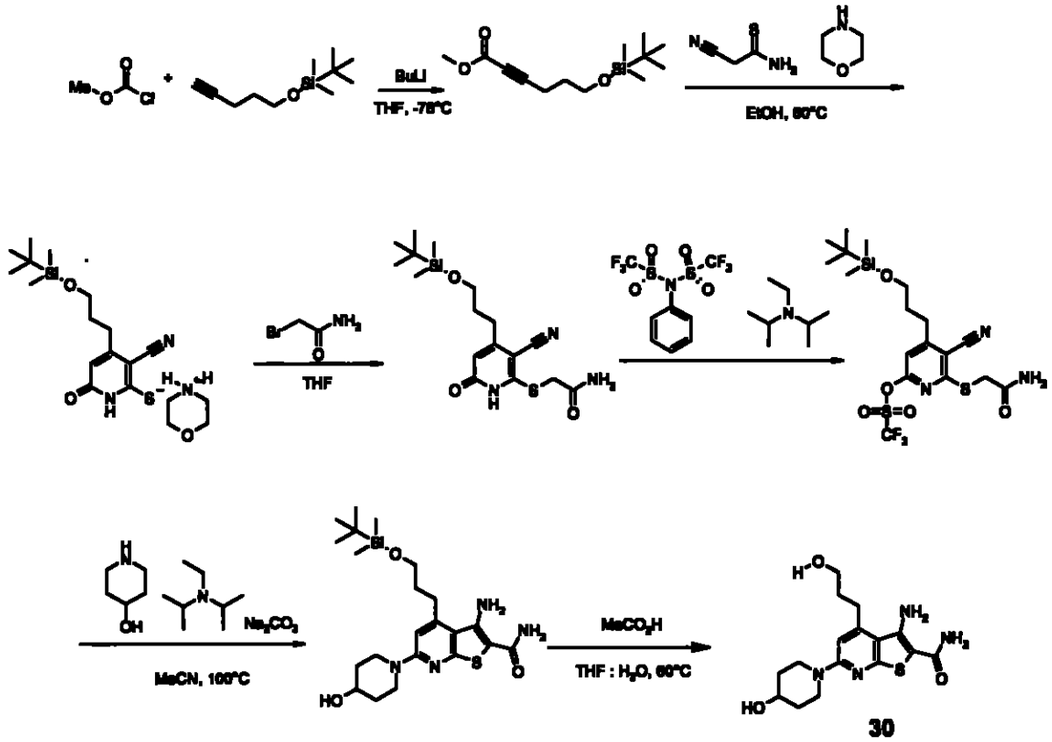
Se colocaron tioacetamida (326,0 mg, 4,339 mmol) y 2-bromometil-naftaleno (959,0 mg, 4,337 mmol) en un matraz de fondo redondo de 50 ml. Se añadieron 20 ml de $CHCl_3$ y la mezcla se llevó a reflujo durante 3 h, momento en el que se formó un precipitado blanco. La mezcla se enfrió y el precipitado se recogió. El precipitado se lavó con 20 ml de CH_2Cl_2 y se colocó bajo vacío para secar y producir 1,01 g de sal de hidrocromuro de éster naftaleno-2-ilmetílico de ácido tioacetimídico en forma de un polvo blanco fino.

La sal de hidrobromuro anterior (850,0 mg, 2,869 mmol) se colocó en un matraz de fondo redondo de 25 ml. A este se añadieron 10 ml de EtOH dando lugar a una suspensión. El matraz se colocó en un baño con hielo y se añadió en una porción éster terc-butílico de ácido piperazino-1-carboxílico (534,4 mg, 2,869 mmol). La reacción se dejó calentar a temperatura ambiente y se agitó 3 h adicionales. La solución heterogénea se diluyó con 40 ml de EtOAc y se lavó con 2 x 30 ml de H_2O. La fase acuosa se concentró casi hasta sequedad, se sometió a destilación azeotrópica con 2 x 20 ml de tolueno para proporcionar un sólido blanco. El sólido se puso en suspensión en CH_2Cl_2/hexano y se concentró hasta sequedad. El material se coloró bajo vacío durante una noche suministrando 769 mg de sal de hirobromuro de éster terc-butílico de ácido 4-(1-imino-etil)-piperazin-1-

carboxílico en forma de un sólido blanco.

El grupo protector t-Boc del intermedio anterior se separó como se describió en el Ejemplo 28 y el intermedio resultante se hizo reaccionar adicionalmente como se describió en el Ejemplo 26 para proporcionar el compuesto del título.

Ejemplo 30: Síntesis de amica de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-(3-hidroxi-propil)-tieno[2,3-b]piridin-2-carboxílico



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A una solución de 7,98 g (40,2 mmol) de t-butil-dimetil-pent-4-iniloxi-silano (J.A. Marshall y B.S. DeHoff, *J. Org. Chem.*, 1986, *51*, 863) en THF (100 ml) enfriada a -78°C se añadió una solución de n-butil-litio en hexanos (28,0 ml de una solución 1,6 M). La mezcla se agitó a -78°C durante 1 h y seguidamente se transfirió, a través de una cánula, a un matraz que contenía una solución de 45 ml (58 mmol) de cloroformiato de metilo en YHF (100 ml) enfriada a -78°C. La reacción se agitó a -78°C durante 2 h y seguidamente la base en exceso se consumió mediante la adición de una solución acuosa saturada de NH_4Cl. La mezcla se diluyó con H_2O y se lavó con Et_2O. La fase orgánica combinada se secó sobre Na_2SO_4 anhidro y se concentró bajo presión reducida. El residuo en bruto se purificó por cromatografía de gel de sílice rápida usando una solución al 5% de EtOAc en hexanos como eluyente para proporcionar, después de concentrar el disolvente, 6,18 g (60%) del éster deseado en forma de un aceite transparente.

A una solución de 6,18 g (24,1 mmol) del éster anterior en EtOH (120 ml) se añadieron 2,2 ml (25 mmol) de morfolina. La mezcla se calentó a 60°C durante 3 h. La mezcla de reacción se enfrió a temperatura ambiente y se añadieron 2,5 g

(25 mmol) de 2-cianoacetamida en forma de un sólido en una porción. La mezcla de reacción se calentó seguidamente a 60°C durante 15 h y seguidamente se enfrió a temperatura ambiente y se concentró bajo presión reducida. El residuo se puso en suspensión en Et_2O y se lavó con H_2O. La fase acuosa combinada se volvió a extraer con Et_2O. La fase acuosa se liofilizó para proporcionar 3,5 g (30,8%) de sal de morfolina de 4-[3-(*t*-butil-dimetil-silaniloxi)-propil]-3-ciano-6-oxo-1,6-dihidro-piridin-2-tiolate; en forma de un polvo amarillo.

A una solución de 0,940 g (2,28 mmol) de la sal de morfolina anterior en THF (15 ml), enfriada a 0°C, se añadieron 0,315 g (0,280 mmol) de 2-bromoacetamida en forma de un sólido en una porción. La mezcla se agitó y se dejó calentar lentamente a temperatura ambiente durante un período de 2 h, tiempo durante el cual precipitaron sales de la solución. La mezcla se filtró a través de tierra de diatomeas para separar los sólidos y el cartucho de filtració nse lavó con EtOAc. La mezcla se concentró bajo presión reducida para proporcionar 0,385 g (44%) de 2-{4-[3-(*t*-butil-dimetil-silaniloxi)-propil]-3-ciano-6-oxo-1,6-dihidro-piridin-2-ilsulfanil}-acetamida en forma de una espuma naranja.

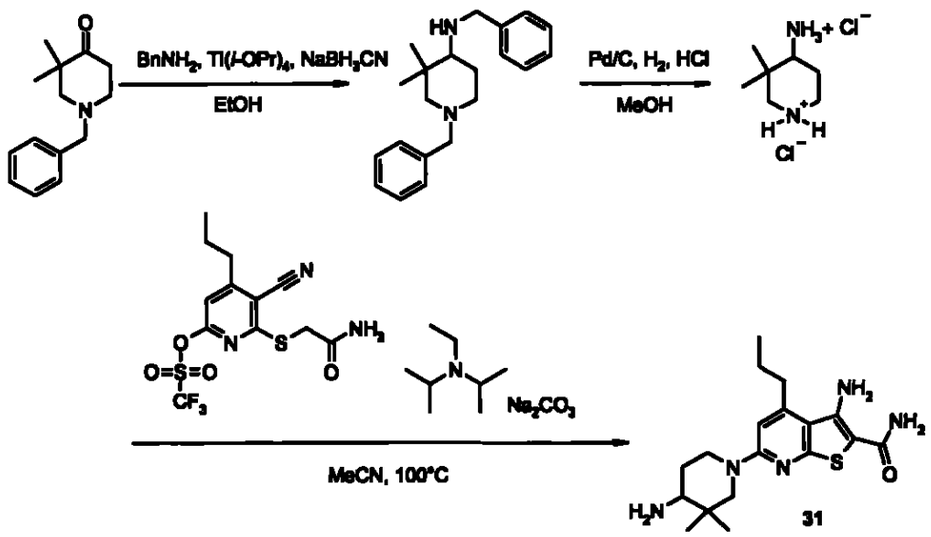
A una solución de 2,32 g (6,08 mmol) de la acetamida anterior en THF (25 ml), enfriada a 0°C, se añadieron 2,2 g (6,2 mmol) de N-feniltrifluorometanosulfonimida y 1,2 ml (6,7 mmol) de N,N-diisopropiletilamina. La mezcla se agitó durante 3 h a medida que se calentaba lentamente a temperatura ambiente. La mezcla se vertió en H_2O y se lavó con EtOAc. La fase orgánica combinada se secó sobre Na_2SO_4 anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía rápida sobre gel de sílice usando 0-50% de gradiente de A (MeOH al 10% en CH_2Cl_2) a B (CH_2Cl_2) para proporcionar, después de concentrar el eluyente, 0,832 g (26%) del éster de trifluorometanosulfonilo deseado en forma de un aceite color naranja.

A una solución de 0,832 g (1,62 mmol) del éster de trifluorometanosulfonilo anterior en 1,4-dioxano (30 ml) se añadieron 0,175 g (1,73 mmol) de 4-hidroxipiperidina y 0,32 ml (1,79 mmol) de N,N-diisopropiletilamina. La mezcla se calentó a 80°C durante 5 h. La reacción se enfrió a temperatura ambiente y se añadió una solución acuosa de Na_2CO_3 (8,0 ml de una solución 2,0 M). La mezcla se calentó a 100°C durante 3 días y seguidamente se enfrió a temperatura ambiente y se diluyó con H_2O. La mezcla se lavó con CH_2Cl_2 y la fase orgánica combinada se secó sobre Na_2SO_4 anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía rápida de gel de sílice usando un gradiente de 0-50% de A (MeOH al 10% en CH_2Cl_2) a B (CH_2Cl_2) para proporcionar, después de concentrar el eluyente, 0,232 g (31%) de amida de ácido 3-amino-4-[3-(*t*-butil-dimetil-silaniloxi)-propil]-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2-

carboxílico en forma de un polvo amarillo.

A una solución de 0,23 g (0,49 mmol) de la amida anterior en una mezcla 1:1 de THF:H_2O (1,0 ml) se añadieron 0,50 ml (8,7 mmol) de ácido acético glacial. La mezcla se calentó a 50°C durante 15 h y seguidamente se enfrió a temperatura ambiente y se concentró bajo presión reducida, lo que provocó que precipitara un sólido de la solución. El material se recogió por filtración y se lavó con H_2O y CH_2Cl_2 y seguidamente se secó bajo vacío para proporcionar 0,106 (61%) del compuesto del título en forma de un sólido blanco.

Ejemplo 31: Síntesis de amida de ácido 3-amino-6-(4-amino-3,3-dimetil-piperidin-1-il)-4-propil-tieno[2,3-*b*]piridin-2-carboxílico (5).



Una mezcla de 0,10 g (0,46 mol) de 1-bencil-3,3-dimetil-piperidin-4-ona, 0,055 ml (0,50 mmol) de bencil-amina y 0,19ml (0,64 mol) de isopropóxido de titanio se agitó a temperatura ambiente durante 1 h. La mezcla se diluyó con EtOH (1 ml) lo que provocó que la solución amarilla se volviera turbia. A la reacción se añadieron 0,031 g (0,49 mmol) de cianoborohidruro de sodio y la mezcla se agitó a temperatura ambiente durante 20 h. La mezla se diluyó con H_2O (1 ml) y seguidamente se filtró a través de tierra de diatomeas para separar los precipitados. El cartucho de filtración se lavó con MeOH y la mezcla se concentró bajo presión reducida. El residuo se purificó por cromatografía rápida sobre gel de sílice usando un gradiente de 0-40% de A (MeOH al 10% en CH_2Cl_2) a B (CH_2Cl_2) para proporcionar, después de concentrar el eluyente, 0,069 g (44%) de la bencil-amina deseada en forma de un aceite transparente.

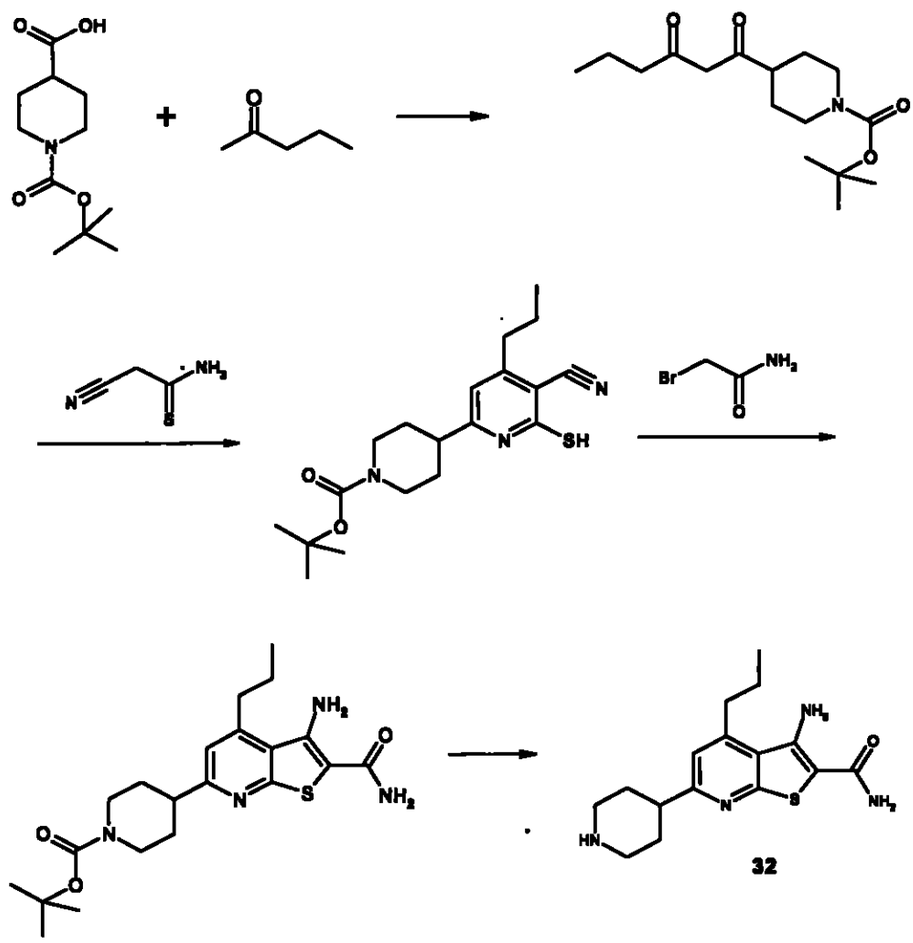
A una solución de 0,069 g (0,22 mmol) de la bencil-amina anterior en MeOH

(5 ml) colocada en un recipiente a presión de paredes gruesas se añadieron 0,049 g (0,046 mmol) de paladio sobre carbono y 0,050 ml (0,60 mmol) de HCl concentrado. La mezcla se colocó bajo una atmósfera de hidrógeno y se agitó durante 24 h. La mezcla se filtró a través de un cartucho de tierra de diatomeas y la torta de filtración se lavó con MeOH. La fase orgánica se concentró bajo presión reducida para proporcionar 0,041 g (91%) de la sal de di-HCl de 4-amino-3,3-dimetilpiperidina deseada en forma de un sólido blanco.

A una solución de 0,075 g (0,20 mmol) de éster 6-carbamoilmetilsulfanil-5-ciano-4-propil-piridin-2-ílico de ácido trifluorometanosulfónico en 1,4-dioxano (5 ml) se añadieron 0,041 g (0,20 mmol) de la sal de di-HCl anterior y 0,11 ml (0,61 mmol) de N,N-diisopropiletilamina. La mezcla se calentó a 60ºC durante 15 h y seguidamente se enfrió a temperatura ambiente y se añadió una solución acuosa de Na_2CO_3 (0,5 ml de una solución 2 M). La mezcla se calentó seguidamente a 100ºC durante 3 h y seguidamente se enfrió a temperatura ambiente, se diluyó con H_2O y se lavó con CH_2Cl_2. La fase orgánica combinada se secó sobre Na_2SO_4 anhidro y se concentró bajo presión reducida. El residuo en bruto se purificó por cromatografía rápida sobre gel de sílice usando un gradiente de 0-50ºC de A (10% de MeOH en CH_2Cl_2) a B (CH_2Cl_2) para proporcionar, después de concentrar el eluyente, 0,019 g (27%) del compuesto del título en forma de un sólido amarillo.

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Ejemplo 32: Síntesis de dihidrocloruro de amida de ácid 3-amino-6-piperidin-4-il-4-propil-3a,7a-dihidro-tieno[2,3-*b*]piridin-2-carboxílico



Se calentó a reflujo durante 3 h ácido 1-Boc-piperidino-4-carboxílico (4,4 g, 19,2 mmol) en cloruro de oxalilo (50 ml) y seguidamente se concentró y se secó a vacío para proporcionar el cloruro de ácido, éster-butílico de ácido 4-clorocarbonil-piperidino-1-carboxílico.

A una solución agitada de LDA (1,8 M en THF/heptano/etil-benceno, 21,3 ml, 38,4 mmol) en THF seco (50ml) a -50°C se añadió 2-pentanona (4,1 ml, 38,4 mmol) y después de 10 minutos se añadió una solución del cloruro de ácido anterior en THF seco (50 ml). La reacción se dejó calentar a temperatura ambiente y se agitó durante una noche. Se diluyó con HCl 1 N (500 ml), se extrajo con diclorometano, se lavó con bicarbonato de sodio saturado y salmuera, se secó sobre sulfato de sodio y se concentró. Se purificó por cromatografía sobre gel de sílice (EtOAc/diclorometano = 1/10) para proporcionar el intermedio de dicetona deseado: éster terc-butílico de ácido 4-(3-oxo-hexanoil)-piperidin-1-carboxílico (2,1 g).

Una mezcla agitada de la dicetona (2,1 g, 7,1 mmol) y 2-cianotioacetamida (1,42 g, 14,2 mmol) en EtOH (30 ml) se calentó a 70°C durante una noche. Se

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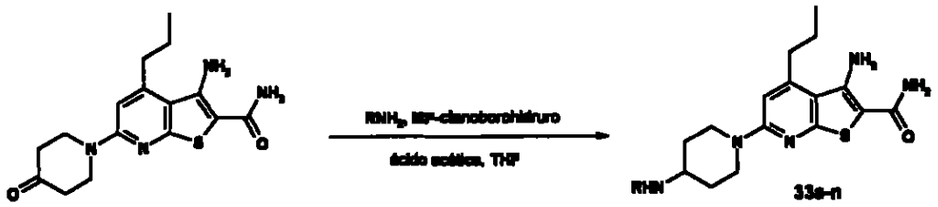
concentró y una cromatografía sobre gel de sílice (MeOH/diclorometano = 1/10) proporcionó 1,8 g de éster terc-butílico de ácido 5-ciano-6-mercapto-4-propil-3',4',5',6'-tetrahidro-2'*H*-[2,4']bipi-ridinil-1'-carboxílico.

Una mezcla agitada del éster terc-butílico anterior (0,9 g, 2,49 mmol) y bromoacetamida (0,38 g, 2,75 mmol) en dioxano seco (20 ml) se calentó a 80°C durante 2 h. Se añadió una solución de carbonato de sodio (400 mg) en agua (7 ml) y la reacción se calentó a reflujo durante una noche. Se diluyó con agua (100 ml) y los precipitados se filtraron y se secaron para proporcionar 0,85 g de éster terc-butílico de ácido 4-(3-amino-2-carbamoil-4-propil-3a,7a-dihidro-tieno[2,3-*b*]piridin-6-il)-piperidin-1-carboxílico.

A una solución agitada del éster terc-butílico anterior (600 mg, 1,43 mmol) en diclorometano seco (35 ml) se añadió HCl/dioxano (4 N, 2 ml). Aparecieron inmediatamente precipitados. Se concentró y se secó a vacío para proporcionar el compuesto del título en forma de la sal de dihidrocloruro (570 mg).

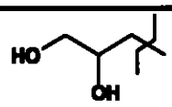
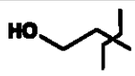
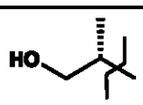
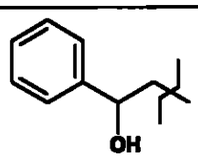
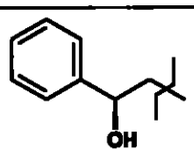
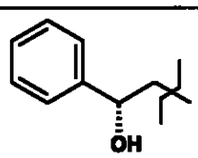
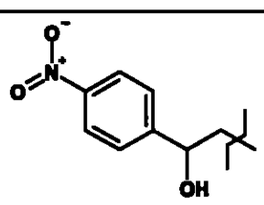
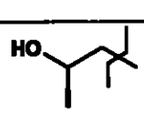
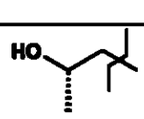
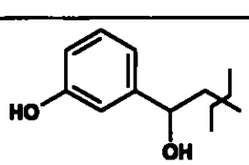
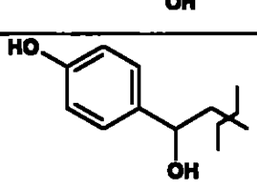
Ejemplo 33: Aminación reductora en fase sólida

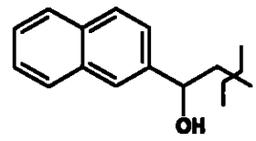
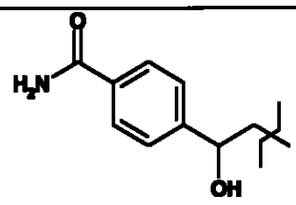
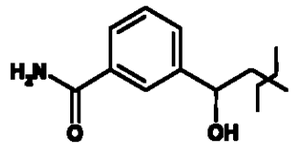
El siguiente procedimiento general describe el método mediante el que se prepararon diversos compuestos de amida de ácido 3-amino-6-(4-sustituido-amino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico:



A la amida de ácido 3-amino-6-(4-oxo-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico se añadieron 1,5-3,00 equivalentes de la amina deseada, 1,42 de cianoborohidruro en soporte sólido y 8-9 equivalentes de ácido acético en THF. La mezcla de reacción se agitó en un agitador orbital durante 15-72 h. Seguidamente la reacción se filtró, el cianoborohidruro en soporte sólido se agitó con MeOH durante 5-15 minutos y seguidamente se filtró. A los filtrados combinados se añadió NH_3 5 M en MeOH y la mezcla resultante se concentró a vacío. Una purificación a través de TLC preparatoria (5-10% de (NH_3/MeOH 5 M)/EtOAc como eluyente) o a través de cromatografía rápida sobre sílice (2,5-10% de (NH_3/MeOH 5 M)/CH_2Cl_2 como eluyente) proporcionó los compuestos descritos en la tabla siguiente:

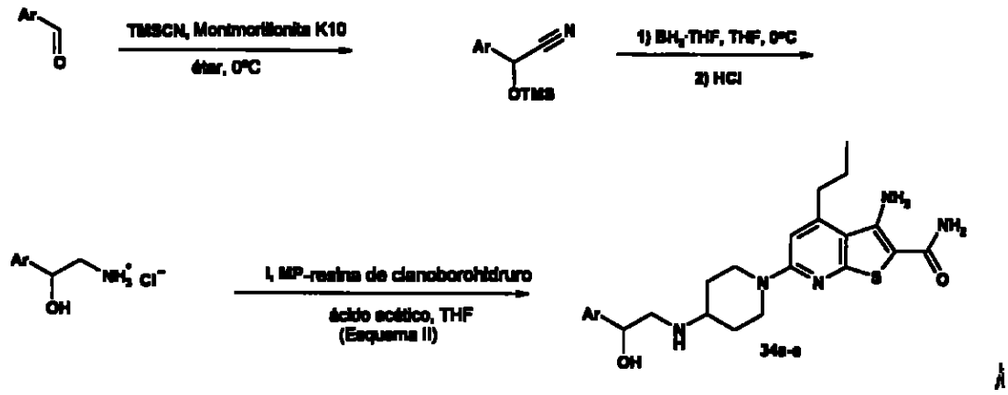
Comp.	R	Porcentaje de rendimiento

Comp.	R	Porcentaje de rendimiento
33a		45%
33b		65%
33c		51%
33d		44%
33e		56%
33f		53%
33g		26%
33h		18%
33l		9%
33j		41%
33k		54%

Comp.	R	Porcentaje de rendimiento
33l		62%
33m		34%
33n		55%

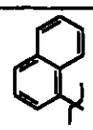
Ejemplo 34: Aminación reductora en fase sólida

El siguiente procedimiento general describe el método mediante el que se prepararon diversos intermedios de aminas para ser usados en la preparación de compuestos de amida de ácido 3-amino-6-(4-amino sustituido-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico usando el método del Ejemplo anterior:

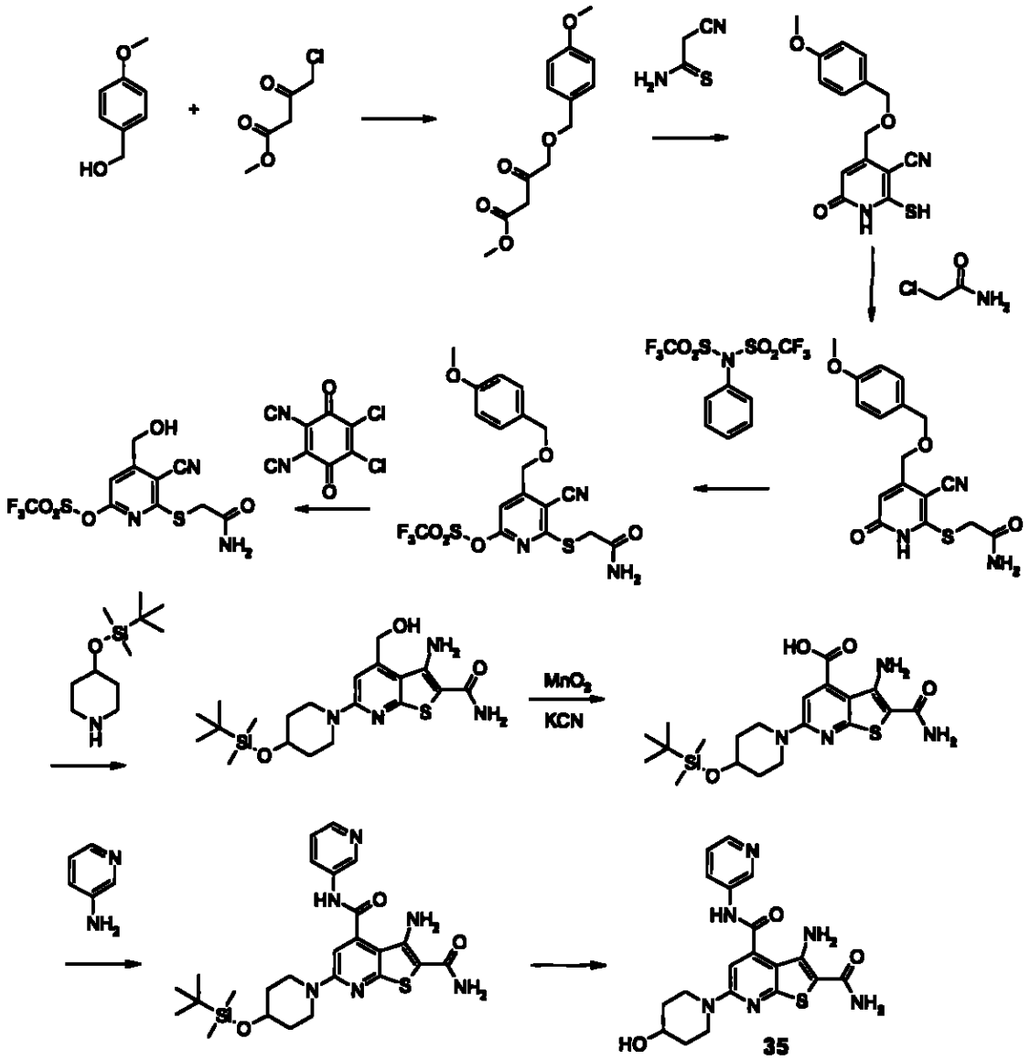


El aldehído de arilo deseado se disolvió en éter y se hizo reaccionar con cianuro de trimetilsililo (1-2 eq) a 0°C usando Montmorillonita K 10 (0,1-0,2 eq.) como catalizador ácido. La reacción se agitó 1-3 h y seguidamente se filtró, y el filtrado se concentró a vacío para proporcionar el correspondiente trimetilsilil-éter. El éter se disolvió en THF y se añadió a una solución de borano/THF a 0°C. La reacción se agitó durante 17-24 h mientras se agotaba el baño frío. La reacción se volvió a enfriar hasta 0°C y se inactivo con MeOH, y seguidamente se concentró a vacío. El residuo se recogió en EtOAc/CH_2Cl_2 y se añadió HCl/MeOH o HCl/dioxano. El sólido blanco que resultó se aisló mediante filtración con succión o por concentración a vacío para proporcionar las correspondientes sales de HCl de

hidroxil-amina. Estas sales de HCl se hicieron reaccionar seguidamente y se purificaron según el método descrito en el Ejemplo 33 para proporcionar los compuestos 34a-34e mostrados en la siguiente tabla:

	Ar	% rend.
34a	*p*-MeOPh	13%
34b	*p*-ClPh	17%
34c	*p*-MeO_2CPh	61%
34d		58%
34e	*m*-MeO_2CPh	52%

Ejemplo 35: Síntesis 2-amida-4-piridin-3-ilamida de ácido 3-amin -6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico



Se añadió por partes alcohol 4-metoxibencílico (11,0 g, 79,7 mmol) a una suspensión de 6,38 g de NaH al 60% en 110 ml de THF a 40°C y la reacción se agitó 30 minutos bajo Ar. Se hizo gotear a 40°C una solución de 10,00 g de 4-cloroacetoacetato de metilo en 40 ml de THF y la reacción se agitó a temperatura ambiente durante una noche. Se añadió NH_4Cl acuoso y el producto se extrajo en EtOAc, se lavó con NH_4Cl acuoso y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró para dar 18,5 g de un aceite. Este se sometió a cromatografía rápida eluyendo con 15% de acetona/éter de petróleo para proporcionar una fracción de 2,99 g de un aceite que se mostró por RMN ($CDCl_3$) que contenía 80% de éster metílico de ácido 4-(4-metoxi-benciloxi)-3-oxo-butírico puro. Se obtuvo una segunda fracción de 12,01 g de aceite que contenía 55% de éster metílico de ácido 4-(4-metoxi-benciloxi)-3-oxo-butírico por RMN, y el resto era principalmente material de partida sin reaccionar.

Se convirtió éster metílico de ácido 4-(4-Metoxi-benciloxi)-3-oxo-butírico en 2-[3-ciano-6-trifluoro-metanosulfoniloxi-4-(4-metoxi-benciloximetil)-piridin-2-ilsulfanil]-acetamida mediante los procedimientos anteriormente descritos en los Ejemplos 8 y 30.

El intermedio anterior (9,00 g) se disolvió en 171 ml de CH_2Cl_2 y 9 ml de agua. Se añadió 2,3-dicloro-5,6-diciano-1,4-benzoquinona (DDQ) (12,47 g) y la suspensión oscura se agitó durante 6 h y seguidamente se añadieron otros 4,16 g de DDQ y la reacción se agitó durante una noche. La reacción se sometió a decantación y el precipitado rojo gomoso restante se trituró 2X con CH_2Cl_2 y se sometió a decantación. El precipitado se disolvió en EtOAC, se lavó con agua (4X) y $NaHCO_3$ acuoso, se secó y se concentró hasta dar un sólido marrón. Este se trituró en CH_2Cl_2, se filtró y se secó para proporcionar 4,61 g (68%) del intermedio de hidroximetilpiridina deseado en forma de un sólido color castaño.

Se añadió cloruro de terc-butildimetilsililo (8,94 g) a una solución de 5,00 g de 4-hidroxipiperidina en 25 ml de DMF y la reacción exotérmica se colocó en un baño con hielo durante 10 minutos y seguidamente se añadieron 10,10 g de imidazol y la reacción se agitó a temperatura ambiente bajo Ar durante una noche. Una TLC mostró principalmente el material de partida. Se añadieron 4-dimetilaminopiridina (0,60 g) y 7,45 g de más cloruro de terc-butildimetilsililo y la reacción se agitó durante una noche. Esta se vertió en Na_2CO_3 acuoso, se extrajo con EtOAc (3X), se lavó con agua (4X), se secó y se concentró hasta dar 15,3 g de un aceite amarillo. Este se sometió a cromatografía rápida eluyendo con 0-10% de MeOH/CH_2Cl_2 para proporcionar varias fracciones de pureza variable. La mejor contenía 2,9 g de aceite amarillo que se determinó por RMN ($CDCl_3$) que contenía 55% en moles de 4-(*terc*-butil-dimetil-silaniloxi)-piperidine:45% en moles de cloruro

de terc-butil-dimetilsililo.

La 4-(terc-butil-dimetil-silaniloxi)-piperidina en bruto se acopló con el intermedio de 4-hidroximetilpiridina que antecede mediante el procedimiento descrito en el Ejemplo 30 para proporcionar amida de ácido 3-amino-6-[4-(*terc*-butil-dimetil-silaniloxi)-piperidin-1-il]-4-hidroximetil-tieno[2,3-b]piridin-2-carboxílico.

Una mezcla de 400 mg de la amida anterior, 298 mg de KCN, 1,59 g de MnO_2 y 157 microlitros de ácido acético se puso en suspensión en 16 ml de MeOH y la reacción se tapó y se agitó durante 2 días. La mezcla de reacción se filtró a través de tierra de diatomeas, se concentró y se sometió a cromatografía rápida eluyendo con 5% de MeOH/CH_2Cl_2 para proporcionar 254 mg (60%) de éster metílico de ácido 3-amino-6-[4-(*terc*-butil-dimetil-silaniloxi)-piperidin-1-il]-2-carbamoil-tieno[2,3-b]piridin-4-carboxílico según se determinó por RMN (DMDO). Una elución adicional con 25% de MeOH/CH_2Cl_2/1% de HOAc produjo 151 mg (36%) del correspondiente ácido carboxílico según se determinó por RMN (DMDO).

Se añadieron 81 mg de hidrocloruro de 1-[dimetilaminopropil]-3-etilcarbodiimida a una solución de 9,5 mg del ácido carboxílico anterior en 0,5 ml de DMF seca a 0°C. Después de 15 minutos se añadieron 99 mg de 3-aminopiridina y la reacción se agitó a temperatura ambiente durante una noche. Esta se diluyó con EtOAc, se lavó con agua (4X) y NH_4Cl acuoso (3X), se secó, se concentró y se purificó por TLC preparativa en 7,5% de MeOH/CH_2Cl_2/0,5% de NH_4OH. La banda principal se eluyó con 50% de MeOH/CH_2Cl_2 para proporcionar 12,8 mg de aceite que se mostró que era una mezcla de 2-amida-4-piridin-3-ilamida de ácido 3-amino-6-[4-(*terc*-butil-dimetil-silaniloxi)-piperidin-1-il]-tieno[2,3-b]piridin-2,4-dicarboxílico y material de partida sin reaccionar por RMN (CD_3OD). La mezcla se disolvió en 0,5 ml de CH_2Cl_2 y se añadieron 50 microlitros de complejo de HF-piridina y la reacción se agitó durante una noche. La solución transparente se separó por decantación y el precipitado gomoso se lavó y se separó por decantación 2 veces más con CH_2Cl_2. El precipitado se disolvió en 10% de MeOH/CH_2Cl_2, se neutralizó con una gota de NH_4OH concentrado, se aplicó a una placa de TLC preparativa y se desarrolló dos veces en 10% de MeOH/CH_2Cl_2/1% de NH_4OH. La banda se eluyó con 50% de MeOH/CH_2Cl_2 para proporcionar3-Amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico 2,0 mg (23%) del compuesto del título.

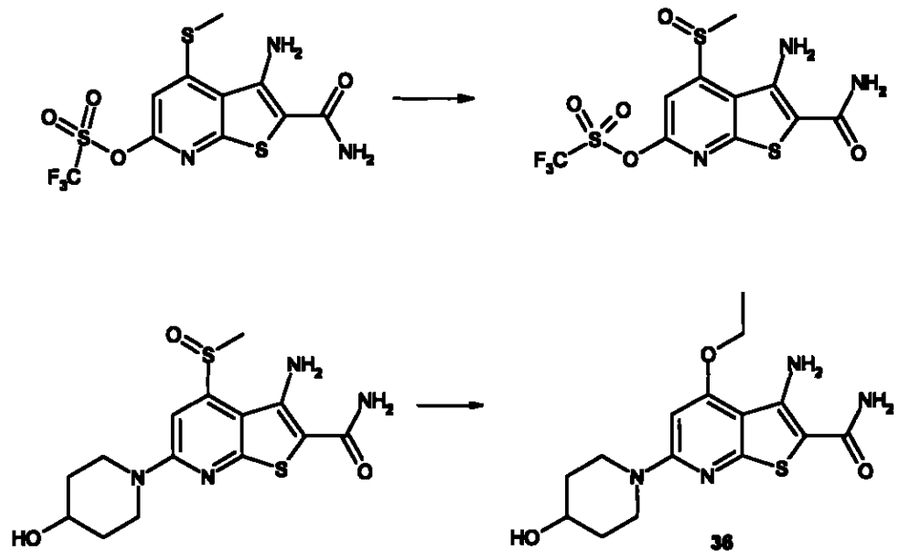
2-amida-4-metilamida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico:

Este compuesto se preparó a partir del éster metílico de ácido 3-amino-6-[4-(*terc*-butil-dimetil-silaniloxi)-piperidin-1-il]-2-carbamoil-tieno[2,3-b]piridin-4-carboxílico anterior combinando 10 mg del éster en 1 ml de CH_2Cl_2 con 0,5 ml añadidos

de metilamina 2 M en THF. La reacción se tapó y se agitó 2 días. La reacción se concentró para proporcionar 2-amida-4-metilamida de ácido 3-amino-6-[4-(*terc*-butil-dimetil-silaniloxi)-piperidin-1-il]-tie-no[2,3-b]piridin-2,4-dicarboxílico en forma de un sólido amarillo. Este se disolvió en 0,5 ml de 10% de MeOH/CH_2Cl_2 y se añadieron 50 microlitros de HF-piridina y la reacción se tapó y se agitó durante una noche. La reacción fue barrida con N_2, se disolvió en EtOAc, se lavó con $NaHCO_3$ acuoso y NH_4Cl acuoso, se secó, se concentró y se purificó por TLC preparativa eluyendo con 10% de MeOH/CH_2Cl_2. La banda se eluyó con 25% de MEOH/CH_2Cl_2 para proporcionar 2,7 mg (35%) del compuesto del título en forma de un sólido amarillo.

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Ejemplo 36: Síntesis de amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-etoxi-tieno[2,3-b]piridin-2-carboxílico



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Se disolvió éster 3-amino-2-carbamoil-4-metilsulfanil-tieno[2,3-b]piridin-6-ílico de ácido trifluorometanosulfónico (500 mg, 1,29 mmol) en MeOH (10 ml), enfriado a 0°C, y se añadió peroximonosulfato de potasio (950 mg, 1,55 mmol) disuelto en agua (15 ml). La mezcla se agitó durante 18 h después de lo cual se filtró para proporcionar el éster 3-amino-2-carbamoil-4-metilsulfinil-tieno[2,3-b]piridin-6-ílico de ácido trifluorometanosulfónico con un rendimiento de 86%.

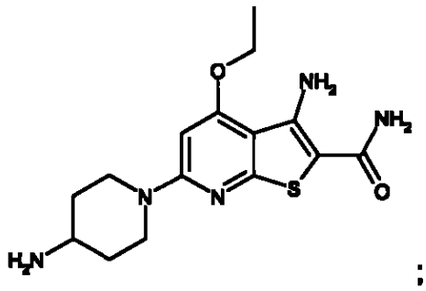
El éster anterior (100 mg, 0,25 mmol) se disolvió en dioxano (5 ml), se añadió 4-hidroxipiperidina (100 mg, 1,0 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla se diluyó con solución saturada de cloruro de amonio y la fase acuosa se extrajo con diclorometano varias veces. Las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se evaporaron. El producto se purificó finalmente por cromatografía de columna para producir 43 mg de amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-metanosulfinil-tieno[2,3-b]piridin-2-carboxílico (49%).

El producto anterior se disolvió en EtOH y se añadieron 235 microlitros de una solución 2,7 M de etóxido de sodio en EtOH, la solución se calentó a 80°C durante 6 h. La mezcla se vertió en una solución acuosa de NH_4Cl y la fase acuosa se extrajo tres veces con diclorometano. Las fases combinadas se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El producto se purificó por cromatografía de columna para producir 23 mg del compuesto del título (54%).

Los siguientes compuestos se prepararon en la manera anteriormente descrita:

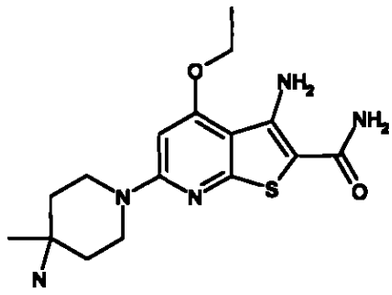
318

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-etoxi-tieno[2,3-b]piridin-2-carboxílico:



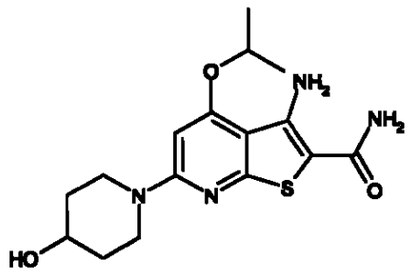
;

Amida de ácido 3-amino-6-(4-amino-4-metil-piperidin-1-il)-4-etoxi-tieno[2,3-b]piridin-2-carboxílico:



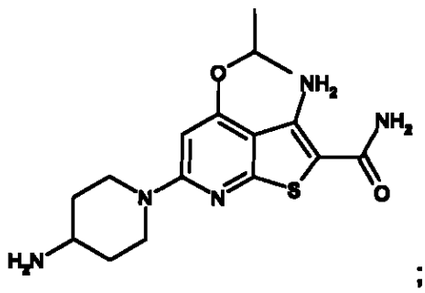
;

Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-isopropoxi-tieno[2,3-b]piridin-2-carboxílico:



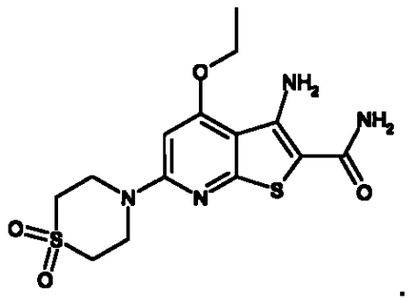
;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-isopropoxi-tieno[2,3-b]piridin-2-carboxílico:



;

Amida de ácido 3-amino-6-(1,1-dioxo-1-tiomorfolin-4-il)-4-etoxi-tieno[2,3-b]piridin-2-carboxílico:



VALORACIÓN DE LAS PROPIEDADES BIOLÓGICAS

La inhibición de IKKα e IKKβ por los compuestos de la presente invención se determinó con el siguiente ensayo que mide la fosforilación del sustrato IκBα por las respectivas quinasas. Las enzimas usadas en este ensayo fueron versiones con etiquetas marcadoras en el N terminal de IKKβ o IKKα humanos y el sustrato fue una proteína de fusión GST con IκBα (aminoácidos 1-54).

Las mezclas de reacción (60 l) contenían HEPES 20 mM, pH 7,5, $MgCl_2$ 10 mM, $MnCl_2$ 2 mM, NaCl 100 mM, Na_3VO_4 100 m, β-glicerofosfato 20 mM, DTT 1 mM, 2% de DMSO, ATP 250 nM [P^{133}]ATP 0,4 nM (actividad esopecífica, 3000 Ci/mmol), sustrato IκBα, enzima IKK y compuesto del ensayo. Las mezclas de reacción contenían 3,6 g/ml de IKKα y 245 g/ml de IKKα o 0,9 g/ml de IKKβ y 53 g/ml de IκBα.

Las reacciones se iniciaron añadiendo una solución de sustrato IκBα y ATP a placas de polipropileno que contenían enzima IKK que fue previamente incubada durante 5 minutos con compuesto del ensayo. Seguidamente las mezclas de la reacción se incubaron durante 1 hora a 25°C, se colocaron sobre hielo y se inactivaron mediante la adición de 150 l de ácido tricloroacético al 10% y pirofosfato de disodio al 5%. Después de mezclar, el contenido completo de las mezclas de reacción inactivadas se transfirió a una placa de filtración Packard UniFilter previamente humedecida, se aspiró y se lavó 6 veces con 250 µl de H_2O usando el dispositivo de recolección Packard Filtermater Harvester. Seguidamente las placas de filtración se secaron con aire, se complementaron con 40 µL de fluido de escintilación Microscint 20 y los productos de reacción marcados con P^{133} se cuantificaron usando el contador de escintilación Packard TopCount.

Los compuestos se ensayaron en diluciones en serie de tres veces y las concentraciones de inhibidor para conseguir una inhibición de 50% de la actividad enzimática (es decir, IC_{50}) se derivaron a partir de curvas de respuesta a la dosis usando un software SAS (SAS Institute, Cary NC). Se aplicó un análisis de regresión no lineal basado en la ecuación de Hill al porcentaje de la inhibición frente a

los datos de concentración. En todos los casos, las concentraciones del compuesto se verificaron por HPLC.

Los compuestos en las Tablas en la sección de la descripción detallada de la invención se evaluaron todos en el ensayo en cuanto a la inhibición de IKKβ y tenían valores de IC_{50} de 10 μM o por debajo. Los compuestos citados a continuación tenían valores de IC_{50} por debajo de 1 μM en este ensayo:

Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-metil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-4-[(E)-2-(4-cloro-fenil)-vinil]-6-metil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-imidazol-1-il-4-metil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-4-metil-6-piperazin-1-il-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-carbamoil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-metil-piperazin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-piperazin-1-il-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-metanosulfonil-piperazin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(3-hidroxi-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

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Amida de ácido 3-amino-6-[4-(3-amino-propanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-4-(4-hidroxi-4-fenil-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2-amino-etanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-oxo-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-carbamoil-piperazin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-((S)-3-amino-pirrolidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-((R)-3-amino-pirrolidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-dimetilamino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-4-ciano-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Éster metílico de ácido 4-(3-Amino-2-carbamoil-4-propil-tieno[2,3-b]piridin-6-il)-piperazin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(4-amino-butanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-((R)-2-amino-propanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-((S)-2-amino-propanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

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Amida de ácido 6-(4-acetilamino-piperidin-1-il)-3-amino-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(piperidin-4-ilamino)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-hidroxi-4-metil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-metilamino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-metanosulfonil-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-metilsulfanil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-((E)-estiril)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-nitro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-[(E)-2-(4-cloro-fenil)-vinil]-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-fenetil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-aminometil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-fenil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-[(E)-2-(2-cloro-fenil)-vinil]-tieno[2,3-b]piridin-2-carboxílico;

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Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-fluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-metoxi-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[1,4]diazepan-1-il-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2,4-diamino-butanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(1-piperidin-4-il-metanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-metil-[1,4]diazepan-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(3-nitro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-[(E)-2-(4-metoxi-fenil)-vinil]-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(3-amino-propilamino)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(3-carbamoil-piperazin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(3-metil-ureido)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 6-(4-acetil-[1,4]diazepan-1-il)-3-amino-4-propil-tieno[2,3-b]piridin-2-carboxílico;

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Amida de ácido 3-amino-6-(3-carbamoil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(3-amino-perhidro-azepin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(3-aminometil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(2-aminometil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-trifluorometil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-piperazin-1-il-4-trifluorometil-tieno[2,3-b]piridin-2-carboxílico; y

Amida de ácido 3-amino-6-(2-hidroximetil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico.

Los compuestos seleccionados a partir de la Tabla en la sección de la descripción detallada de la invención se evaluaron en cuanto a la inhibición de IKKα. Los compuestos citados tenian valores de IC_{50} de 10 μM o por debajo en este ensayo:

Amida de ácido 3-amino-4-furan-2-il-6-metil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-4-isopropoxi-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-metil-4-(4-nitro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-metil-4-((E)-estiril)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-4-(4-metanosulfonil-fenil)-6-metil-tieno[2,3-b]piridin-2-carboxílico;

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Amida de ácido 3-amino-4-[(E)-2-(4-fluoro-fenil)-vinil]-6-metil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-4-[(E)-2-(4-cloro-fenil)-vinil]-6-metil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-metil-piperazin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-piperazin-1-il-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-((R)-3-amino-pirrolidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-4-ciano-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-metilamino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-metilsulfanil-tieno[2,3-b]piridin-2-carboxílico;

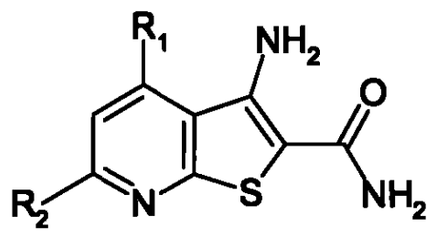
Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-((E)-estiril)-tieno[2,3-b]piridin-2-carboxílico; y

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-nitro-fenil)-tieno[2,3-b]piridin-2-carboxílico.

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REIVINDICACIONES

1. Un compuesto de fórmula (I):



(I)

en la cual:

R_1 es

(a) fenilo o heteroarilo seleccionado entre furanilo, tienilo, piridilo, pirrolilo, imidazolilo y benzofuranilo, opcionalmente sustituidos con uno a dos R_3,

(b) heterociclilo seleccionado entre 1-piperidinilo, 1-piperazinilo, 1-pirrolidinilo y 4-morfolinilo, opcionalmente sustituidos con uno a dos grupos seleccionados entre alquilo C_{1-6}, $-CO_2$-alquilo C_{1-5}, fenilo, bencilo, -OH y C(O)heteroarilo, en los que el grupo heteroarilo se selecciona entre furanilo, tienilo, piridilo y pirrolilo,

(c) $R_6(CH_2)_mO$-,

(d) R_6OCH_2-,

(e) $R_6(CH_2)_mNH$-,

(f) $R_6(CH_2)_p(CH=CH)_m$-,

(g) alquilo C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(h) alcoxi C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(i) alquilo C_{1-6}-$S(O)_n$-, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(j) $-N(R_4)(R_5)$, o

(k) -C(O)NHR', en donde R' es R_6, piridilo o $-CH_3$;

R_2 es

(a) alquilo C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(b) alcoxi C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(c) alquilamino C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

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(d) alquiltio C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(e) heterociclil-$(CH_2)_m$- en donde dicho heterociclo se selecciona entre piperidinilo, piperazinilo, morfolinilo, azepanilo, pirrolidinilo, 1,4-diazacicloheptanilo, azepanilo, 2,5-diazabiciclo[2.2.1]heptanilo, oxazepanilo y tiomorfolino y está opcionalmente sustituido con uno o tres R_7,

(f) heterociclil-CH_2O- en donde el heterociclilo se selecciona entre 1-piperidinilo, 1-piperazinilo, 4-morfolinilo y 1-pirrolidinilo, opcionalmente sustituidos con alquilo C_{1-6},

(g) fenilo, opcionalmente sustituido con uno o tres R_3,

(h) -$N(R_4)(R_5)$,

(i) heteroarilo seleccionado entre furanilo, tienilo, imidazolilo, piridilo y pirrolilo, o

(j) -H;

R_3 se escoge entre alquilo C_{1-6}, alcoxi C_{1-6}, hidroxi-alquilo C_{1-6}, halógeno, -CN, $-CO_2H$, $-CO_2$-alquilo C_{1-6}, $-S(O)_n$-alquilo C_{1-6}, $-NO_2$, -OH, $-CF_3$, $-N(R_4)(R_5)$, -NHC(O)NH-alquilo C_{1-6}, $-C(O)N(R_4)(R_5)$ y fenilo opcionalmente sustituido con halógeno, alquilo C_{1-6}, -CN o alcoxi C_{1-6};

R_4 y R_5 se seleccionan independientemente entre H, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, $-SO_2$-alquilo C_{1-6}, fenilo, piridilo, bencilo, piperidinilo, feniletilo y $(CH_3)_3COC(O)$-;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre halógeno, alquilo C_{1-6}, -CN, $-CO_2$-alquilo C_{1-6}, $-C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ y alcoxi C_{1-6}, o R_6 es cicloalquilo C_{3-6}, $-CH_2OH$, naftalen-2-ilo, naftalen-1-ilo o 2-tienilo;

R_7 se selecciona entre –OH, -CN, oxo, $-CO_2$alquilo C_{1-6}, $-CO_2H$, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, $-CH_2OH$, alquilo C_{1-6}, $-CO_2$bencilo, hidroxialquilo C_{1-6}, -C(O)-alquil $C_{1-6}N(R_4)(R_5)$, $-NHCO_2$alquilo C_{1-6}, $-NHC(O)N(R_4)(R_5)$, $-S(O)_n$alquilo C_{1-6}, $(CH_3)_3COC(O)$-, fenilo, piridilo, $H_2NCH(R_6)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_6)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- y -C(O)heterociclilo, en donde dicho heterociclilo se selecciona piperidinilo, piperazinilo, morfolinilo y pirrolidinilo, o R_7 is 2-hidroxietilamino, metilcarbamidoilo, hidroxiimino, hidrazinocarbonilo, sulfamoilo, metanosulfonilamino, metilsulfonilhidrazino, 2-hidroxipropilamino, 2,3-dihidroxipropilamino, 2-hidroxi-1-metiletilamino, carbamoilmetilamino, N'-fenilhidrazinocarbonilo o tolueno-4-sulfonilamino;

R_8 se selecciona entre alquilo C_{1-6}, $-(CH_2)_{1-4}NH_2$, fenilo o bencilo;

R_9 se selecciona entre oxo, -OH, $-NR_4R_5$, $-CO_2H$ y alcoxi C_{1-6};

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R_{10} se selecciona entre oxo, -OH, -N(R_4)(R_5), alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)N(R_4)(R_5), R_6 y heteroarilo seleccionado entre furanilo, tienilo, imidazolilo, piridilo, indolilo y pirrolilo;

m es 0 ó 1;

n es 0, 1 ó 2; y

p es 0, 1, 2 ó 3;

y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables;

con la condición de que si R_1 es fenilo o heteroarilo, alquilo C_{1-6}, -CF_3, -C(O)NR_4R_5 o heterociclilo, entonces R_2 no es alquilo C_{1-6}, fenilo, heteroarilo, -CF_3 o H.

2.El compuesto según la reivindicación 1, en el cual:

R_1 es

(a) fenilo o heteroarilo seleccionado entre furanilo, tienilo, piridilo, pirrolilo, imidazolilo y benzofuranilo opcionalmente sustituidos con uno a dos R_3,

(b) $R_6(CH_2)_mO$-,

(c) R_6OCH_2-,

(d) $R_6(CH_2)_mNH$-,

(e) $R_6(CH_2)_p(CH{=}CH)_m$-,

(f) alquilo C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(g) alcoxi C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9;

(h) alquiltio C_{1-6},

(i) -N(R_4)(R_5), o

(j) -C(O)NHR', en donde R' es R_6, piridilo o -CH_3,

R_2 es

(a) alquilo C_{1-6}, opcionalmente sustituido con R_{10},

(b) alcoxi C_{1-6}, opcionalmente sustituido con R_{10},

(c) alquilamino C_{1-6}, opcionalmente sustituido con R_{10},

(d) heterociclilo seleccionado entre 1-piperidinilo, 1-piperazinilo, 4-morfolinilo, 1-azepanilo, 1-pirrolidinilo, 1,4-diazacicloheptan-1-ilo, 1-azepanilo, 2,5-diazabiciclo[2.2.1]heptan-2-ilo, oxazepan-4-ilo y 4-tiomorfolino, y que está opcionalmente sustituido con uno a tres R_7,

(e) heterociclil-CH_2O- en donde el grupo heterociclilo se selecciona entre 1-piperidinilo, 1-piperazinilo, 4-morfolinilo y 1-pirrolidinilo, opcionamlente sustituidos con alquilo C_{1-6}, o

(f) -N(R_4)(R_5);

R_3 se escoge entre alquilo C_{1-6}, alcoxi C_{1-6}, hidroxi-alquilo C_{1-6}, halógeno, -CN, $-CO_2H$, $-CO_2$-alquilo C_{1-6}, $-S(O)_n$alquilo C_{1-6}, $-NO_2$, -OH, $-CF_3$, $-N(R_4)(R_5)$, -NHC(O)NHalquilo C_{1-6}, $-C(O)N(R_4)(R_5)$ y fenilo opcionalmente sustituido con halógeno, alquilo C_{1-6}, -CN o alcoxi C_{1-6};

R_4 y R_5 se seleccionan independientemente entre H, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, piridilo, bencilo, piperidinilo y feniletilo;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre Cl, F, alquilo C_{1-6}, -CN, $-CO_2$alquilo C_{1-6}, $-C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ y alcoxi C_{1-6}, o R_6 es cicloalquilo C_{3-6}, $-CH_2OH$, naftaleno-2-ilo, naftaleno-1-ilo o 2-tienilo; o

R_6 es cicloalquilo C_{3-6}, $-CH_2OH$, naftalen-2-ilo, naftalen-1-ilo o 2-tienilo;

R_7 se selecciona entre –OH, -CN, oxo, $-CO_2$alquilo C_{1-6}, $-CO_2H$, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, $-CH_2OH$, alquilo C_{1-6}, -C(O)-alquilo $C_{1-6}N(R_4)(R_5)$, $-NHC(O)N(R_4)(R_5)$, $-S(O)_n$alquilo C_{1-6}, fenilo, piridilo, $H_2NCH(R_8)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_8)CH_2NH$-, $R_8CH_2CH(OH)CH_2NH$-, $R_8OCH_2CH(OH)CH_2NH$- y -C(O)heterociclilo, en donde dicho heterociclilo se selecciona entre piperidinilo, piperazinilo, morfolinilo y pirrolidinilo, o R_7 es 2-hidroxietilamino, metilcarbamidoilo, hidroxiimino, hidrazinocarbonilo, sulfamoilo, metanosulfonilamino, metilsulfonilhidrazino, 2-hidroxipropilamino, 2,3-dihidroxipropilamino, 2-hidroxi-1-metiletilamino, carbamoilmetilamino, N'-fenilhidrazinocarbonilo o tolueno-4-sulfonilamino;

R_8 se selecciona entre alquilo C_{1-6}, $-(CH_2)_{1-4}NH_2$, fenilo o bencilo;

R_9 es -OH;

R_{10} se selecciona entre -OH, $-N(R_4)(R_5)$, alquilo C_{1-6} y heteroarilo seleccionado entre furanilo, tienilo y piridilo;

m es 0 ó 1;

n es 0, 1 ó 2; y

p es 0, 1, 2 ó 3;

y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables;

con la condición de que si R_1 es fenilo o heteroarilo, alquilo C_{1-6}, $-CF_3$, $-C(O)NR_4R_5$ o heterociclilo, entonces R_2 no es alquilo C_{1-6}, fenilo, heteroarilo, $-CF_3$ o H.

3. El compuesto según la reivindicación 1, en el cual:

R_1 es

(a) fenilo o heteroarilo seleccionado entre furanilo, tienilo y piridilo, opcionalmente sustituidos con uno a dos R_3,

(a) fenilo o heteroarilo seleccionado entre furanilo, tienilo y piridilo, opcio-

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nalmente sustituido con uno a dos R_3,

(b) $R_6(CH_2)_mO$-,

(c) R_6OCH_2-,

(d) $R_6(CH_2)_mNH$-,

(e) $R_6(CH_2)_p(CH=CH)_m$-,

(f) alquilo C_{1-6},

(g) alquilo C_{1-6}-OH,

(h) -CF_3,

(i) alcoxi C_{1-6},

(j) -O-alquilo C_{1-6}-OH,

(k) alquiltio C_{1-6},

(l) –$N(R_4)(R_5)$, o

(m) –C(O)NHR', en donde R' es R_6, piridilo o –CH_3;

R_2 es heterociclilo en donde dicho heterociclo se selecciona entre 1-piperidinilo, 1-piperazinilo, 4-morfolinilo, 1-azepanilo, 1-pirrolidinilo, 1,4-diazacicloheptan-1-ilo y 1-azepanilo, 2-5-diazabiciclo[2.2.1]heptan-2-ilo, oxazepan-4-ilo y 4-tioformolino y está opcionalmente sustituido con uno a tres R_7,

R_3 se escoge entre alquilo C_{1-6}, alcoxi C_{1-6}, hidroxi-alquilo C_{1-6}, halógeno, -CN, -CO_2H, -CO_2-alquilo C_{1-6}, -$S(O)_n$-alquilo C_{1-6}, -NO_2, -OH, -CF_3, -$N(R_4)(R_5)$, -NHC(O)NH-alquilo C_{1-6}, -$C(O)N(R_4)(R_5)$ y fenilo opcionalmente sustituido con halógeno, alquilo C_{1-6}, -CN o alcoxi C_{1-6};

R_4 y R_5 se seleccionan independientemente entre H, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, piridilo, bencilo, piperidinilo y feniletilo;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre Cl, F, alquilo C_{1-6}, -CN, CO_2alquilo C_{1-6}, $C(O)NR_4R_5$, -SO_2NH_2, -NO_2, -OH, -NH_2, -CF_3 y alcoxi C_{1-6} o R_6 es cicloalquilo C_{3-6}, -CH_2OH, naftaleno-2-ilo, naftaleno-1-ilo o 2-tienilo;

R_7 se selecciona entre –OH, -CN, oxo, -CO_2alquilo C_{1-6}, -CO_2H, -$C(O)N(R_4)(R_5)$, -$N(R_4)(R_5)$, -$CH_2N(R_4)(R_5)$, CH_2OH, alquilo C_{1-6}, -C(O)alquilo $C_{1-6}N(R_4)(R_5)$, -$NHC(O)N(R_4)(R_5)$, -$S(O)_n$alquilo C_{1-6}, fenilo, piridilo, $H_2NCH(R_8)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_8)CH_2NH$-, $R_6CH_2CH(OH)CH_2NH$-, $R_6OCH_2CH(OH)CH_2NH$- y -C(O)heterociclilo, en donde dicho heterociclilo se selecciona entre piperidinilo, piperazinilo, morfolinilo y pirrolidinilo, o R_7 es 2-hidroxietilamino, metilcarbamidoilo, hidroxiimino, hidrazinocarbonilo, sulfamoilo, metanosulfonilamino, metilsulfonilhidrazino, 2-hidroxipropilamino, 2,3-dihidroxipropilamino, 2-hidroxi-1-metiletilamino, carbamoilmetilamino, N'-fenilhidrazinocarbonilo o tolueno-4-sulfonilamino;

R_8 se selecciona entre alquilo C_{1-6}, -$(CH_2)_{1-4}NH_2$, fenilo o bencilo;

m es 0 ó 1;

n es 0, 1 ó 2; y

p es 0, 1, 2 ó 3;

y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables.

4. El compuesto según la reivindicación 1, en el cual:

R_1 es

(a) fenilo, opcionalmente sustituido con uno a dos R_3,

(b) $R_6CH=CH-$

(c) alquilo C_{1-6},

(d) alquilo C_{2-3}-OH,

(e) $-CF_3$,

(f) alcoxi C_{1-6},

(g) -O-alquilo C_{2-3}-OH,

(h) alquiltio C_{1-6}, o

(i) -C(O)NHR', en donde R' es R_6, piridilo o $-CH_3$;

R_2 es

heterociclilo, en donde dicho heterociclo se selecciona entre 1-piperidinilo, 1-piperazinilo, 1-azepanilo, 1,4-diazacicloheptan-1-ilo y 1-azepanilo y está opcionalmente sustituido con uno a tres R_7;

R_3 se escoge entre $-CH_3$, $-OCH_3$, F, Cl, $-CO_2CH_3$, $-SO_2CH_3$ y $-NO_2$;

R_4 y R_5 se seleccionan independientemente entre H, $-CH_3$ y bencilo;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre Cl, F, alquilo C_{1-6}, -CN, CO_2alquilo C_{1-6}, $C(O)NR_4R_5$, $-SO_2NH_2$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ y alcoxi C_{1-6} o R_6 es cicloalquilo C_{3-6}, $-CH_2OH$, naftalen-2-ilo, naftalen-1-ilo o 2-tienilo;

R_7 se selecciona entre –OH, -CN, oxo, $-CO_2$alquilo C_{1-6}, $-C(O)N(R_4)(R_5)$, $-N(R_4)(R_5)$, $-CH_2N(R_4)(R_5)$, CH_2OH, alquilo C_{1-6}, $-C(O)$ alquil $C_{1-6}N(R_4)(R_5)$, $-NHC(O)N(R_4)(R_5)$, $-S(O)_n$alquilo C_{1-6}, $H_2NCH(R_8)C(O)-$, $HO(CH_2)_mCH_2CH(NH_2)C(O)-$, $HOCH(R_8)CH_2NH-$, $R_6CH_2CH(OH)CH_2NH-$, $R_6OCH_2CH(OH)CH_2NH-$ y -C(O)heterociclilo, en los que dicho heterociclilo se selecciona entre piperidinilo, piperazinilo, morfolinilo y pirrolidinilo, o R_7 es 2-hidroxietilamino, metilcarbamidoilo, hidroxiimino, hidrazinocarbonilo, sulfamoilo, metanosulfonilamino, metilsulfonilhidrazino, 2-hidroxipropilamino, 2,3-dihidroxipropilamino, 2-hidroxi-1-metiletilamino, carbamoilmetilamino, N'-fenilhidrazinocarbonilo o tolueno-4-sulfonilamino;

R_8 se selecciona entre alquilo C_{1-6}, $-(CH_2)_{1-4}NH_2$, fenilo o bencilo;

y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isóme-

ros farmacéuticamente aceptables.

5. El compuesto según la reivindicación 4, en el cual:

R_1 es

(a) $-CH_2CH_2CH_3$,

(b) $-OCH_2CH_3$,

(c) $-SCH_3$,

(d) -C(O)NHR', en donde R' es 3-piridilo o fenilo sustituido en la posición 4 con -OH, $-C(O)NH_2$ o $-SO_2NH_2$;

R_2 es heterociclilo en el que dicho heterociclo se selecciona entre 1-piperidinilo y 1-piperazinilo y está opcionalmente sustituido con uno a tres R_7;

R_4 y R_5 se seleccionan independientemente entre H, $-CH_3$ y bencilo;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre Cl, F, $-CH_3$, -CN, $-CO_2CH_3$, $-C(O)NR_4R_5$, $-NO_2$, -OH, $-NH_2$, $-CF_3$ y $-CH_3$, o R_6 es naftalen-2-ilo, naftalen-1-ilo o 2-tienilo;

R_7 se selecciona entre –OH, -CN, oxo, $-C(O)NH_2$, $-NH_2$, $-CH_2NH_2$, $-CH_3$, $-NHC(O)NH_2$, $H_2NCH(R_6)C(O)$-, $HOCH(R_6)CH_2NH$- , $R_6CH_2CH(OH)CH_2NH$- y $R_6OCH_2CH(OH)CH_2NH$-, o R_7 es 2-hidroxietilamino, metilcarbamidoilo, metanosulfonilamino, metilsulfonilhidrazino, 2-hidroxipropilamino, 2,3-dihidroxipropilamino, carbamoilmetilamino o N'-fenilhidrazinocarbonilo;

R_8 es $-(CH_2)_{1-4}NH_2$;

con la condición de queen cada una de las realizaciones anteriores de nuevos compuestos, si R_1 es fenilo o heteroarilo, alquilo C_{1-6}, $-CF_3$, $-C(O)NR_4R_5$ o heterociclilo, entonces R_2 no es alquilo C_{1-6}, fenilo, heteroarilo, $-CF_3$ o H,

y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables.

6. Un compuesto, seleccionado entre el grupo que consiste en:

Amida de ácido 3-amino-6-(4-oxo-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-4-ciano-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-metanosulfonil-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-metilsulfanil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-((E)-estiril)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-nitro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[1,4]diazepan-1-il-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2,4-diamino-butanoil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-[(E)-2-(4-metoxi-fenil)-vinil]-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(2-aminometil-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-trifluorometil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-piperazin-1-il-4-trifluorometil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-((E)-2-p-tolil-vinil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2,3-dihidroxi-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-((E)-2-m-tolil-vinil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-metanosulfonilamino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Éster metílico de ácido 4-[3-amino-6-(4-amino-piperidin-1-il)-2-carbamoil-tieno[2,3-b]piridin-4-il]-benzoico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-2-fenil-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-piperidin-4-il-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(2,5-difluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(N'-fenil-hidrazinocarbonil)-piperazin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-((S)-2-hidroxi-2-fenil-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-((R)-2-hidroxi-2-fenil-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(4-nitro-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-etoxi-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-((S)-2-hidroxi-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-((S)-2-hidroxi-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(3-hidroxi-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(4-hidroxi-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-azepan-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-3-hidroxi-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(2,4-difluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-(4-ciano-3-fluoro-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-piperidin-1-il)-4-isopropoxi-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[(1H-indol-3-ilmetil)-amino]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-trifluorometil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(4-amino-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(4-metoxi-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(4-cloro-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-(4-metanosulfonil-fenil)-tieno[2,3-b]piridin-2-carboxílico;

Éster metílico de ácido 4-{2-[1-(3-amino-2-carbamoil-4-propil-tieno[2,3-b]piridin-6-il)-piperidin-4-ilamino]-1-hidroxi-etil}-benzoico;

Amida de ácido 3-amino-4-(4-ciano-3-fluoro-fenil)-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-4-etoxi-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico;

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Amida de ácido 3-amino-4-propil-6-(4-ureido-piperidin-1-il)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-((S)-3,4-dihidroxi-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-metilsulfanil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-4-(3-hidroxi-propil)-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(4-carbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

2-Amida-4-piridin-3-ilamida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico;

Amida de ácido 3-amino-6-((S)-3-hidroxi-4-metanosulfonilamino-piperidin-1-il)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-2-naftalen-2-il-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(N'-metilsulfonil-hidrazino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-2-naftalen-1-il-etilamino)-piperidin-1-il]-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Éster metílico de ácido 3-{2-[1-(3-amino-2-carbamoil-4-propil-tieno[2,3-b]piridin-6-il)-piperidin-4-ilamino]-1-hidroxi-etil}-benzoico;

Amida de ácido 3-amino-6-(4-amino-4-metil-piperidin-1-il)-4-etoxi-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-hidroxi-2-(4-metilcarbamoil-fenil)-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(4-dimetilcarbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(4-bencilcarbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[2-(3-carbamoil-fenil)-2-hidroxi-etilamino]-piperidin-1-il}-4-propil-tieno[2,3-b]piridin-2-carboxílico;

2-Amida-4-[(4-hidroxi-fenil)-amida] de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico;

2-Amida-4-[(4-carbamoil-fenil)-amida] de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico;

2-Amida-4-[(4-sulfamoil-fenil)-amida] de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico;

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2-Amida-4-piridin-4-ilamida de ácido 3-amino-6-(4-hidroxi-piperidin-1-il)-tieno[2,3-b]piridin-2,4-dicarboxílico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-3-fenoxi-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-*b*]piridin-2-carboxílico;

Amida de ácido 3-amino-6-[4-(2-hidroxi-3-fenil-propilamino)-piperidin-1-il]-4-propil-tieno[2,3-*b*]piridin-2-carboxílico;

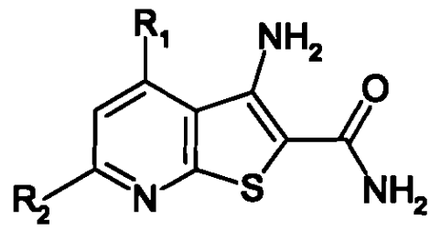
Amida de ácido 3-amino-6-{4-[2-hidroxi-3-(4-metoxi-fenoxi)-propilamino]-piperidin-1-il}-4-propil-tieno[2,3-*b*]piridin-2-carboxílico;

Amida de ácido 3-amino-6-{4-[3-(4-carbamoil-fenoxi)-2-hidroxi-propilamino]-piperidin-1-il}-4-propil-tieno[2,3-*b*]piridin-2-carboxílico;

Amida de ácido 3-amino-6-(4-amino-3,3-dimetil-cyclohexil)-4-propil-tieno[2,3-b]piridin-2-carboxílico;

y sus sales, ésteres, tautómeros, isómeros individuales y mezclas farmacéuticamente aceptables.

7. Un método para tratar estados inflamatorios y autoinmunes, método que comprende administrar a un paciente que necesita este tratamiento una cantidad terapéuticamente eficaz de un compuesto según la fórmula (I):



(I)

en la cual:

R_1 es

(a) fenilo o heteroarilo seleccionado entre furanilo, tienilo, piridilo, pirrolilo, imidazolilo y benzofuranilo, opcionalmente sustituidos con uno a dos R_3,

(b) heterociclilo seleccionado entre 1-piperidinilo, 1-piperazinilo, 1-pirrolidinilo y 4-morfolinilo, opcionalmente sustituidos con uno a dos grupos seleccionados entre alquilo C_{1-6}, $-CO_2$-alquilo C_{1-5}, fenilo, bencilo, -OH y C(O)heteroarilo, en los que el grupo heteroarilo se selecciona entre furanilo, tienilo, piridilo y pirrolilo,

(c) $R_6(CH_2)_mO$-,

(d) R_6OCH_2-,

(e) $R_6(CH_2)_mNH$-,

(f) $R_6(CH_2)_p(CH=CH)_m$-,

(g) alquilo C_{1-6}, opcional, parcial o completamente halogenado y opcional-

mente sustituido con uno a dos R_9,

(h) alcoxi C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(i) alquilo C_{1-6}-$S(O)_n$-, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_9,

(j) -$N(R_4)(R_5)$, o

(k) -C(O)NHR', en donde R' es R_8, piridilo o -CH_3;

R_2 es

(a) alquilo C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(b) alcoxi C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(c) alquilamino C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(d) alquiltio C_{1-6}, opcional, parcial o completamente halogenado y opcionalmente sustituido con uno a dos R_{10},

(e) heterociclil-$(CH_2)_m$- en donde dicho heterociclo se selecciona entre piperidinilo, piperazinilo, morfolinilo, azepanilo, pirrolidinilo, 1,4-diazacicloheptanilo, azepanilo, 2,5-diazabiciclo[2.2.1]heptanilo, oxazepanilo y tiomorfolino y está opcionalmente sustituido con uno o tres R_7,

(f) heterociclil-CH_2O- en donde el heterociclilo se selecciona entre 1-piperidinilo, 1-piperazinilo, 4-morfolinilo y 1-pirrolidinilo, opcionalmente sustituidos con alquilo C_{1-6},

(g) fenilo, opcionalmente sustituido con uno o tres R_3,

(h) -$N(R_4)(R_5)$,

(i) heteroarilo seleccionado entre furanilo, tienilo, imidazolilo, piridilo y pirrolilo, o

(j) -H;

R_3 se escoge entre alquilo C_{1-6}, alcoxi C_{1-6}, hidroxi-alquilo C_{1-6}, halógeno, -CN, -CO_2H, -CO_2-alquilo C_{1-6}, -$S(O)_n$-alquilo C_{1-6}, -NO_2, -OH, -CF_3, -$N(R_4)(R_5)$, -NHC(O)NH-alquilo C_{1-6}, -$C(O)N(R_4)(R_5)$ y fenilo opcionalmente sustituido con halógeno, alquilo C_{1-6}, -CN o alcoxi C_{1-6};

R_4 y R_5 se seleccionan independientemente entre H, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, -SO_2-alquilo C_{1-6}, fenilo, piridilo, bencilo, piperidinilo, feniletilo y $(CH_3)_3COC(O)$-;

R_6 es un grupo fenilo opcionalmente sustituido con uno o dos grupos seleccionados entre halógeno, alquilo C_{1-6}, -CN, -CO_2-alquilo C_{1-6}, -$C(O)NR_4R_5$, -SO_2NH_2, -NO_2, -OH, -NH_2, -CF_3 y alcoxi C_{1-6}, o R_6 es cicloalquilo C_{3-6}, -CH_2OH,

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naftalen-2-ilo, naftalen-1-ilo o 2-tienilo;

R_7 se selecciona entre –OH, -CN, oxo, -CO_2alquilo C_{1-6}, -CO_2H, -$C(O)N(R_4)(R_5)$, -$N(R_4)(R_5)$, -$CH_2N(R_4)(R_5)$, -CH_2OH, alquilo C_{1-6}, -CO_2bencilo, hidroxialquilo C_{1-6}, -C(O) alquil $C_{1-6}N(R_4)(R_5)$, -$NHCO_2$alquilo C_{1-6}, -$NHC(O)N(R_4)(R_5)$, -$S(O)_n$alquilo C_{1-6}, $(CH_3)_3COC(O)$-, fenilo, piridilo, $H_2NCH(R_8)C(O)$-, $HO(CH_2)_mCH_2CH(NH_2)C(O)$-, $HOCH(R_8)CH_2NH$-$R_8CH_2CH(OH)CH_2NH$-, $R_8OCH_2CH(OH)CH_2NH$- y -C(O)heterociclilo, en donde dicho heterociclilo se selecciona entre piperidinilo, piperazinilo, morfolinilo y pirrolidinilo, o R_7 is 2-hidroxietilamino, metilcarbamidoilo, hidroxiimino, hidrazinocarbonilo, sulfamoilo, metanosulfonilamino, metilsulfonilhidrazino, 2-hidroxipropilamino, 2,3-dihidroxipropilamino, 2-hidroxi-1-metiletilamino, carbamoilmetilamino, N'-fenilhidrazinocarbonilo o tolueno-4-sulfonilamino;

R_8 se selecciona entre alquilo C_{1-6}, -$(CH_2)_{1-4}NH_2$, fenilo o bencilo;

R_9 se selecciona entre oxo, -OH, -NR_4R_5, -CO_2H y alcoxi C_{1-6};

R_{10} se selecciona entre oxo, -OH, -$N(R_4)(R_5)$, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -$C(O)N(R_4)(R_5)$, R_6 y heteroarilo seleccionado entre furanilo, tienilo, imidazolilo, piridilo, indolilo y pirrolilo;

m es 0 ó 1;

n es 0, 1 ó 2; y

p es 0, 1, 2 ó 3; y sus sales, ésteres, tautómeros, isómeros individuales y mezclas de isómeros farmacéuticamente aceptables.

8. Una composición farmacéutica, que comprende una cantidad terapéuticamente eficaz de un compuesto según la reivindicación 1.

9. Un método para tratar un estado de enfermedad inflamatoria o autoinmune, comprendiendo dicho método administrar a un paciente que necesita este tratamiento una cantidad terapéuticamente eficaz de un compuesto según la reivindicación 1.

10. El método según la reivindicación 9, en el que la enfermedad o estado inflamatorio o autoinmune se selecciona entre la lista que consiste en osteoartritis, herida de reperfusión, asma, esclerosis múltiple, síndrome de Guillain-Barre, enfermedad de Crohn, colitis ulcerativa, psoriasis, enfermedad de injerto frente a hospedante, lupus sistémico eritematoso, artritis reumatoide, enfermedad de Alzheimer, síndrome de choque tóxico, diabetes mellitus dependiente de insulina, dolor agudo y crónico, herida térmica, síndrome de angustia respiratoria en adultos (ARDS), enfermedad de obstrucción pulmonar crónica (COPD), herida múltiple de órganos secundaria por trauma, glomerulonefritis aguda, dermatosis con componentes inflamatorios agudos, meningitis purulenta aguda y otros trastornos del sistema nervioso central, enfermedad de Grave, miastenia grave, esclerodema y

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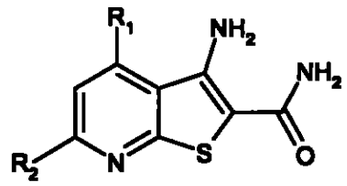
dermatitis atópica.

11. El método según la reivindicación 9, en el que la enfermedad inflamatoria o autoinmune se selecciona entre osteoartritis, artritis reumatoide, enfermedad de Chrohn, colitis ulcerativa, asma, síndrome de angustia respiratoria en adultos (ARDS) y enfermedad de obstrucción pulmonar crónica (COPD).

12. Un método para tratar aterosclerosis, infarto de miocardio o apoplejía, comprendiendo dicho método administrar a un paciente que necesita este tratamiento una cantidad terapéuticamente eficaz de un compuesto según la reivindicación 1.

13. Un método para tratar cáncer seleccionado entre enfermedades malignas de derivación linfoide, mieloide y epitelial, leucemia, linfomas, cáncer de mamas, cáncer gástrico, cáncer de colon-rectal, cáncer de pulmón y cáncer pancreático, comprendiendo dicho método administrar a un paciente que necesita este tratamiento una cantidad terapéuticamente eficaz de un compuesto según la reivindicación 1.

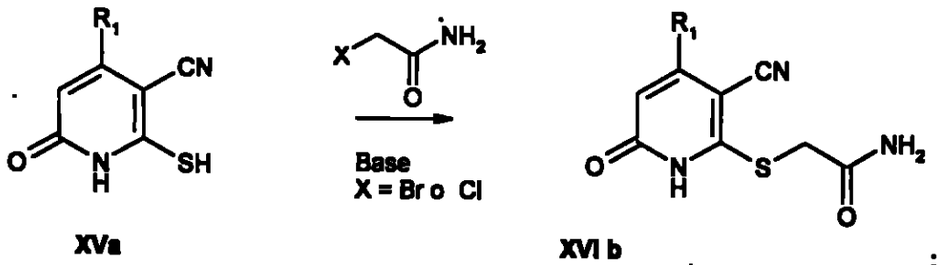
14. Un método para preparar un compuesto de fórmula (I):



I

en la que R_1 y R_2 son como se definieron en la reivindicación 4, método que comprende:

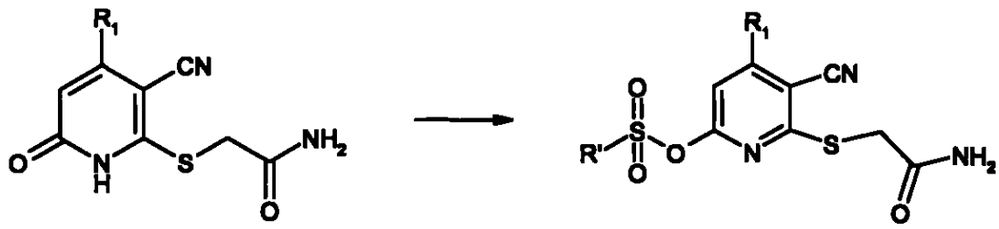
(a) hacer reaccionar un compuesto de fórmula (XVa) con 2-cloro- o 2-bromo-acetamida en presencia de una base adecuada, en un disolvente adecuado, para formar el intermedio de fórmula (XVIb)



XVa XVI b ;

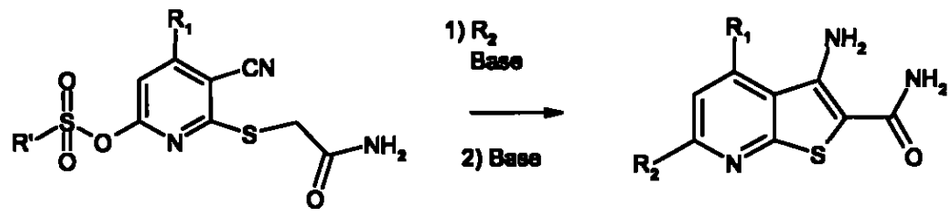
(b) hacer reaccionar el intermedio de fórmula (XVIb) con un reactivo sulfonante adecuado en presencia de una base adecuada en un disolvente adecuado para formar el éster de sulfonilo de fórmula (XVIIb)

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XVI b XVII b

(c) hacer reaccionar el intermedio de fórmula (XVIIb) con R_2 en presencia de una base adecuada como trietilamina, seguido de la adición de una segunda base adecuada y una reacción adicional para formar el compuesto deseado de fórmula (I)



XVII b I

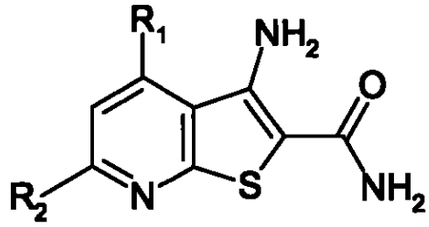
COLO 07612-841-007-3

PRP/WPCL7612/ID-000226

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RESUMEN

Se describen compuestos de fórmula (I):



I

en la que R_1 y R_2 se definen en la presente memoria descriptiva, que son útiles como inhibidores de la actividad de quinasa del complejo de IκB quinasa (IKK). Por lo tanto, los compuestos son útiles en el tratamiento de enfermedades mediadas por IKK que incluyen enfermedades inmunes, enfermedades inflamatorias y cáncer. Se describen también composiciones farmacéuticas que comprenden estos compuestos y procedimientos para preparar estos compuestos.

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royni Technologies S.A.

Item	Expediente No		No de Folio
		No de Unidades	√
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA X	2	1
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones: Contiene Acta Final

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343

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04129793 00000000 Folios: 342
Fecha (AMD): 2004-12-29 18:05:56
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 39,407
FECHA : DICIEMBRE 27 DE 2004

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	32758702	27/12/2004	21,068,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50003-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
		TOTAL : $	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 07612-841-0073

343
344

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04129793 00000000 Folios: 342
Fecha (AMD): 2004-12-29 18:05:56
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓	MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.		( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		( )	( )
- Descripción de la invención.		( )	( )
- Dibujos de ser estos pertinentes.		( )	( )
- Comprobante de Pago de las tasas establecidas.			
COMPLETA (✓)	INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )			
- Indicación de que se solicita el registro de Diseño Industrial		( )	( )
- Datos de identificación del solicitante o de la persona que presenta		( )	( )
- la solicitud.			
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.		( )	( )
Comprobante de pago de las tasas establecidas		( )	( )
COMPLETA ( )	INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )			
- Indicación de que solicita el registro de un Esquema de trazado.		( )	( )
- Datos de identificación del solcitante o de la persona que presenta La solicitud.		( )	( )
Representación gráfica del esquema de trazado		( )	( )
Comprobante de pago de las tasas establecidas.		( )	( )
COMPLETA ( )	INCOMPLETA	( )	( )

Firma Responsable:

Fecha:

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345

Industria y Comercio
SUPERINTENDENCIA

2020
.Bogotá D C

Doctor(a)
EMILIO FERRERO
Apoderado(a)
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Oficio N° 1921

ASUNTO:

Radicación N°	04-129793
Solicitud internacional	PCT/US03/17343
Fecha inicio fase nacional	06/01/2005
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de 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,
21 ENE 2005

202044

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Conmutador: 3 820840 Fax: 3 505220
Sede CAN: Tr. 40A No. 38-50 3153265 al 69
Fax: 3 505230. Línea 9800-910 165
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Bogotá D.C. - Colombia