80

Industria y Comercio

SUPERINTENDENCIA

CSA055556

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

EXPEDIENTE No. 09-107316

TÍTULO COMPUESTOS DE PIRIMIDINA HIDRAZIDA COMO INHIBIDORES DE PGDS

CLASIFICACIÓN INTERNACIONAL A61K 31/506 A61P

SOLICITANTE SANOFI-AVENTIS

DOMICILIO PARIS, FRANCIA

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

BOGOTÁ, D.C.,

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

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: **SANOFI-AVENTIS** sociedad constituida y existente bajo las leyes de Francia.

Dirección: 174 Avenue de France, 75013 Paris, Francia

Domicilio: Paris, Francia

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

3 REPRESENTANTE O APODERADO

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

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

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5 **PCT (86)**

Solicitud Internacional No. PCT/US2008/058347 Fecha: 27 de marzo de 2008

Publicación Internacional No. WO 2008/121670 A1 Fecha: 9 de octubre de 2008

6 **Título (54)**

COMPUESTOS DE PIRIMIDINA HIDRAZIDA COMO INHIBIDORES DE PGDS

7 **Clasificación Internacional (51)** C07D 239/028

- A61K 31/506 A61P 29/00

8 **Prioridad** SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	30 de marzo de 2007	60/909,171

9 **Comprobante de pago No.:** 09-70,589 **Fecha:** 21 de septiembre de 2009

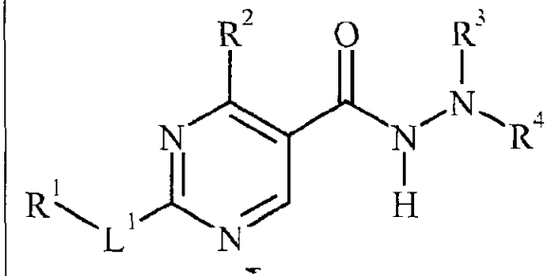
Comprobante de pago No.: 09-68,504 **Fecha:** 14 de septiembre de 2009

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 540.000.oo.
- ☒ Comprobante de pago por 9 reivindicaciones adicionales después de la decimoquinta reivindicación por $225.000.00.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



(I)

12 Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PÁEZ

FIRMA : Luz Clemencia de Páez

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

JGG

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2008/121670 A1

   Descripción:

   Páginas 233 en el idioma original

   Páginas 229 en español

   Reivindicaciones: Número (s) 24

   Figuras: Número (s)

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

3. ☒ Extracto de publicación.

O SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

ME-43

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 72-35
BOGOTÁ, D - COLOMBIA

179

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

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

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

10475
7804

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

domiciliado (s) en/of **174, avenue de France**
F-75013 Paris, Francia, hereby ratify the patent application No. 05.057.645 filed by EMILIO FERRERO on June 14, 2005 and

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

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos, b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa 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

in due compliance with the terms of paragraph 1st of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929, GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa 23555 and GERMAN CAVELIER, tpa. 832, 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 of its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

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

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.

the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this _____

en/in _____

por/by _____

Firma / Signature

Sanofi-Aventis Dr. Markus Jacobi

Vu pour certification matérielle de la signature de M. Markus JACOBI apposée ci-dessus

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

.....

1. - République Française
   Le présent acte public
2. - a été signé par Mc Koenig
3. - agissant en qualité de NOTAIRE
4. - est revêtu du sceau de la Cour

ATTESTE

5. - à Paris le 21 JUIN 2005
6. - Par le Procureur Gal près la Cour d'Appel
8. - Sous N° 81902/2005
9. - Sceau Le signature

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA
15 ENE 2009
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

K. L. ASSOCIÉS
Notaires
20, rue de la Paix
75002 PARIS
Tél. 01 55 04 70 00 - Fax 01 40 20 42 43

CERTIFICAT NOTARIE (SOCIETE)

Le Notaire soussigné certifie : que la signature qui précède de :
Markus JACOBI

Est authentique et que le signataire occupe actuellement le poste de Directeur Operations Brevets Europe
De la société sanofi-aventis,
et que ladite société fonctionne et est régie par le droit français
que la société est sise174 avenue de France, 75013 PARIS, France
et que le signataire est habilité à octroyer le présent pouvoir.

Tous les faits susmentionnés sont connus du Notaire qui a examiné les documents correspondants et les certifie.

Etabli et signé à Paris
Le 20/06/05

Le Notaire
(signature – cachet)

Alain KOENIG
NOTAIRE
de la Paix - 75002 PARIS Cedex 01

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Pays :
   Le présent acte public
2. a été signé par
3. agissant en qualité de
4. est revêtu du sceau/cachet de/du

Attesté

5. à
6. le
7. par
8. N°
9. Sceau/cachet :
10. Signature :

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
15 ENE 2009
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

Traducción Oficial No. 20050708 de un documento escrito en Francés y en INGLES, el cual, para su identificación se sella con el sello de María Eugenia Sanint Traductora Oficial según Resolución 1448 del Ministerio de Justicia.

LEGALIZACIONES

Escritas en FRANCES, al pie de un PODER escrito en ESPAÑOL, otorgado por **SANOFI- AVENTIS**, a favor de **EMILIO FERRERO, GONZALO PERDOMO, LUZ CLEMENCIA PAEZ Y GERMAN CAVELIER** (por el cual se ratifica la solicitud de patente NO. 05.057.645 presentada por **EMILIO FERRERO** el 14 de junio de 2005.)

(Firma Ilegible)
Dr. Markus Jacobi
Sanofi-Aventis

Visto para la certificación material de la firma del Sr. Markus Jacobi, puesta anteriormente.
(Firma Ilegible)
.L. ASSOCIES
Notarios
20, rue de la Paix
75002 PARIS

Sello del Notario

CERTIFICADO NOTARIAL (SOCIEDAD)
El Notario suscrito certifica que la firma puesta anteriormente de:

Marcus Jacobi

es auténtica, y que el signatario ocupa actualmente el cargo de Director de Operaciones Patentes Europa, de la sociedad Sanofi-Aventis, y que la dicha sociedad funciona y está regida por el derecho francés; que la sociedad tiene su sede en el 174, avenue de France, 75013, PARIS, Francia, y que el signatario está habilitado para otorgar el presente poder.

Todos los hechos mencionados anteriormente son de conocimiento del Notario, quien examinó los documentos correspondientes y los certifica:

Dado y firmado en París, hoy, 20 de junio de 2005.

El Notario
(Firma – sello)

MARIA EUGENIA SANINT
TRADUCTORA OFICIAL
RESOLUCION No. 671 BIS
DEL MINISTERIO DE JUSTICIA

MARIA EUGENIA SANINT
TRADUCTORA OFICIAL
RESOLUCION No. 1448 DEL
5 DE SEPTIEMBRE DE 30
del Ministerio de Justicia

COMO NOTARIA SEXTA (E) DEL CÍRCULO DE BOGOTÁ, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTÁ D.C. REPÚBLICA DE COLOMBIA
15 ENE 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

(Ilegible)
Alain Koenig
NOTARIO
20, rue de la Paix, París

APOSTILLA
(Convenio de La Haya del 5 de octubre de 1961)

1. País: República Francesa

   El presente Documento Público

2. Fue firmado por el Abogado Koenig

3. Quien actúa en calidad de NOTARIO

4. Lleva el sello de SU DESPACHO

Certifica

5. En París 6. El 21 de junio de 2005

7. Por el Procurador General ante el Tribunal de Primera Instancia

8. Bajo el Número 81903

9. Sello/Estampilla:

   Sello del Tribunal de Primera Instancia de París.

10- Firma: (Ilegible)

ES TRADUCCIÓN FIEL Y COMPLETA.
Traductora : Maria Eugenia Sanint
Bogotá, 8 de julio de 2005

MARIA EUGENIA SANINT
TRADUCTORA OFICIAL
RESOLUCION No. 671 DE
DEL MINISTERIO DE JUSTICIA

MARIA EUGENIA SANINT
TRADUCTORA OFICIAL
RESOLUCION 118 DEL
DE SE... 30.
del Ministerio de Justicia

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
15 ENE 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

COMO NOTARIO SEXTO DEL CIRCULO DE SAN[illegible] DE
[illegible]OTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIR
[illegible]A.S) PUESTA(S) POR
María Eugenia Sanin
IDENTIFICADOS CON C.C. No.(s)
ESTAMPA(S) AUTENTICA(S)
SANTAFE DE BOGOTA 12 JUL 2005

NOTARIA SEXTA
PABLO MENDEZ BARAHAS
Notario Sexto Encargado

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

MINISTERIO DE RELACIONES EXTERIORES

2005 JUL 12 P 1:28

449243

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

COMO NOTARIA SEXTA (E) DEL CÍRCULO DE BOGOTÁ, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA
15 ENE 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

UL

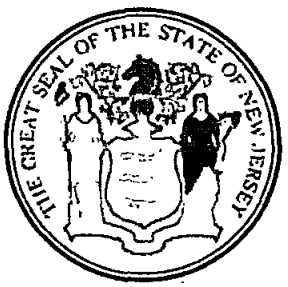
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
   NANCY J INGRAM
3. ACTING IN THE CAPACITY OF:
   NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
   NANCY J INGRAM, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 9TH DAY OF SEPTEMBER 2009
7. BY: R. David Rousseau, NEW JERSEY TREASURER
8. NO: A374113
9. SEAL/STAMP:
10. SIGNATURE



Certificate Number: 115258006
Verify this certificate at
https://www1.state.nj.us/TYTR_StandingCert/JSP/Verify_Cert.jsp

NOTARIAL TRUE COPY

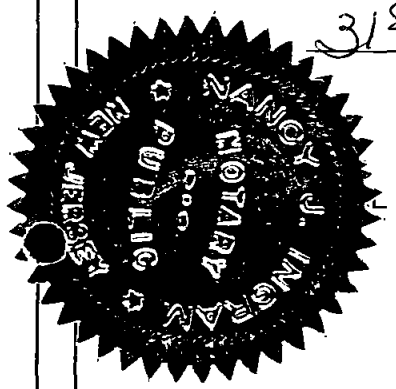
UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF SOMERSET)

I, Tina M. Wisbeski, do hereby swear or affirm and verify that the annexed document(s) are TRUE COPIES of the original document(s) which I have compared.

Tina M Wisbeski
Signature

UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF SOMERSET)

Subscribed and sworn to before me at Bridgewater, New Jersey, this 31st day of August, 2009.



Nancy J Ingram
Notary Public
Nancy J. Ingram
Notary Public, State of New Jersey
My Commission Expires August 2, 2009

US2007/050 CO

ASSIGNMENT AND AGREEMENT

For value received and intending to be legally bound, I/we, the undersigned joint inventor(s) (Assignor(s)), sell, assign and transfer to **SANOFI-AVENTIS** (Assignee), 174 Avenue de France, Paris, 75013, France, and its successors, assigns and legal representatives, the entire right, title and interest in and to my/our invention and any improvements thereon for all countries of the world, relating in and to the application for Letters Patent therefor, assigned Attorney Docket No. **US2007/050 WO PCT,** and entitled

PYRIMIDINE HYDRAZIDE COMPOUNDS AS PGDS INHIBITORS

and for all patent applications which claim priority to or are derived from said priority applications:

Provisional Application Filing Date:	March 30, 2007
Provisional Application No.:	60/909,171
International Application Filing Date:	March 27, 2008
International Application No.:	PCT/US2008/058347

and all the rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, including the right to claim priority based on said United States application, and under any and all Letters Patent which may be granted therefor, and all right, title and interest in and to every patent application filed or to be filed on said invention in any other country or patent organization, including continuations, divisions, renewals, revivals, and any substitute applications of said United States application, and any and all patents which may issue thereon, and any reissues, pipelines and extensions, and governmental exclusivity rights of the same.

I/we authorize and request competent authorities to grant and issue any and all patents on said invention to said assignee or its successor, assigns and legal representatives, or to such nominees as said assignee may designate.

I/we agree that, when requested, I/we will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining patents for said invention in any and all countries and for vesting title thereto in said assignee, its successors, assigns, legal representatives or nominees.

I/we covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that I/we have full right to convey the same as herein expressed.

Signed at Bridgewater (City, State and Nation) on this 1st day of April, 2008.

Signature: _____

Inventor's Name: Christopher VanDeusen

Residential Address: ~~East Windsor, NJ 08520~~ Bridgewater, NJ 08807

Witnessed by:

Nancy J Ingram
NANCY J INGRAM
Bridgewater, NJ 08807

Tina M Wisbeski
Tina M. Wisbeski
Bridgewater, NJ 08807

TRADUCCION OFICIAL NO. 808/2009-.

EL TEXTO QUE SIGUE ES TRADUCCION FIEL Y COMPLETA DE UN DOCUMENTO ESCRITO EN INGLES. LLEVA LA FIRMA Y EL SELLO DE HELENA URIBE DE LEMOINE, TRADUCTORA E INTERPRETE OFICIAL SEGUN RESOLUCION NO. 3618 DEL MINISTERIO DE JUSTICIA DE COLOMBIA, DE FECHA 6 DE SEPTIEMBRE DE 1972.

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sanofi-aventis Ref No. US2007/050 WO PCT

CESIÓN Y CONTRATO

Por el valor recibido y con la intención de que sea legalmente obligatorio, yo/nosotros, el abajo firmante inventor (s) Cesionario (s) conjuntamente, vendo y transfiero a **SANOFI-AVENTIS** (Cesionario), 174 avenue de France, 75013, PARIS, Francia, y sus sucesores, cesionarios y representantes legales, todos los derechos, título e intereses en mi invento y cualquier mejora a este en todos los países del mundo, relacionados con y para la aplicación de Cartas Patente, registro de Sumarios Legales No. **US2007/050 WO PCT**, y titulado

"COMPUESTOS DE PIRIMIDINA HIDRAZIDA COMO INHIBIDORES DE PGDS"

y para todas las aplicaciones de patentes que reclaman prioridad a o que se derivan de aplicaciones de dicha prioridad:

Fecha de registro de la Solicitud Provisional	MARZO 30, 2007
Solicitud Provisional No.:	60/909.171;
Fecha de Registro de la Solicitud Internacional:	MARZO 27, 2008
Solicitud Internacional No.:	PCT/US2008/058347

Y todos los derechos y privilegios, incluyendo cualquiera o todos los beneficios bajo la Convención Internacional para la Protección de la Propiedad Industrial, incluyendo el derecho a reclamar la prioridad con base en la mencionada solicitud de los Estados Unidos y bajo cualquiera y todas las Cartas Patente que puedan ser otorgadas como consecuencia de estos actos, y todos los derechos, y el derecho, título e interés en y a toda solicitud de patente registrada o a ser registrada sobre el mencionado invento en cualquier otro país u organización de patentes, incluyendo las continuaciones, divisiones, renovaciones, reactivaciones y cualesquiera aplicaciones sustitutas de dichas aplicaciones de los Estados Unidos, y cualquiera y todas las patentes que se expidan sobre esto, y cualquier reemisión, oleoductos y extensiones y derechos exclusivos del gobierno del mismo.

HELENA URIBE DE LEMOINE
RES No 3618
SEP 6 '97
MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 808/2009-.

Yo/nosotros autorizo y solicito a las autoridades competentes otorgar y expedir cualquiera y todas la patentes sobre dicho invento al mencionado cesionario o a sus sucesores, cesionarios y representantes legales, o a las personas propuestas que dicho cesionario designe.

Yo/nosotros acordamos que, mediante solicitud, Yo/nosotros firmaré todos los documentos, tomaré todos los juramentos de ley y realizaré todos los actos que sean deseables o convenientes necesarios para asegurar y mantener las patente para el mencionado invento en cualquier y todos los paises y para conferir el título de esto en dicho cesionario, sus sucesores, cesionarios, representantes legales o designados, sin cargo para el mencionado cesionario pero a su expensa.

Yo/nosotros pacto con el mencionado cesionario, sus sucesores, cesionarios y representantes legales, que los derechos y propiedad traspasada por medio de este documento está libre y saneada de cualquier gravamen y que Yo/nosotros tengo todo el derecho a traspasar la misma como se expresa en este documento.

Firmado en Bridgewater el 1° de Abril de 2008
Firmado: CHRISTOPHER VANDEUSEN
Nombre del Inventor: CHIRSTOPHER VANDEUSEN
Dirección: BRIDGEWATER, NJ, 08807

TESTIGOS:

Firmado: Ilegible
NOMBRE:NANCY J. INGRAM
BRIDGEWATER NJ, 08807

Firmado: Ilegible
NOMBRE: TINA M. WISBESKI
BRIDGEWATER NJ, 08807

HELENA URIBE DE LEMOINE
RES No 3619 SEPT 6 1972 MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 808/2009-.

COPIA NOTARIAL AUTENTICA

ESTADOS UNIDOS DE AMERICA
ESTADO DE NEW JERSEY
CONDADO DE SOMERSET

A TODOS A QUIENES LOS PRESENTES LLEGUEN,

Yo, TINA M. WISBESKI, POR MEDIO DEL PRESENTE CERTIFICO BAJO JURAMENTO Y EL SELLO DE MI DESPACHO, QUE EL DOCUMENTO ADJUNTO ES UNA COPIA VERDADERA DEL DOCUMENTO ORIGINAL CON EL CUAL LO HE COMPARADO.

FIRMADO: TINA M. WISBESKI

ESTADOS UNIDOS DE AMERICA

ESTADO DE NEW JERSEY

CONDADO DE SOMERSET

SUSCRITO Y JURADO ANTE MI EN BRIDGEWATER, NEW JERSEY, ESTE DIA 31 DE AGOSTO DE 2009.

FIRMADO: NANCY J. INGRAM, NOTARIO PUBLICO, ESTADO DE NEW JERSEY, CON COMISION HASTA EL 2 DE AGOSTO DE 2009.

HAY SELLO DEL NOTARIO.

HELENA LEMOINE
RES No
3618
SEPT 6 1972
MINISTERIO
JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 808/2009-.

APOSTILLA

CONVENIO DE LA HAYA DEL 5 DE OCTUBRE DE 1961

1. PAIS: ESTADOS UNIDOS DE AMÉRICA

EL PRESENTE DOCUMENTO PUBLICO

2. HA SIDO FIRMADO POR: **NANCY J. INGRAM**
3. ACTUANDO EN SU CAPACIDAD DE: NOTARIO PUBLICO DE NEW JERSEY
4. LLEVA EL SELLO DE: NANCY J. INGRAM, NOTARIO

CERTIFICADO

5. EN: TRENTON, NEW JERSEY
6. EL: 9 DE SEPTIEMBRE DE 2009
7. POR: R. DAVID ROUSSEAU, TESORERO DE NEW JERSEY
8. BAJO EL NO.: **A374113**
9. SELLO: DESPACHO DEL SECRETARIO DE ESTADO
10. FIRMADO: ILEGIBLE.

CERTIFICADO NUMERO: 115258006

LA TRADUCTORA OFICIAL

HELENA URIBE DE LEMOINE

HELENA URIBE DE LEMOINE
RES No 3618
SEPT 6 1972
MINISTERIO JUSTICIA

4841
UL

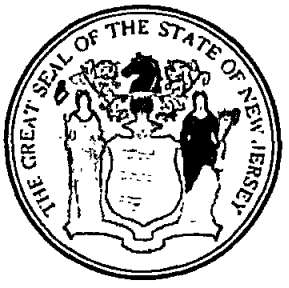
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
   NANCY J INGRAM
3. ACTING IN THE CAPACITY OF:
   NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
   NANCY J INGRAM, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 9TH DAY OF SEPTEMBER 2009
7. BY: R. David Rousseau, NEW JERSEY TREASURER
8. NO: A374113
9. SEAL/STAMP:



10. SIGNATURE

Certificate Number: 115257979
Verify this certificate at
https://www1.state.nj.us/TYTR_StandingCert/JSP/Verify_Cert.jsp

NOTARIAL TRUE COPY

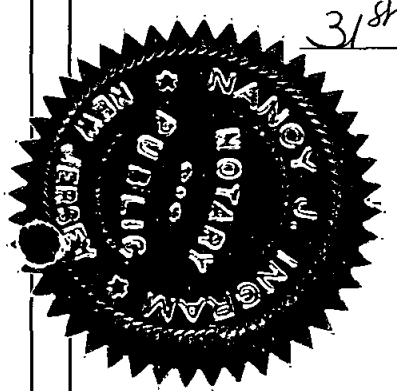
UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF SOMERSET)

I, Tina M. Wisbeski, do hereby swear or affirm and verify that the annexed document(s) are TRUE COPIES of the original document(s) which I have compared.

Tina M Wisbeski
Signature

UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF SOMERSET)

Subscribed and sworn to before me at Bridgewater, New Jersey, this 31st day of August, 2009.



Nancy J Ingram
Notary Public
Nancy J Ingram
Notary Public, State of New Jersey
My Commission Expires August 2. 2009

US2007/050 CO

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

500467627A

FEBRUARY 20, 2008

PTAS

JIANG LIN
ROUTE 202-206
BRIDGEWATER, NJ 08807

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 02/20/2008 REEL/FRAME: 020530/0748
NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: US2007-050 US PSP

ASSIGNOR:
SANOFI-AVENTIS U.S. LLC. DOC DATE: 02/19/2008

ASSIGNEE:
SANOFI-AVENTIS
174 AVENUE DE FRANCE
PARIS, FRANCE 75013

SERIAL NUMBER: 60909171 FILING DATE: 03/30/2007
PATENT NUMBER: ISSUE DATE:
TITLE: PYRIMIDINE HYDRAZIDE COMPOUNDS AS PGDS INHIBITORS

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

02/20/2008
500467627

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
Sanofi-Aventis U.S. LLC.	02/19/2008

RECEIVING PARTY DATA

Name:	Sanofi-Aventis
Street Address:	174 Avenue de France
City:	Paris
State/Country:	FRANCE
Postal Code:	75013

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	60909171

CH $40.00 60909171

CORRESPONDENCE DATA

Fax Number: (908)231-2626
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 908-231-3582
Email: maribel.mendez@sanofi-aventis.com
Correspondent Name: Jiang Lin
Address Line 1: Route 202-206
Address Line 4: Bridgewater, NEW JERSEY 08807

ATTORNEY DOCKET NUMBER:	US2007-050 US PSP
NAME OF SUBMITTER:	Maribel Mendez

Total Attachments: 1
source=US2007050 USPSP Corp Assignment to SAFR#page1.tif

ASSIGNMENT AND AGREEMENT

For value received and intending to be legally bound, we, **SANOFI-AVENTIS U.S. LLC.** (Assignor), 55 Corporate Drive, Bridgewater, New Jersey 08807, sell, assign and transfer to **SANOFI-AVENTIS** (Assignee), 174 Avenue de France, Paris, 75013, France, and its successors, assigns and legal representatives, the entire right, title and interest in and to my/our invention and any improvements thereon for all countries of the world, relating in and to the application for United States Letters Patent therefor, assigned Attorney Docket No. **US2007/050 US PSP** and (if filed prior to the execution hereof) filed on **March 30, 2007**, as Serial No. **60/909,171**, entitled

PYRIMIDINE HYDRAZIDE COMPOUNDS AS PGDS INHIBITORS

and all the rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, including the right to claim priority based on said United States application, and under any and all Letters Patent which may be granted therefor, and all right, title and interest in and to every patent application filed or to be filed on said invention in any other country or patent organization, including continuations, divisions, renewals, revivals, and any substitute applications of said United States application, and any and all patents which may issue thereon, and any reissues, pipelines and extensions, and governmental exclusivity rights of the same.

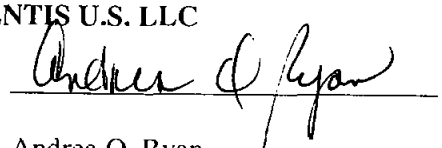
We authorize and request competent authorities to grant and issue any and all patents on said invention to said assignee or its successor, assigns and legal representatives, or to such nominees as said assignee may designate.

We agree that, when requested, we will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining patents for said invention in any and all countries and for vesting title thereto in said assignee, its successors, assigns, legal representatives or nominees.

We covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that we have full right to convey the same as herein expressed.

IN WITNESS THEREOF, the parties hereto agree to accept the terms of this Assignment with an effective date of March 31, 2007.

Assignor:
SANOFI-AVENTIS U.S. LLC

Signature:  Date: February 19, 2008

Name: Andrea Q. Ryan

Title: Attorney-In-Fact

Assignee:
SANOFI-AVENTIS

Signature:  Date: February 19, 2008

Name: Andrea Q. Ryan

Title: Authorized Signatory

TRADUCCION OFICIAL NO.806/2009-.

EL TEXTO QUE SIGUE ES TRADUCCION FIEL Y COMPLETA DE UN DOCUMENTO ESCRITO EN INGLES. LLEVA LA FIRMA Y EL SELLO DE HELENA URIBE DE LEMOINE, TRADUCTORA E INTERPRETE OFICIAL SEGUN RESOLUCION NO. 3618 DEL MINISTERIO DE JUSTICIA DE COLOMBIA, DE FECHA 6 DE SEPTIEMBRE DE 1972.

(HAY UN SELLO DE LA OFICINA DE
PATENTES Y MARCAS REGISTRADAS DE LOS ESTADOS UNIDOS)
Oficina de Patentes Y Marcas Registradas de los Estados Unidos

Subsecretario de Comercio para Propiedad Intelectual y
Director de la Oficina de Patentes y Marcas Registradas

20 de Febrero de 2008 *500467627A*

PTAS

JIANG LIN
ROUTE 202-206
BRIDGEWATER, NJ 08807

OFICINA DE PATENTES Y MARCAS REGISTRADAS
DE LOS ESTADOS UNIDOS
NOTIFICACIÓN DE REGISTRO DE DOCUMENTO DE CESIÓN

EL DOCUMENTO ADJUNTO HA SIDO REGISTRADO POR LA DIVISIÓN DE CESIONES DE LA OFICINA DE PATENTES Y MARCAS REGISTRADAS DE LOS ESTADOS UNIDOS. HAY UNA COPIA COMPLETA EN MICROFILM DISPONIBLE EN LA SALA DE BÚSQUEDA DE CESIONES BAJO EL NÚMERO DEL CARRETE Y MICROFICHA CUYA REFERENCIA APARECE ABAJO.

POR FAVOR, REVISE TODA LA INFORMACIÓN CONTENIDA EN ESTA NOTIFICACIÓN. LA INFORMACIÓN CONTENIDA EN ESTA NOTIFICACIÓN DE RECORDATORIO CONTIENE LOS DATOS PRESENTES EN EL SISTEMA DE ASIGNACIÓN DE PATENTES Y MARCAS REGISTRADAS. EN CASO DE QUE USTED ENCUENTRE UN ERROR O SI TIENE PREGUNTAS REFERENTES A ESTA NOTIFICACIÓN, PUEDE PONERSE EN CONTACTO CON EL EMPLEADO CUYO NOMBRE APARECE EN ESTA NOTIFICACIÓN, EN EL TELÉFONO 571-272-3350. POR FAVOR, ENVÍE LA SOLICITUD PARA REALIZAR LA CORRECCIÓN A: UNITED STATES PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VIRGINIA 22313.

FECHA DE REGISTRO: 02/20/2008
CARRETE/MICROFICHA: 020530/0748 NUMERO DE PÁGINAS: 2

HELENA URIBE DE LEMOINE
RES No
3618
SEPT 6 1972
MINISTERIO
JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO.806/2009-.

SUMARIO: CESIÓN DEL INTERÉS DEL CEDENTE (VEA EL DOCUMENTO PARA OBTENER DETALLES).

EXPEDIENTE NUMERO: US2007 – 050 US PSP

CEDENTE:
SANOFI-AVENTIS U.S. LLC FECHA DOCUMENTO: 02/19/2008

CECIONARIO:
SANOFI-AVENTIS
174 AVENUE DE FRANCE
PARIS, FRANCIA 75013

NÚMERO DE SERIE: 60909171 FECHA DE RADICACIÓN: 03/30/2007
NÚMERO DE PATENTE: (en blanco) FECHA DE EMISIÓN: (en blanco)

TITULO:

"COMPUESTOS DE PIRIMIDINA HIDRAZIDA COMO INHIBIDORES DE PGDS"

SUCURSAL DE SERVICIOS DE CESIÓN
OFICINA DE REGISTROS PÚBLICOS

HELENA URIBE DE LEMOINE
RES No 3618 SEPT 6 1972 MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO.806/2009-.

CESIÓN DE PATENTE

Versión Electrónica v1.1 **02/20/2008**
Versión Impresa v1.1 **500467627**

TIPO DE PRESENTACIÓN	NUEVA CESIÓN
NATURALEZA DEL TRASPASO	CESIÓN

DATOS DE LA PARTE CEDENTE

NOMBRE	FECHA DE EJECUCIÓN
Sanofi-Aventis U.S. LLC.	02/19/2008

DATOS DE LA PARTE RECEPTORA

Nombre:	**Sanofi-Aventis**
Dirección	174 Avenue de France
CIUDAD	Paris
ESTADO	Francia
CÓDIGO POSTAL	75013

TOTAL NÚMEROS DE PROPIEDAD: 1

Tipo de Propiedad	Número
Número de Solicitud	60909171

DATOS PARA LA CORRESPONDENCIA
Numero Fax: (908) 231-2626
La correspondencia será enviada por el servicio postal de los Estados Unidos cuando el envío por fax no sea posible.
Teléfono: 908 231 3582
Email: maribel.mendez@sanofi-aventis.com
Nombre del Corresponsal: Jiang Lin
Dirección Línea 1: Route 202-206
Dirección Línea 4: Bridgewater, New Jersey 08807

NUMERO DEL EXPEDIENTE	US2007-050USPSP
NOMBRE DEL PRESENTADOR:	Maribel Mendez

TOTAL ANEXOS: 1

Fuente = US2007050 USPSP Corp CESIÓN a SAFR#pág. 1. tif

HELENA URIBE DE LEMOINE
RES No 3618
SEPT 6 1972
MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO.806/2009-.

CESIÓN Y CONTRATO

Por el valor recibido y con la intención de que sea legalmente obligante, nosotros **SANOFI-AVENTIS U.S. LLC.,** (el "Cedente") de 55 Corporate Drive, Bridgewater, New Jersey 08807, vendemos, cedemos y transfiere a **SANOFI-AVENTIS,** (el "Cesionario") de 174 Avenue de France, Paris 75013, Francia y sus sucesores, cesionarios y representantes legales, todos los derechos, título e intereses en nuestro invento y cualquier mejora a este en todos los países del mundo, relacionados con y para la aplicación de Cartas Patente, registro de Sumarios Legales No. **US2007/050 US PSP** y (si fueren radicados antes de la ejecución del presente) radicado el 30 de Marzo de 2007, No. Serie **60/909.171,** y titulado

"COMPUESTOS DE PIRIMIDINA HIDRAZIDA COMO INHIBIDORES DE PGDS"

Y todos los derechos y privilegios, incluyendo cualquiera o todos los beneficios bajo la Convención Internacional para la Protección de la Propiedad Industrial, incluyendo el derecho a reclamar la prioridad con base en la mencionada solicitud de los Estados Unidos y bajo cualquiera y todas las Cartas Patente que puedan ser otorgadas como consecuencia de estos actos, y todos los derechos, y el derecho, título e interés en y a toda solicitud de patente registrada o a ser registrada sobre el mencionado invento en cualquier otro país u organización de patentes, incluyendo las continuaciones, divisiones, renovaciones, reactivaciones y cualesquiera aplicaciones sustitutas de dichas aplicaciones de los Estados Unidos, y cualquiera y todas las patentes que se expidan sobre esto, y cualquier reemisión, oleoductos y extensiones y derechos exclusivos del gobierno del mismo.

HELENA URIBE DE LEMOINE
RES No
3618
SEPT 6 1972
MINISTERIO
JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO.806/2009-.

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Yo/nosotros pacto con el mencionado cesionario, sus sucesores, cesionarios y representantes legales, que los derechos y propiedad traspasada por medio de este documento está libre y saneada de cualquier gravamen y que Yo/nosotros tengo todo el derecho a traspasar la misma como se expresa en este documento.

En testimonio de lo anterior las partes del presente aceptan los términos del presente Documento de Cesión con fecha efectiva el 31 de Marzo de 2007

CEDENTE:

SANOFI-AVENTIS U.S. LLC

FIRMADO: ANDREA Q. RYAN FECHA: 19 DE FEBRERO DE 2008

CARGO: APODERADO

CESIONARIO:
SANOFI AVENTIS

FIRMADO: ANDREA Q. RYAN FECHA: 19 DE FEBRERO DE 2008

CARGO: FIRMANTE AUTORIZADO

HELENA URIBE DE LEMOINE
RES No 3618
SEPT 6 1972
MINISTERIO JUSTICIA

TRADUCCION OFICIAL NO.806/2009-.

COPIA NOTARIAL AUTENTICA

ESTADOS UNIDOS DE AMERICA
ESTADO DE NEW JERSEY
CONDADO DE SOMERSET

A TODOS A QUIENES LOS PRESENTES LLEGUEN,

Yo TINA M. WISBESKI, POR MEDIO DEL PRESENTE CERTIFICO BAJO JURAMENTO Y EL SELLO DE MI DESPACHO, QUE EL DOCUMENTO ADJUNTO ES UNA COPIA VERDADERA DEL DOCUMENTO ORIGINAL CON EL CUAL LO HE COMPARADO.

FIRMADO: TINA M. WISBESKI

ESTADOS UNIDOS DE AMERICA

ESTADO DE NEW JERSEY

CONADO DE SOMERSET

SUSCRITO Y JURADO ANTE MI EN BRIDGEWATER, NEW JERSEY, ESTE DIA 31 DE AGOSTO DE 2009

FIRMADO: NANCY J. INGRAM, NOTARIO PUBLICO, ESTADO DE NEW JERSEY, CON COMISION HASTA EL 2 DE AGOSTO DE 2009.

HAY SELLO DEL NOTARIO.

HELENA URIBE DE LEMOINE
RES No 3618
SEPT 6 1972
MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO.806/2009-.

APOSTILLA

CONVENIO DE LA HAYA DEL 5 DE OCTUBRE DE 1961

1. PAIS: ESTADOS UNIDOS DE AMÉRICA

EL PRESENTE DOCUMENTO PUBLICO

2. HA SIDO FIRMADO POR: **NANCY J. INGRAM**
3. ACTUANDO EN SU CAPACIDAD DE: NOTARIO PUBLICO DE NEW JERSEY
4. LLEVA EL SELLO DE: NANCY J. INGRAM, NOTARIO

CERTIFICADO

5. EN: TRENTON, NEW JERSEY
6. EL: 9 DE SEPTIEMBRE DE 2009
7. POR: R. DAVID ROUSSEAU, TESORERO DE NEW JERSEY
8. BAJO EL NO.: **A374113**
9. SELLO: DESPACHO DEL SECRETARIO DE ESTADO
10. FIRMADO: ILEGIBLE.

CERTIFICADO NUMERO: 115257979

LA TRADUCTORA OFICIAL

HELENA URIBE DE LEMOINE

HELENA URIBE DE LEMOINE
RES No 3618
SEPT 6 1972
MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

UL

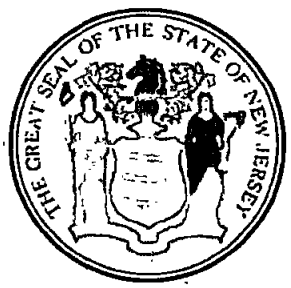
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
   NANCY J INGRAM
3. ACTING IN THE CAPACITY OF:
   NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
   NANCY J INGRAM, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 9TH DAY OF SEPTEMBER 2009
7. BY: R. David Rousseau, NEW JERSEY TREASURER
8. NO: A374113
9. SEAL/STAMP:
10. SIGNATURE



Certificate Number: 1152580210
Verify this certificate at
https://www1.state.nj.us/TYTR_StandingCert/JSP/Verify_Cert.jsp

NOTARIAL TRUE COPY

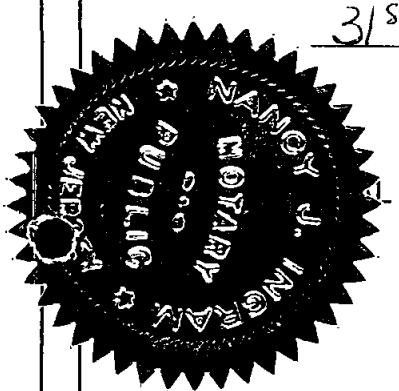
UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF SOMERSET)

I, Tina M. Wisbeski, do hereby swear or affirm and verify that the annexed document(s) are TRUE COPIES of the original document(s) which I have compared.

Tina M Wisbeski
Signature

UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF SOMERSET)

Subscribed and sworn to before me at Bridgewater, New Jersey, this 31st day of August, 2009.



Nancy J Ingram
Notary Public
Nancy J. Ingram
Notary Public, State of New Jersey
My Commission Expires August 2, 2009

US2007/050 Co

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

500472646A

FEBRUARY 26, 2008

PTAS

JIANG LIN
1041 ROUTE 202-206
BRIDGEWATER, NJ 08807

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 02/26/2008

REEL/FRAME: 020560/0946
NUMBER OF PAGES: 8

BRIEF: CORRECTIVE ASSIGNMENT TO CORRECT THE SPELLING OF THE ASSIGNOR PREVIOUSLY RECORDED ON REEL 020514 FRAME 0184. ASSIGNOR(S) HEREBY CONFIRMS THE CORRECT SPELLING OF ASSIGNOR SHOULD BE JOHN Z. JIANG..

DOCKET NUMBER: US2007-050 US PSP

ASSIGNOR:
ALDOUS, SUZANNE C. DOC DATE: 01/16/2008

ASSIGNOR:
FENNIE, MICHAEL W. DOC DATE: 01/16/2008

ASSIGNOR:
JIANG, JOHN Z. DOC DATE: 01/17/2008

ASSIGNOR:
JOHN, STANLY DOC DATE: 01/16/2008

ASSIGNOR:
MU, LAN DOC DATE: 01/16/2008

020560/0946 PAGE 2

ASSIGNOR:
PEDGRIFT, BRIAN DOC DATE: 01/16/2008

ASSIGNOR:
PRIBISH, JAMES R. DOC DATE: 01/16/2008

ASSIGNOR:
RAUCKMAN, BARBARA S. DOC DATE: 01/16/2008

ASSIGNOR:
SABOL, JEFFREY S. DOC DATE: 01/16/2008

ASSIGNOR:
STOKLOSA, GRZEGORZ T. DOC DATE: 01/16/2008

ASSIGNOR:
THURAIRATNAM, SUKANTHINI DOC DATE: 01/18/2008

ASSIGNEE:
SANOFI-AVENTIS U.S. LLC
55 CORPORATE DRIVE
BRIDGEWATER, NEW JERSEY 08807

SERIAL NUMBER: 60909171 FILING DATE: 03/30/2007
PATENT NUMBER: ISSUE DATE:
TITLE: PYRIMIDINE HYDRAZIDE COMPOUNDS AS PGDS INHIBITORS

TARA WASHINGTON, EXAMINER
ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

02/26/2008
500472646

SUBMISSION TYPE:	CORRECTIVE ASSIGNMENT
NATURE OF CONVEYANCE:	Corrective Assignment to correct the spelling of the assignor previously recorded on Reel 020514 Frame 0184. Assignor(s) hereby confirms the correct spelling of assignor should be John Z. Jiang..

CONVEYING PARTY DATA

Name	Execution Date
Suzanne C. Aldous	01/16/2008
Michael W. Fennie	01/16/2008
John Z. Jiang	01/17/2008
Stanly John	01/16/2008
Lan Mu	01/16/2008
[illegible]ian Pedgrift	01/16/2008
James R. Pribish	01/16/2008
Barbara S. Rauckman	01/16/2008
Jeffrey S. Sabol	01/16/2008
Grzegorz T. Stoklosa	01/16/2008
Sukanthini Thurairatnam	01/18/2008

RECEIVING PARTY DATA

Name:	Sanofi-Aventis U.S. LLC
Street Address:	55 Corporate Drive
City:	Bridgewater
State/Country:	NEW JERSEY
Postal Code:	08807

CH $40.00 60909171

[illegible]ROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	60909171

CORRESPONDENCE DATA

Fax Number: (908)231-2626
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 908-231-3582

Email: maribel.mendez@sanofi-aventis.com
Correspondent Name: Jiang Lin
Address Line 1: 1041 Route 202-206
Address Line 4: Bridgewater, NEW JERSEY 08807

ATTORNEY DOCKET NUMBER:	US2007-050 US PSP
NAME OF SUBMITTER:	Maribel Mendez

Total Attachments: 6
source=US2007-050 US PSP - Executed Assignment#page1.tif
source=US2007-050 US PSP - Executed Assignment#page2.tif
source=US2007-050 US PSP - Executed Assignment#page3.tif
source=US2007-050 US PSP - Executed Assignment#page4.tif
source=US2007-050 US PSP- Electronic Confirmation#page1.tif
source=US2007-050 US PSP- Electronic Confirmation#page2.tif

ASSIGNMENT AND AGREEMENT

For value received and intending to be legally bound, I/we, the undersigned joint inventor(s) (Assignor(s)), sell, assign and transfer to **sanofi-aventis U.S. LLC** (Assignee), 55 Corporate Drive, Bridgewater, New Jersey 08807, United States of America, and its successors, assigns and legal representatives, the entire right, title and interest in and to my/our invention and any improvements thereon for all countries of the world, relating in and to the application for United States Letters Patent therefor, assigned Attorney Docket No. **US2007/050 US PSP** and (if filed prior to the execution hereof) filed on **March 30, 2007**, as Serial No. **60/909,171**, entitled

PYRIMIDINE HYDRAZIDE COMPOUNDS AS PGDS INHIBITORS

and all the rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, including the right to claim priority based on said United States application, and under any and all Letters Patent which may be granted therefor, and all right, title and interest in and to every patent application filed or to be filed on said invention in any other country or patent organization, including continuations, divisions, renewals, revivals, and any substitute applications of said United States application, and any and all patents which may issue thereon, and any reissues, pipelines and extensions, and governmental exclusivity rights of the same.

I/we authorize and request competent authorities to grant and issue any and all patents on said invention to said assignee or its successor, assigns and legal representatives, or to such nominees as said assignee may designate.

I/we agree that, when requested, I/we will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining patents for said invention in any and all countries and for vesting title thereto in said assignee, its successors, assigns, legal representatives or nominees.

I/we covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that I/we have full right to convey the same as herein expressed.

Signed at Bridgewater, NJ (City/State and Nation) USA on this 16th day of January, 2008.

Signature: Suzanne Aldous

Inventor's Name: Suzanne C. ALDOUS

Residential Address: Gillette, NJ 07933

Signed at Bridgewater, NJ, USA on this 16th day of January, 2008.
(City, State and Nation)

Signature: Michael W. Fennie
Inventor's Name: Michael W. FENNIE
Residential Address: East Stroudsburg, PA 18301

Signed at Bridgewater NJ USA on this 17th day of January, 2008.
(City, State and Nation)

Signature:
Inventor's Name: John Z. JIANG
Residential Address: Hillsborough, NJ 08844

Signed at Bridgewater, NJ, USA on this 16th day of January, 2008.
(City, State and Nation)

Signature:
Inventor's Name: Stanly JOHN
Residential Address: Basking Ridge, NJ 07920

Signed at Bridgewater, NJ, USA on this 16th day of January, 2008.
(City, State and Nation)

Signature:
Inventor's Name: Lan MU
Residential Address: Bedminster, NJ 07921

Signed at BRIDGEWATER, NJ, USA on this 16 day of JANUARY, 2008.
(City, State and Nation)

Signature: _____
Inventor's Name: Brian PEDDRIFT
Residential Address: Flemington, NJ 08822

Signed at Bridgewater, NJ USA on this 16th day of January, 2008.
(City, State and Nation)

Signature: _____
Inventor's Name: James R. PRIBISH
Residential Address: Piscataway, NJ 08854

Signed at Bridgewater, NJ, USA on this 16th day of January, 2008.
(City, State and Nation)

Signature: Barbara S Rauckman
Inventor's Name: Barbara S. RAUCKMAN
Residential Address: Flemington, NJ 08822

Signed at BRIDGEWATER, NJ, USA on this 16 day of JANUARY, 2008.
(City, State and Nation)

Signature: _____
Inventor's Name: Jeffrey S. SABOL
Residential Address: Bridgewater, NJ 08807

Signed at Bridgewater, NJ, USA on this 16 day of January, 2008.
(City, State and Nation)

Signature: _____
Inventor's Name: Grzegorz T. STOKLOSA
Residential Address: Hillsborough, NJ 08844

Signed at Bridgewater, NJ, USA on this 18th day of January, 2008.
(City, State and Nation)

Signature: _____
Inventor's Name: Sukanthini THURAIRATNAM
Residential Address: Bedminster, NJ 07921

TRADUCCION OFICIAL NO. 807/2009-.

EL TEXTO QUE SIGUE ES TRADUCCION FIEL Y COMPLETA DE UN DOCUMENTO ESCRITO EN INGLES. LLEVA LA FIRMA Y EL SELLO DE HELENA URIBE DE LEMOINE, TRADUCTORA E INTERPRETE OFICIAL SEGUN RESOLUCION NO. 3618 DEL MINISTERIO DE JUSTICIA DE COLOMBIA, DE FECHA 6 DE SEPTIEMBRE DE 1972.

(HAY UN SELLO DE LA OFICINA DE
PATENTES Y MARCAS REGISTRADAS DE LOS ESTADOS UNIDOS)
Oficina de Patentes Y Marcas Registradas de los Estados Unidos

Subsecretario de Comercio para Propiedad Intelectual y
Director de la Oficina de Patentes y Marcas Registradas

26 de Febrero de 2008 *500472646A*

PTAS

JIANG LIN
ROUTE 202-206
BRIDGEWATER, NJ 08807

OFICINA DE PATENTES Y MARCAS REGISTRADAS
DE LOS ESTADOS UNIDOS
NOTIFICACIÓN DE REGISTRO DE DOCUMENTO DE CESIÓN

EL DOCUMENTO ADJUNTO HA SIDO REGISTRADO POR LA DIVISIÓN DE CESIONES DE LA OFICINA DE PATENTES Y MARCAS REGISTRADAS DE LOS ESTADOS UNIDOS. HAY UNA COPIA COMPLETA EN MICROFILM DISPONIBLE EN LA SALA DE BÚSQUEDA DE CESIONES BAJO EL NÚMERO DEL CARRETE Y MICROFICHA CUYA REFERENCIA APARECE ABAJO.

POR FAVOR, REVISE TODA LA INFORMACIÓN CONTENIDA EN ESTA NOTIFICACIÓN. LA INFORMACIÓN CONTENIDA EN ESTA NOTIFICACIÓN DE RECORDATORIO CONTIENE LOS DATOS PRESENTES EN EL SISTEMA DE ASIGNACIÓN DE PATENTES Y MARCAS REGISTRADAS. EN CASO DE QUE USTED ENCUENTRE UN ERROR O SI TIENE PREGUNTAS REFERENTES A ESTA NOTIFICACIÓN, PUEDE PONERSE EN CONTACTO CON EL EMPLEADO CUYO NOMBRE APARECE EN ESTA NOTIFICACIÓN, EN EL TELÉFONO 571-272-3350. POR FAVOR, ENVÍE LA SOLICITUD PARA REALIZAR LA CORRECCIÓN A: UNITED STATES PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VIRGINIA 22313.

FECHA DE RECORDATORIO: 02/26/2008
CARRETE/MICROFICHA: 020560/0946 NUMERO DE PÁGINAS:8

HELENA URIBE DE LEMOINE
RES No 3618
SEPT 6 1972
MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 807/2009-.

RESUMEN:

CESIÓN CORREGIDA PARA CORREGIR LA ORTOGRAFIA DEL NOMBRE DEL CEDENTE CUYO NOMBRE FUE PREVIAMENTE REGISTRADO DEL INTERÉS DEL CEDENTE QUE FUE PREVIAMENTE REGISTRADO EN EL CARRETE 020514 MICROFICHA 0184. POR MEDIO DEL PRESENTE EL CEDENTE CONFIRMA QUE SU NOMBRE DEBE SER JOHN Z JIANG

EXPEDIENTE NUMERO: US2007 – 050 US PSP

CEDENTE:
ALDOUS, SUZANNE C. FECHA DOCUMENTO: 01/16/2008

CEDENTE:
FENNIE, MICHAEL W. FECHA DOCUMENTO: 01/16/2008

CEDENTE:
JIANG, JOHN Z. FECHA DOCUMENTO: 01/16/2008

CEDENTE:
JOHN, STANLY FECHA DOCUMENTO: 01/16/2008

CEDENTE:
MU, LAN FECHA DOCUMENTO: 01/16/2008

CEDENTE:
PEDGRIFT, BRIAN FECHA DOCUMENTO: 01/16/2008

CEDENTE:
PRIBISH, JAMES R. FECHA DOCUMENTO: 01/16/2008

CEDENTE:
RAUCKMAN, BARBARA S. FECHA DOCUMENTO: 01/16/2008

CEDENTE:
SABOL, JEFFREY S. FECHA DOCUMENTO: 01/16/2008

CEDENTE:
STOKLOSA, GRZEGORZ T. FECHA DOCUMENTO: 01/16/2008

HELENA URIBE DE LEMOINE
RES No 3618
SEPT 6 1972
MINISTERIO JUSTICIA

TRADUCCION OFICIAL NO. 807/2009-.

CEDENTE:
THURAIRATNAM SUKANTHINI FECHA DOCUMENTO: 01/16/2008

CESIONARIO:
SANOFI-AVENTIS U.S. LLC
55 CORPORATE DRIVE
BRIDGEWATER,NEW JERSEY 02207

NÚMERO DE SERIE: 60909171 FECHA DE RADICACIÓN: 03/30/2007
NÚMERO DE PATENTE: (en blanco) FECHA DE EMISIÓN: (en blanco)

TITULO:

"COMPUESTOS DE PIRIMIDINA HIDRAZIDA COMO INHIBIDORES DE PGDS"

TARA WASHINGTON, EXAMINADOR
SUCURSAL DE SERVICIOS DE CESIÓN
OFICINA DE REGISTROS PÚBLICOS

HELENA URIBE DE LEMOINE
RES No 3618 SEPT 6 1972 MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 807/2009-.

CESIÓN DE PATENTE

Versión Electrónica v1.1 **02/26/2008**
Versión Impresa v1.1 **500472646**

TIPO DE PRESENTACIÓN	CORRECCION DE CESIÓN
NATURALEZA DEL TRASPASO	CORRECCION DE CESIÓN PARA CORREGIR LA ORTOGRAFIA DEL CEDENTE, QUE FUE PREVIAMENTE REGISTRADA EN EL CARRETE 020514 MICROFICHA 0184. POR MEDIO DEL PRESENTE EL CEDENTE CONFIRMA QUE SU NOMBRE DEBE SER JOHN Z. JIANG.

DATOS DE LA PARTE CEDENTE:

NOMBRE	FECHA DE EJECUCIÓN
Suzanne C. Aldous	01/16/2008
Michael W. Fennie	01/16/2008
John Z. Jiang	01/17/2008
Stanly John	01/16/2008
Lan Mu	01/16/2008
Brian Pedgrift	01/16/2008
James R. Prisbish	01/16/2008
Barbara S Rauckman	01/16/2008
Jeffrey S. Sabol	01/16/2008
Grzegorz T. Stoklosa	01/16/2008
Sukanthini Thurairatnam	01/18/2008

DATOS DE LA PARTE RECEPTORA

Nombre:	**Sanofi-Aventis U.S. LLC**
Dirección	55 Corporate Drive
CIUDAD	Bridgewater
ESTADO	New Jersey
CÓDIGO POSTAL	08807

TOTAL NÚMEROS DE PROPIEDAD: 1

Tipo de Propiedad	Número
Número de Solicitud	60909171

HELENA URIBE DE LEMOINE
RES No 3618 SEPT 6 1972 MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 807/2009-.

DATOS PARA LA CORRESPONDENCIA
Numero Fax: (908) 231-2626
La correspondencia será enviada por el servicio postal de los Estados Unidos cuando el envío por fax no sea posible.
Teléfono: 908 231 3582
Email: maribel.mendez@sanofi-aventis.com

Nombre del Corresponsal: Jiang Lin
Dirección Línea 1: Route 202-206
Dirección Línea 4: Bridgewater, New Jersey 08807

NUMERO DEL EXPEDIENTE	US2007 -050- US PSP
NOMBRE DEL PRESENTADOR:	Maribel Mendez

TOTAL ANEXOS: 6

Fuente = US2007-050-US PSP Cesión ejecutada#pág1.tif
Fuente = US2007-050-US PSP Cesión ejecutada#pág2.tif
Fuente = US2007-050-US PSP Cesión ejecutada#pág3.tif
Fuente = US2007-050-US PSP Cesión ejecutada#pág4.tif
Fuente = US2007-050-US PSP Confirmación electrónica#pág1.tif
Fuente = US2007-050-US PSP Confirmación electrónica#pág2.tif

HELENA URIBE DE LEMOINE
RES No 3613 SEPT 6 1972 MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 807/2009-.

CESIÓN Y CONTRATO

Por el valor recibido y con la intención de que sea legalmente obligante, nosotros los inventores conjuntos (el "Cedente") vendemos, cedemos y transrferimos a **SANOFI-AVENTIS U.S. LLC.,** (el "Cesionario") de 55 Corporate Drive, Bridgewater, New Jersey 08807, y a sus sucesores, cesionarios y representantes legales, todos los derechos, título e intereses en nuestro invento y cualquier mejora a este en todos los países del mundo, relacionados con y para la aplicación de Cartas Patente, registro de Sumarios Legales No. **US2007/050 US PSP** y (si fueren radicados antes de la ejecución del presente) radicado el 30 de Marzo de 2007, No. Serie **60/909.171,** y titulado

"COMPUESTOS DE PIRIMIDINA HIDRAZIDA COMO INHIBIDORES DE PGDS"

Y todos los derechos y privilegios, incluyendo cualquiera o todos los beneficios bajo la Convención Internacional para la Protección de la Propiedad Industrial, incluyendo el derecho a reclamar la prioridad con base en la mencionada solicitud de los Estados Unidos y bajo cualquiera y todas las Cartas Patente que puedan ser otorgadas como consecuencia de estos actos, y todos los derechos, y el derecho, título e interés en y a toda solicitud de patente registrada o a ser registrada sobre el mencionado invento en cualquier otro país u organización de patentes, incluyendo las continuaciones, divisiones, renovaciones, reactivaciones y cualesquiera aplicaciones sustitutas de dichas aplicaciones de los Estados Unidos, y cualquiera y todas las patentes que se expidan sobre esto, y cualquier reemisión, oleoductos y extensiones y derechos exclusivos del gobierno del mismo.

HELENA URIBE DE LEMOINE
RES No 3618 SEPT 6 1972 MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 807/2009-.

Yo/nosotros autorizamos y solicitamos a las autoridades competentes otorgar y expedir cualquiera y todas la patentes sobre dicho invento al mencionado cesionario o a sus sucesores, cesionarios y representantes legales, o a las personas propuestas que dicho cesionario designe.

Yo/nosotros acordamos que, mediante solicitud, Yo/nosotros firmaremos todos los documentos, tomaré todos los juramentos de ley y realizaré todos los actos que sean deseables o convenientes necesarios para asegurar y mantener las patente para el mencionado invento en cualquier y todos los países y para conferir el título de esto en dicho cesionario, sus sucesores, cesionarios, representantes legales o designados, sin cargo alguno para el mencionado cesionario pero a sus expensas.

Yo/nosotros pactamos con el mencionado cesionario, sus sucesores, cesionarios y representantes legales, que los derechos y la propiedad traspasada por medio de este documento está libre y saneada de cualquier gravamen y que Yo/nosotros tengo todo el derecho a traspasar la misma como se expresa en este documento.

Firmado en Bridgewater NJ, este día 16 de Enero de 2008
FIRMADO: SUSANNE C. ALDOUS
NOMBRE DEL INVENTOR: SUSANNE C. ALDOUS
DIRECCION: GILLETTE, NJ 07933

Firmado en Bridgewater NJ, este día 16 de Enero de 2008
FIRMADO: MICHAEL W. FENNIE
NOMBRE DEL INVENTOR: MICHAEL W. FENNIE
DIRECCION: East Stroudsburg, PA 18301

HELENA URIBE DE LEMOINE
RES No 3616
SEPT 6 1972
MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 807/2009-.

Firmado en Bridgewater NJ, este día 17 de Enero de 2008
FIRMADO: JOHN Z. HANG
NOMBRE DEL INVENTOR: JOHN Z. HANG
DIRECCION: HILLSBOROUGH, NJ 08844

Firmado en Bridgewater NJ, este día 16 de Enero de 2008
FIRMADO: STANLY JOHN
NOMBRE DEL INVENTOR: STANLY JOHN
DIRECCION: BASKING RIDGE, NJ 07920

Firmado en Bridgewater NJ, este día 16 de Enero de 2008
FIRMADO: LAN MU
NOMBRE DEL INVENTOR: LAN MU
DIRECCION: BEDMINSTER, NJ 07921

Firmado en Bridgewater NJ, este día 16 de Enero de 2008
FIRMADO: BRIAN PEDGRIFT
NOMBRE DEL INVENTOR: BRIAN PEDGRIFT
DIRECCION: FLERNINGTON, NJ 08822

Firmado en Bridgewater NJ, este día 16 de Enero de 2008
FIRMADO: JAMES R. PRIBISH
NOMBRE DEL INVENTOR: JAMES PRIBISH
DIRECCION: PISCATAWAY, NJ 08854

HELENA URIBE DE LEMOINE
RES No
3616
SEPT 6 1972
MINISTERIO
JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 807/2009-.

Firmado en Bridgewater NJ, este dia 16 de Enero de 2008
FIRMADO: BARBARA S. RAUCKMAN
NOMBRE DEL INVENTOR:BARBARA S. RAUCKMAN
DIRECCION: FLEMINGTON, NJ 08822

Firmado en Bridgewater NJ, este día 16 de Enero de 2008
FIRMADO: JEFFREY S. SABOL
NOMBRE DEL INVENTOR: JEFFREY S. SABOL
DIRECCION: BRIDGEWATER, NJ 08807

Firmado en Bridgewater NJ, este día 16 de Enero de 2008
FIRMADO: GRZEGORZ T. STOKLOSA
NOMBRE DEL INVENTOR:GRZEGORZ T. STOKLOSA
DIRECCION: HILLSBOROUGH, NJ 08844

Firmado en Bridgewater NJ, este día 18 de Enero de 2008
FIRMADO: SUKANTHINI THURAIRATNAM
NOMBRE DEL INVENTOR: SUKANTHINI THURAIRATNAM
DIRECCION: BEDMINSTER, NJ 07921

HELENA URIBE DE LEMOINE
RES No 3618 SEPT 6 1972 MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 807/2009-.

COPIA NOTARIAL AUTENTICA

ESTADOS UNIDOS DE AMERICA
ESTADO DE NEW JERSEY
CONDADO DE SOMERSET

A TODOS A QUIENES LOS PRESENTES LLEGUEN,

Yo TINA M. WISBESKI, POR MEDIO DEL PRESENTE CERTIFICO BAJO JURAMENTO Y EL SELLO DE MI DESPACHO, QUE EL DOCUMENTO ADJUNTO ES UNA COPIA VERDADERA DEL DOCUMENTO ORIGINAL CON EL CUAL LO HE COMPARADO.
FIRMADO: TINA M. WISBESKI

ESTADOS UNIDOS DE AMERICA
ESTADO DE NEW JERSEY
CONADO DE SOMERSET
SUSCRITO Y JURADO ANTE MI EN BRIDGEWATER, NEW JERSEY, ESTE DIA 31 DE AGOSTO DE 2009
FIRMADO: NANCY J. INGRAM, NOTARIO PUBLICO, ESTADO DE NEW JERSEY, CON COMISION HASTA EL 2 DE AGOSTO DE 2009.
HAY SELLO DEL NOTARIO.

HELENA URIBE DE LEMOINE
RES No 3618 SEPT 6 1972 MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

TRADUCCION OFICIAL NO. 807/2009-.

APOSTILLA

CONVENIO DE LA HAYA DEL 5 DE OCTUBRE DE 1961

1. PAIS: ESTADOS UNIDOS DE AMÉRICA

EL PRESENTE DOCUMENTO PUBLICO

2. HA SIDO FIRMADO POR: **NANCY J. INGRAM**
3. ACTUANDO EN SU CAPACIDAD DE: NOTARIO PUBLICO DE NEW JERSEY
4. LLEVA EL SELLO DE: NANCY J. INGRAM, NOTARIO

CERTIFICADO

5. EN: TRENTON, NEW JERSEY
6. EL: 9 DE SEPTIEMBRE DE 2009
7. POR: R. DAVID ROUSSEAU, TESORERO DE NEW JERSEY
8. BAJO EL NO.: **A374113**
9. SELLO: DESPACHO DEL SECRETARIO DE ESTADO
10. FIRMADO: ILEGIBLE.

CERTIFICADO NUMERO: 1152580210

LA TRADUCTORA OFICIAL

HELENA URIBE DE LEMOINE

HELENA URIBE DE LEMOINE
RES No 3618 SEPT 6 1972 MINISTERIO JUSTICIA
TRADUCTORA OFICIAL

11

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 October 2008 (09.10.2008)

PCT

(10) International Publication Number
WO 2008/121670 A1

(51) International Patent Classification:
C07D 239/28 (2006.01) *C07D 417/14* (2006.01)
C07D 403/12 (2006.01) *A61K 31/506* (2006.01)
C07D 403/14 (2006.01) *A61P 29/00* (2006.01)
C07D 413/12 (2006.01)

(21) International Application Number:
PCT/US2008/058347

(22) International Filing Date: 27 March 2008 (27.03.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/909,171 30 March 2007 (30.03.2007) US

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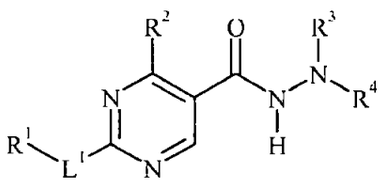

(I)

(57) **Abstract:** This invention is directed to a compound wherein R^1, R^2, R^3, R^4 and L^1 are as defined herein, a pharmaceutical composition comprising the compound, and the use of the compound to treat allergic and/or inflammatory disorders, particularly disorders such as allergic rhinitis, asthma and/or chronic obstructive pulmonary disease (COPD).

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PYRIMIDINE HYDRAZIDE COMPOUNDS AS PGDS INHIBITORS

FIELD OF THE INVENTION

The present invention is directed to pyrimidine hydrazide compounds, their preparation, pharmaceutical compositions containing these compounds, and their pharmaceutical use in the treatment of disease states capable of being modulated by the inhibition of the prostaglandin D synthase.

BACKGROUND OF THE INVENTION

Allergic rhinitis, the most common atopic disease, has an estimated prevalence ranging from about 5 to about 22 percent of the general human population and is characterized by the symptoms of sneezing, nasal discharge, and nasal congestion. These symptoms are believed to be triggered by multiple mediators released from mast cells and other inflammatory cells. Current therapies, such as antihistamines, deal effectively with the sneezing and nasal discharge, but have little effect on congestion, which is a key symptom affecting the quality of life of patients.

Local allergen challenge in patients with allergic rhinitis, bronchial asthma, allergic conjunctivitis and atopic dermatitis has been shown to result in rapid elevation of prostaglandin D2 "(PGD2)" levels in nasal and bronchial lavage fluids, tears and skin chamber fluids. PGD2 has many inflammatory actions, such as increasing vascular permeability in the conjunctiva and skin, increasing nasal airway resistance, airway narrowing

and eosinophil infiltration into the conjunctiva and trachea. PGD2 is the major cyclooxygenase product of arachidonic acid produced from mast cells on immunological challenge [Lewis, RA, Soter NA, Diamond PT, Austen KF, Oates JA, Roberts LJ II, Prostaglandin D2 generation after activation of rat and human mast cells with anti-IgE, *J. Immunol.* **129**, 1627-1631, 1982]. Activated mast cells, a major source of PGD2, are one of the key players in driving the allergic response in conditions such as asthma, allergic rhinitis, allergic conjunctivitis, allergic dermatitis and other diseases [Brightling CE, Bradding P, Pavord ID, Wardlaw AJ, New Insights into the role of the mast cell in asthma, *Clin. Exp. Allergy* **33**, 550-556, 2003].

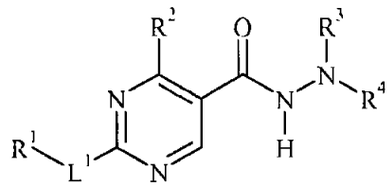
In the presence of sulfhydryl compounds, PGD2 is formed by the isomerization of PGH2, a common precursor of prostanoids, by catalytic action of prostaglandin D synthase "(PGDS)". There are two isoforms of the PGDS enzyme: L-PGDS; and H-PGDS. H-PGDS is a cytosolic enzyme, which is distributed in the peripheral tissues, and which is localized in the antigen-presenting cells, mast cells, megakaryocytes, and Th2 lymphocytes. The action of the product PGD2 is mediated by G-protein coupled receptors: D prostaglandin "(DP)" and crTH2. See (1) Prostaglandin D Synthase: Structure and Function. T. Urade and O. Hayaishi, *Vitamin and Hormones*, 2000, 58, 89-120, (2) J. J. Murray, *N. Engl. J. Med.*, 1986 Sept. 25; 315(13):800, and (3) Urade et. al,, *J. Immunology* 168: 443-449, 2002.

We believe that inhibiting the formation of PGD2 should have an effect on nasal congestion and, therefore, be of therapeutic benefit in allergic rhinitis. In addition, we believe that a PGDS inhibitor should be of therapeutic benefit in a number of other indications such as bronchial asthma.

PGDS inhibitors have been reported. The compound, HQL-79, is reported to be a weak PGDS inhibitor, and is antiasthmatic in guinea pig and rat models (Matsusshita, et al., Jpn. J. Pharamcol. 78: 11, 1998). The compound Tranilast is described as a PGDS inhibitor. (Inhibitory Effect of Tranilast on Prostaglandin D Synthesase. K. Ikai, M. Jihara, K. Fujii, and Y. Urade. *Biochemical Pharmacology*, 1989, 28, 2773-2676).

SUMMARY OF THE INVENTION

The present invention is directed to a compound of formula (I):



(I)

wherein:

R^1 is $(C_1\text{-}C_6)$-alkyl optionally substituted one or more times independently by halo, hydroxy, $(C_1\text{-}C_6)$-alkoxy, or $(C_1\text{-}C_4)$-haloalkoxy, or

$(C_3\text{-}C_6)$-cycloalkyl, aryl or heteroaryl, each of which is optionally substituted one or more times independently by halo, $(C_1\text{-}C_6)$-alkyl, hydroxy, $(C_1\text{-}C_6)$-alkoxy, $(C_1\text{-}C_4)$-haloalkyl or $(C_1\text{-}C_4)$-haloalkoxy;

R^2 is hydrogen or $(C_1\text{-}C_4)$-alkyl optionally substituted one or more times by halo;

R^3 is hydrogen, alkyl, aryl or heteroaryl,

R^4 is hydrogen, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylsulfonyl, heteroarylsulfonyl, $-C(=O)-NY^1Y^2$, $-C(=S)-NY^1Y^2$, R^5, $-C(=O)-R^5$ or $-C(=S)-R^5$, wherein the aryl, heteroaryl or heterocyclyl moiety is optionally substituted one or more times independently by R^6, or

R^3 and R^4 together with the nitrogen atom to which they are attached form heterocyclyl, heterocyclenyl, heteroaryl, arylheterocyclyl, arylheterocylenyl, heteroarylheterocyclyl, heteroarylhetercyclenyl, heterocyclylheteroaryl or heterocyclenylheteroaryl, each of which is optionally substituted one or more times independently by R^6;

R^5 is cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, or multicyclic alkaryl, each of which is optionally substituted one or more times independently by R^6;

L^1 is a bond, -O-, -C(=O)-, -NH-C(=O)-, or $(C_1\text{-}C_2)$-alkylene optionally substituted one or more times by halo;

R^6 is cyano, nitro, halo, hydroxy, carboxy, Y^1Y^2N-, Y^1Y^2N-C(=O)-, Y^1Y^2N-SO_2-,

acyl, acyloxy, alkyl, alkenyl, alkynyl, alkoxy, alkoxycarbonyl, alkylthio, alkylsulfinyl, or alkylsulfonyl, each of which is optionally substituted one or more times independently by:

acyloxy, halo, alkoxy, haloalkoxy, hydroxy, carboxy, alkoxycarbonyl, Y^1Y^2N-, Y^1Y^2N-C(=O)-, Y^1Y^2N-SO_2-,

aryl, aryloxy, aroyl, heteroaryl, heteroaryloxy, heteroaroyl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, or multicyclic alkaryl, each of which is optionally substituted one or more times independently by alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxycarbonyl, or

aryl, heteroaryl, aroyl, heteroaroyl, aryloxy, heteroaryloxy, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, or multicyclic alkaryl, each of which is optionally substituted one or more times independently by alkyl, haloalkyl, halo, alkoxy, haloalkoxy, hydroxy, carboxy, alkoxycarbonyl, Y^1Y^2N-, or Y^1Y^2N-SO_2-,

wherein the heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, or multicyclic alkaryl moiety of R^6 is also optionally substituted one or more times independently by oxo;

Y^1 and Y^2 are each independently:

hydrogen, alkylsulfonyl, aroyl, heteroaroyl, or

alkyl optionally substituted one or more times independently by hydroxy, carboxy, halo, amino, alkylamino, dialkylamino, alkoxy, heterocyclyl, aryl or heteroaryl, or

Y^1 and Y^2 together with the nitrogen atom to which they are attached form heterocyclyl;

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention is a pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to formula (I), or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier.

Another aspect of the present invention is directed to a method of treating allergic and/or inflammatory disorders, particularly disorders such as allergic rhinitis, asthma and/or chronic

obstructive pulmonary disease (COPD) in a patient in need thereof by administering to the patient a compound according to formula (I), or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definition of Terms

As used above, and throughout the description of the invention, the following terms unless otherwise indicated, shall be understood to have the following meanings:

"Acyl" means H-CO- or (aliphatic or cyclyl)-CO-. Particular acyl includes lower alkanoyl that contains a lower alkyl. Exemplary acyl includes formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl, palmitoyl, acryloyl, propynoyl, and cyclohexylcarbonyl.

"Acyloxy" means acyl-O-.

"Alkenyl" means a straight or branched aliphatic hydrocarbon group containing a carbon-carbon double bond and having 2 to about 15 carbon atoms. Particular alkenyl has 2 to about 12 carbon atoms. More particular alkenyl has 2 to about 4 carbon atoms. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain that may be straight or branched. Exemplary alkenyl includes ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl, cyclohexylbutenyl, and decenyl.

"Alkoxy" means alkyl-O-. Exemplary alkoxy includes methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, and heptoxy.

"Alkoxycarbonyl" means alkyl-O-CO-. Exemplary alkoxycarbonyl includes methoxycarbonyl, ethoxycarbonyl, and *t*-butyloxycarbonyl.

"Alkyl" means straight or branched aliphatic hydrocarbon having 1 to about 20 carbon atoms. Particular alkyl has 1 to about 12 carbon atoms. More particular alkyl is lower alkyl. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are

attached to a linear alkyl chain. "Lower alkyl" means 1 to about 4 carbon atoms in a linear alkyl chain that may be straight or branched.

"Alkylamino" means alkyl-NH-. Particular alkylamino is (C_1-C_6)-alkylamino. Exemplary alkylamino includes methylamino and ethylamino.

"Alkylsulfinyl" means alkyl-SO-. Particular alkylsulfonyl is (C_1-C_6)-alkylsulfinyl. Exemplary alkylsulfinyl includes CH_3-SO-, and CH_3CH_2-SO-.

"Alkylsulfonyl" means alkyl-SO_2-. Particular alkylsulfonyl is (C_1-C_6)-alkylsulfonyl. Exemplary alkylsulfonyl includes CH_3-SO_2-, and CH_3CH_2-SO_2-.

"Alkylthio" means an alkyl-S-. Exemplary alkylthio includes CH_3-S-.

"Alkynyl" means straight or branched aliphatic hydrocarbon containing a carbon-carbon triple bond and having 2 to about 15 carbon atoms. Particular alkynyl has 2 to about 12 carbon atoms. More particular alkynyl has 2 to about 6 carbon atoms. Branched means that one or more lower alkyl such as methyl, ethyl or propyl are attached to a linear alkynyl chain. "Lower alkynyl" means 2 to about 4 carbon atoms in a linear alkynyl chain that may be straight or branched. Exemplary alkynyl includes ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl, and decynyl.

"Aroyl" means aryl-CO-. Exemplary aroyl includes benzoyl, and 1-and 2-naphthoyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system of about 6 to about 14 carbon atoms. Particular aryl include about 6 to about 10 carbon atoms. Exemplary aryl include phenyl and naphthyl.

"Arylcycloalkenyl" means a fused aryl and cycloalkenyl. Particular arylcycloalkenyl is one wherein the aryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 7 ring atoms. An arylcycloalkenyl is bonded through any atom of the cycloalkenyl moiety thereof capable of such bonding. Exemplary arylcycloalkenyl includes 1,2-dihydronaphthylene and indene.

"Arylcycloalkyl" means a fused aryl and cycloalkyl. Particular arylcycloalkyl is one wherein the aryl thereof is phenyl and the cycloalkyl consists of about 5 to about 6 ring atoms. An arylcycloalkyl is bonded through any atom of the cycloalkyl moiety thereof capable of such bonding. Exemplary arylcycloalkyl includes 1,2,3,4-tetrahydro-naphthylene.

"Arylheterocyclenyl" means a fused aryl and heterocyclenyl. Particular arylheterocyclenyl is one wherein the aryl thereof is phenyl and the heterocyclenyl consists of about 5 to about 6 ring atoms. An arylheterocyclenyl is bonded through any atom of the heterocyclenyl thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before the heterocyclenyl portion of the arylheterocyclenyl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of an arylheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclenyl portion of the arylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary arylheterocyclenyl includes 3H-indolinyl, 1H-2-oxoquinolyl, 2H-l-oxoisoquinolyl, 1,2-di-hydroquinolinyl, 3,4-dihydroquinolinyl, 1,2-dihydroisoquinolinyl, and 3,4-dihydroisoquinolinyl.

"Arylheterocyclyl" means a fused aryl and heterocyclyl. Particular heterocyclylaryl is one wherein the aryl thereof is phenyl and the heterocyclyl consists of about 5 to about 6 ring atoms. An arylheterocyclyl is bonded through any atom of the heterocyclyl moiety thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before heterocyclyl portion of the arylheterocyclyl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of an arylheterocyclyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclyl portion of the arylheterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary arylheterocyclyl includes indolinyl, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydroquinoline, 1H-2,3-dihydroisoindol-2-yl, 2,3-dihydrobenz[f]isoindol- 2-yl, and 1,2,3,4- tetrahydrobenz[g]-isoquinolin-2-yl.

"Aryloxy" means an aryl-O-. Exemplary aryloxy includes phenoxy and naphthoxy.

"Compounds of the present invention", and equivalent expressions, are meant to embrace compounds of Formula (I) as hereinbefore described, the hydrates, solvates and N-oxides thereof, and the pharmaceutically acceptable salts thereof, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, N-oxides and solvates, where the context so permits.

"Cycloalkenyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, particularly of about 5 to about 10 carbon atoms, and which contains at least one carbon-carbon double bond. Particular rings of the ring system include about 5 to about 6 ring atoms; and such particular ring sizes are also referred to as "lower". Exemplary monocyclic cycloalkenyl includes cyclopentenyl, cyclohexenyl, and cycloheptenyl. An exemplary multicyclic cycloalkenyl is norbornylenyl.

"Cycloalkenylaryl" means a fused aryl and cycloalkenyl. Particular cycloalkenylaryl is one wherein the aryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. A cycloalkenylaryl is bonded through any atom of the aryl moiety thereof capable of such bonding. Exemplary cycloalkenylaryl includes 1,2-dihydronaphthylene and indene.

"Cycloalkenylheteroaryl" means a fused heteroaryl and cycloalkenyl. Particular cycloalkenylheteroaryl is one wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the cycloalkenyl consists of about 5 to about 6 ring atoms. A cycloalkenylheteroaryl is bonded through any atom of the heteroaryl thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before heteroaryl portion of the cycloalkenylheteroaryl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of a cycloalkenylheteroaryl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the cycloalkenylheteroaryl may also be optionally oxidized to the corresponding N-oxide. Exemplary cycloalkenylheteroaryl includes 5,6- dihydroquinolyl, 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalinyl, 5,6-dihydroquinazolinyl, 4,5- dihydro-1H -benzimidazolyl, and 4,5-di-hydrobenzoxazolyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic saturated ring system of about 3 to about 10 carbon atoms, particularly of about 5 to about 10 carbon atoms. Particular ring systems include about 5 to about 7 ring atoms; and such particular ring systems are also

referred to as "lower". Exemplary monocyclic cycloalkyl includes cyclopentyl, cyclohexyl, and cycloheptyl. Exemplary multicyclic cycloalkyl includes 1-decalin, norbornyl, and adamant-(1- or 2-)yl.

"Cycloalkylaryl" means a fused aryl and cycloalkyl. Particular cycloalkylaryl is one wherein the aryl thereof is phenyl and the cycloalkyl consists of about 5 to about 6 ring atoms. A cycloalkylaryl is bonded through any atom of the cycloalkyl moiety thereof capable of such bonding. Exemplary cycloalkylaryl includes 1,2,3,4-tetrahydro-naphthylene.

"Cycloalkylheteroaryl" means a fused heteroaryl and cycloalkyl. Particular cycloalkylheteroaryl is one wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the cycloalkyl consists of about 5 to about 6 ring atoms. A cycloalkylheteroaryl is bonded through any atom of the heteroaryl thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before heteroaryl portion of the fused cycloalkylheteroaryl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of a cycloalkylheteroaryl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the cycloalkylheteroaryl may also be optionally oxidized to the corresponding N-oxide. Exemplary cycloalkylheteroaryl includes 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetra-hydroisoquinolyl, 5,6,7,8-tetrahydroquinoxalinyl, 5,6,7,8-tetrahydroquinazolyl, 4,5,6,7-tetrahydro-1H-benzimidazolyl, and 4,5,6,7-tetrahydrobenzoxazolyl.

"Cyclyl" means cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl.

"Dialkylamino" means $(alkyl)_2$-N-. Particular dialkylamino is $(C_1$-$C_6alkyl)_2$-N-. Exemplary dialkylamino groups include dimethylamino, diethylamino and methylethylamino.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo. Particular halo or halogen is fluoro or chloro.

"Haloalkoxy" means alkoxy substituted by one to three halo groups. Particular haloalkoxy are loweralkoxy substituted by one to three halogens. Most particular haloalkoxy are loweralkoxy substituted by one halogen.

"Haloalkyl" means alkyl substituted by one to three halo groups. Particular haloalkyl are loweralkyl substituted by one to three halogens. Most particular haloalkyl are loweralkyl substituted by one halogen.

"Heteroaroyl" means heteroaryl-CO-. Exemplary heteroaroyl includes thiophenoyl, nicotinoyl, pyrrol-2-ylcarbonyl, and pyridinoyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system of about 5 to about 14 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Particular aromatic ring systems include about 5 to about 10 carbon atoms, and include 1 to 3 heteroatoms. More particular ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The designation of the aza, oxa or thio as a prefix before heteroaryl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. A nitrogen atom of a heteroaryl may be a basic nitrogen atom and may also be optionally oxidized to the corresponding N-oxide. When a heteroaryl is substituted by a hydroxy group, it also includes its corresponding tautomer. Exemplary heteroaryl includes pyrazinyl, thienyl, isothiazolyl, oxazolyl, pyrazolyl, furanyl, pyrrolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, benzofuranyl, azaindolyl, benzimidazolyl, benzothienyl, thienopyridyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl, and triazolyl.

"Heteroarylalkyl" means heteroaryl-alkyl-. Particular heteroarylalkyl contains a (C_1-C_4)-alkyl moiety. Exemplary heteroarylalkyl includes tetrazol-5-ylmethyl.

"Heteroarylcycloalkenyl" means a fused heteroaryl and cycloalkenyl. Particular heteroarylcycloalkenyl is one wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the cycloalkenyl consists of about 5 to about 6 ring atoms. A heteroarylcycloalkenyl is bonded through any atom of the cycloalkenyl thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before heteroaryl portion of

the heteroarylcycloalkenyl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of a heteroarylcycloalkenyl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the heteroarylcycloalkenyl may also be optionally oxidized to the corresponding N-oxide. Exemplary heteroarylcycloalkenyl includes 5,6- dihydroquinolyl, 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalinyl, 5,6-dihydroquinazolinyl, 4,5- dihydro-1H-benzimidazolyl, and 4,5-di-hydrobenzoxazolyl.

"Heteroarylcycloalkyl" means a fused heteroaryl and cycloalkyl. Particular heteroarylcycloalkyl is one wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the cycloalkyl consists of about 5 to about 6 ring atoms. A heteroarylcycloalkyl is bonded through any atom of the cycloalkyl thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before heteroaryl portion of the fused heteroarylcycloalkyl . defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of a heteroarylcycloalkyl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the heteroarylcycloalkyl may also be optionally oxidized to the corresponding N-oxide. Exemplary heteroarylcycloalkyl includes 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetra-hydroisoquinolyl, 5,6,7,8-tetrahydroquinoxalinyl, 5,6,7,8-tetrahydroquinazolyl, 4,5,6,7-tetrahydro-1H-benzimidazolyl, and 4,5,6,7-tetrahydrobenzoxazolyl

"Heteroarylheterocyclenyl" means a fused heteroaryl and heterocyclenyl. Particular heteroarylheterocyclenyl is one wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclenyl consists of about 5 to about 6 ring atoms. A heteroarylheterocyclenyl is bonded through any atom of the heterocyclenyl thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before the heteroaryl or heterocyclenyl portion of the heteroarylheterocyclenyl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of a heteroarylazaheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heteroaryl or heterocyclenyl portion of the heteroarylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S- oxide or S,S-dioxide. Exemplary heteroarylheterocyclenyl includes 7,8-dihydro[1,7]naphthyridinyl, 1,2-dihydro[2,7]-naphthyridinyl, 6,7-dihydro-3H -imidazo [4,5-c]pyridyl, 1,2-dihydro-1,5-naphthyridinyl, 1 ,2-

dihydro-l,6-naphthyridinyl, 1,2-dihydro-l,7 -naphthyridinyl, 1,2-dihydro-l ,8-naphthyridinyl, and 1,2-dihydro-2,6-naphthyridinyl.

"Heteroarylheterocyclyl" means a fused heteroaryl and heterocyclyl. Particular heteroarylheterocyclyl is one wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclyl consists of about 5 to about 6 ring atoms. A heteroarylheterocyclyl is bonded through any atom of the heterocyclyl thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of a fused heteroarylheterocyclyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heteroaryl or heterocyclyl portion of the heteroarylheterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary heteroarylheterocyclyl includes 2,3-dihydro-lH-pyrrol[3,4-b]quinolin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,7]naphthyridin-2-yl, 1,2,3,4-tetrahydrobenz[b][1,6]naphthyridin-2-yl, 1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indol-2yl, 1,2,3,4-tetrahydro-9H-pyrido[4,3-b]indol-2yl, 2,3-dihydro-1H-pyrrolo[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[3,4-b]indol-2-yl, 1H-2,3,4,5-tetra-hydroazepino[4,3-b]indol-3-yl, 1H-2,3,4,5-tetrahydroazepino[4,5-b]indol-2 yl, 5,6,7,8-tetra-hydro[1,7]naphthyridyl, 1,2,3,4-tetrhydro[2,7]naphthyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridyl, 3,4-dihydro-2H-l-oxa[4,6]diazanaphthalenyl, 4,5,6,7- tetrahydro-3H-imidazo[4,5-c]pyridyl, 6,7-dihydro[5,8]diazanaphthalenyl, 1,2,3,4-tetrahydro[1,5]-naphthyridinyl, 1,2,3,4-tetrahydro[1,6]naphthyridinyl, 1,2,3,4-tetrahydro[1,7]naphthyridinyl, 1,2,3,4-tetrahydro[1,8]naphthyridinyl, and 1,2,3,4-tetra-hydro[2,6]naphthyridinyl.

"Heteroaryloxy" means heteroaryl-O- . Exemplary heteroaryloxy includes pyridyloxy.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system of about 3 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur atoms, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. A particular non-aromatic ring system includes about 5 to about 10 carbon atoms, and 1 to 3 heteroatoms. More particular ring sizes of rings of the ring system include about 5 to

about 6 ring atoms; and such particular ring sizes are also referred to as "lower". The designation of the aza, oxa or thio as a prefix before heterocyclenyl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of a heterocyclenyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary monocyclic azaheterocyclenyl includes 1,2,3,4-tetrahydrohydropyridyl, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetra-hydropyridyl, 1,4,5,6-tetrahydro-pyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, and 2-pyrazolinyl. Exemplary oxaheterocyclenyl includes 3,4-dihydro-2H-pyran, dihydrofuranyl, and fluorodihydro-furanyl. An exemplary multicyclic oxaheterocyclenyl is 7-oxabicyclo[2.2.1]heptenyl. Exemplary monocyclic thioheterocyclenyl includes dihydrothiophenyl and dihydrothiopyranyl.

"Heterocyclenylaryl" means a fused aryl and heterocyclenyl. Particular heterocyclenylaryl is one wherein the aryl thereof is phenyl and the heterocyclenyl consists of about 5 to about 6 ring atoms. A heterocyclenylaryl is bonded through any atom of the aryl thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before heterocyclenyl portion of the fused heterocyclenylaryl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of a heterocyclenylaryl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclenyl portion of the heterocyclenylaryl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary heterocyclenylaryl include 3H-indolinyl, IH-2-oxoquinolyl, 2H-l-oxoisoquinolyl, 1,2-di-hydroquinolinyl, 3,4-dihydroquinolinyl, 1,2-dihydroisoquinolinyl, and 3,4-dihydroisoquinolinyl.

"Heterocyclenylheteroaryl" means a fused heteroaryl and heterocyclenyl. Particular heterocyclenylheteroaryl is one wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclenyl consists of about 5 to about 6 ring atoms. A heterocyclenylheteroaryl is bonded through any atom of the heteroaryl thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before the heteroaryl or heterocyclenyl portion of the heterocyclenylheteroaryl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of an azaheterocyclenylheteroaryl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heteroaryl or heterocyclenyl portion of the heterocyclenylheteroaryl may also be optionally

oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary heterocyclenylheteroaryl includes 7,8-dihydro[1,7]naphthyridinyl, 1,2-dihydro[2,7]-naphthyridinyl, 6,7-dihydro-3H-imidazo[4,5-c]pyridyl, 1,2-dihydro-l,5-naphthyridinyl, 1 ,2-dihydro-l,6-naphthyridinyl, 1,2-dihydro-l,7-naphthyridinyl, 1,2-dihydro-l,8-naphthyridinyl and 1,2-dihydro-2,6-naphthyridinyl.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms, in which one or more of the atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. A particular ring system contains about 5 to about 10 carbon atoms, and from 1 to 3 heteroatoms. Particular ring sizes of the ring system include about 5 to about 6 ring atoms; and such particular ring sizes are also referred to as "lower". The designation of the aza, oxa or thio as a prefix before heterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The nitrogen atom of a heterocyclyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary monocyclic heterocyclyl includes piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, THFyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl.

"Heterocyclylaryl" means a fused aryl and heterocyclyl. Particular heterocyclylaryl is one wherein the aryl thereof is phenyl and the heterocyclyl consists of about 5 to about 6 ring atoms. A heterocyclylaryl is bonded through any atom of the aryl moiety thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before heterocyclyl portion of the heterocyclylaryl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of a heterocyclylaryl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclyl portion of the heterocyclylaryl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary heterocyclylaryl includes indolinyl, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydroquinoline, 1H-2,3-dihydroisoindol-2-yl, and 2,3-dihydrobenz[f]isoindol-2-yl, and 1,2,3,4- tetrahydrobenz[g]-isoquinolin-2-yl.

"Heterocyclylheteroaryl" means a fused heteroaryl and heterocyclyl. Particular heterocyclylheteroaryl is one wherein the heteoraryl thereof consists of about 5 to about 6 ring

atoms and the heterocyclyl consists of about 5 to about 6 ring atoms. A heterocyclylheteroaryl is bonded through any atom of the heteroaryl thereof capable of such bonding. The designation of the aza, oxa or thio as a prefix before the heteroaryl or heterocyclyl portion of the heterocyclylheteroaryl defines that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. The nitrogen atom of a heterocyclylheteroaryl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heteroaryl or heterocyclyl portion of the heterocyclylheteroaryl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary heterocyclylheteroaryl includes 2,3-dihydro-1H-pyrrol[3,4-b]quinolin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,7]naphthyridin-2-yl, 1,2,3,4-tetrahydrobenz[b][1,6]naphthyridin-2-yl, 1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indol-2yl, 1,2,3,4-tetrahydro-9H-pyrido[4,3-b]indol-2yl, 2,3-dihydro-1H-pyrrolo[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[3,4-b]indol-2-yl, 1H-2,3,4,5-tetra-hydroazepino[4,3-b]indol-3-yl, 1H-2,3,4,5-tetrahydroazepino[4,5-b]indol-2-yl, 5,6,7,8-tetra-hydro[1,7]naphthyridyl, 1,2,3,4-tetrhydro[2,7]naphthyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridyl, 3,4-dihydro-2H-1-oxa[4,6]diazanaphthalenyl, 4,5,6,7- tetrahydro-3H-imidazo[4,5-c]pyridyl, 6,7-dihydro[5,8]diazanaphthalenyl, 1,2,3,4-tetrahydro[1,5]-naphthyridinyl, 1,2,3,4-tetrahydro[1,6]naphthyridinyl, 1,2,3,4-tetrahydro[1,7]naphthyridinyl, 1,2,3,4-tetrahydro[1,8]naphthyridinyl, and 1,2,3,4-tetra-hydro[2,6]naphthyridinyl.

"Multicyclic alkaryl" means a multicyclic ring system including at least one aromatic ring fused to at least one non-aromatic ring that may be saturated or unsaturated, and may also contain in the ring system one or more heteroatoms, such as nitrogen, oxygen or sulfur. Exemplary multicyclic alkaryl includes arylcycloalkenyl, arylcycloalkyl, arylheterocyclenyl, arylheterocyclyl, cycloalkenylaryl, cycloalkylaryl, cycloalkenylheteroaryl, cycloalkylheteroaryl, heteroarylcycloalkenyl, heteroarylcycloalkyl, heteroarylheterocyclenyl, heteroarylheterocyclyl, heterocyclenylaryl, heterocyclenylheteroaryl, heterocyclylaryl, and heterocyclylheteroaryl. Particular multicyclic alkaryl groups are bicyclic rings that include one aromatic ring fused to one non-aromatic ring and that also may contain in the ring system one or more heteroatoms, such as nitrogen, oxygen or sulfur.

"Patient" includes human and other mammals.

"Pharmaceutically acceptable salts" refers to the non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts may be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. In some cases, the compounds themselves are capable of self-protonating basic sites on the molecule and forming an internal amphoteric salt.

Exemplary acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, sulfamates, malonates, salicylates, propionates, methylene-bis-ß-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfamates and laurylsulfonate salts. See, for example S.M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66, 1-19 (1977) that is incorporated herein by reference. Base addition salts can also be prepared by separately reacting the purified compound in its acid form with a suitable organic or inorganic base and isolating the salt thus formed. Base addition salts include pharmaceutically acceptable metal and amine salts. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, magnesium, and aluminum salts. A particular base addition salt is sodium salt or potassium salt. Suitable inorganic base addition salts are prepared from metal bases which include sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, and zinc hydroxide. Suitable amine base addition salts are prepared from amines which have sufficient basicity to form a stable salt, and particularly include those amines which are frequently used in medicinal chemistry because of their low toxicity and acceptability for medical use. Exemplary amin includes ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium,

tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, e.g., lysine and arginine, and dicyclohexylamine.

"Solvate" means a physical association of a compound of the present invention with one or more solvent molecules. This physical association includes hydrogen bonding. In certain instances, the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and insoluble solvates. Particular solvates include hydrates, ethanolates, and methanolates.

"Substituted one or more times independently" means substituted one or more times by same or different substituent groups, particularly substituted one, two or three times by same or different substituent groups.

Particular Embodiments of the Invention

One particular embodiment of the invention is a compound of formula (I) wherein R^1 is aryl or heteroaryl, each of which is optionally substituted one or more times independently by halo, $(C_1\text{-}C_6)$-alkyl, hydroxy, $(C_1\text{-}C_6)$-alkoxy, $(C_1\text{-}C_4)$-haloalkyl or $(C_1\text{-}C_4)$-haloalkoxy, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein R^1 is phenyl or five or six membered heteroaryl, each of which is optionally substituted one or more times independently by halo, $(C_1\text{-}C_6)$-alkyl, hydroxy, or $(C_1\text{-}C_6)$-alkoxy, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein R^1 is phenyl, pyridyl, pyrimidinyl, thiazolyl, or oxodiazolyl, each of which is optionally substituted one or more times independently by halo, $(C_1\text{-}C_6)$-alkyl, hydroxy, or $(C_1\text{-}C_6)$-alkoxy, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein R^1 is phenyl, pyridyl or pyrimidinyl, each of which is optionally substituted independently at the

ortho or meta position by halo, (C_1-C_6)-alkyl, hydroxy, or (C_1-C_6)-alkoxy, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein R^1 is phenyl optionally substituted independently at the ortho or meta position by halo, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein R^1 is pyridyl, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein R^2 is hydrogen, methyl or trifluoromethyl, or a hydrate solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein R^2 is hydrogen, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein R^2 is methyl, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein L^1 is a bond, -O-, -C(=O)-, or -NH-C(=O)-, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein L^1 is a bond, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein:

R^3 and R^4 together with the nitrogen atom to which they are attached form heterocyclyl, heterocyclenyl, arylheterocyclyl, or heteroaryl, each of which is optionally substituted one or more times independently by R^6;

R^6 is alkoxy, hydroxyl, cycloalkyl, carboxy, cycloalkyl, halo, cyano, alkylsulfonyl,

Y^1Y^2N-, Y^1Y^2N-SO_2-,

alkyl optionally substituted one or more times independently by acyloxy, hydorxy, alkoxycarbonyl, alkoxy, carboxy, aryl, halo, alkylsulfonyl, cyano, Y^1Y^2N-, or Y^1Y^2N-C(=O)-,

acyl or aryl, each of which is optionally substituted one or more times independently by halo,

alkoxycarbonyl optionally substituted one or more times independently by aryl, heteroaroyl optionally substituted one or more times independently by alkyl, heterocyclyl optionally substituted one or more times by oxo, or

aryloxy optionally substituted one or more times independently by haloalkyl; and

Y^1 and Y^2 are each independently hydrogen, alkylsulfonyl, aroyl, or alkyl optionally substituted by morpholinyl, or

Y^1 and Y^2 together with the nitrogen atom to which they are attached form morpholinyl;

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein:

R^3 and R^4 together with the nitrogen atom to which they are attached form [1,2,4]triazolyl, pyrrolyl, indolyl, pyrrolo[2,3-b]pyridyl, pyrrolo[3,2-b]pyridyl, or pyrrolo[2,3-c]pyridyl, each of which is optionally substituted one or more times independently by R^6;

R^6 is alkoxy, carboxy, cycloalkyl, halo, cyano, alkylsulfonyl, Y^1Y^2N-SO_2-,

alkyl optionally substituted one or more times independently by Y^1Y^2N-C(=O)-, hydorxy, alkoxycarbonyl, alkoxy, carboxy, aryl, halo, heterocyclyl, cycloalkyl, alkylsulfonyl, cyano, heterocyclylcarbonyl,

acyl or aryl, each of which is optionally substituted one or more times independently by halo,

alkoxycarbonyl optionally substituted one or more times independently by aryl, heteroaroyl optionally substituted one or more times independently by alkyl, heterocyclyl optionally substituted one or more times by oxo, or

aryloxy optionally substituted one or more times independently by haloalkyl; and

Y^1 and Y^2 are each independently hydrogen, or alkyl optionally substituted by morpholinyl, or

Y^1 and Y^2 together with the nitrogen atom to which they are attached form morpholinyl;

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein:

R^3 and R^4 together with the nitrogen atom to which they are attached form imidazolidinyl, [1,2,4]triazinanyl, piperazinyl, morpholinyl, pyrrolidinyl, 1,2,3,4-tetrahydro-pyrimidinyl, piperidinyl, oxazolidinyl, 2,3-dihydro-indolyl, octahydro-cyclopenta[c]pyrrolyl, or 3,4-dihydro-benzo[1,4]oxazine, each of which optionally substituted one or more times independently by R^6;

R^6 is oxo, alkoxy, carboxy, cycloalkyl, halo, cyano, alkylsulfonyl, $Y^1Y^2N\text{-}SO_2\text{-}$, alkyl optionally substituted one or more times independently by hydorxy, alkoxycarbonyl, alkoxy, carboxy, aryl, halo, heterocyclyl, cycloalkyl, alkylsulfonyl, cyano, heterocyclylcarbonyl,

acyl or aryl, each of which is optionally substituted one or more times independently by halo,

alkoxycarbonyl optionally substituted one or more times independently by aryl,

heteroaroyl optionally substituted one or more times independently by alkyl,

heterocyclyl optionally substituted one or more times by oxo, or

aryloxy optionally substituted one or more times independently by haloalkyl; and

Y^1 and Y^2 are each independently hydrogen, or alkyl optionally substituted by morpholinyl, or

Y^1 and Y^2 together with the nitrogen atom to which they are attached form morpholinyl;

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein:

R^3 and R^4 together with the nitrogen atom to which they are attached form indolyl, optionally substituted one or more times independently by R^6;

R^6 is $Y^1Y^2N\text{-}SO_2\text{-}$, alkoxycarbonyl, carboxyalkyl, cyano, halo, alkylsulfonyl, alkoxy, or acyl optionally substituted one or more times independently by halo; and

Y^1 and Y^2 are each independently independently hydrogen, or alkyl optionally substituted by morpholinyl, or

Y^1 and Y^2 together with the nitrogen atom to which they are attached form morpholinyl;

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I) wherein:

R^5 is phenyl, pyridyl, or benzo[1,3]dioxolyl, each of which is optionally substituted one or more times independently by R^6;

R^6 is $Y^1Y^2N\text{-}SO_2\text{-}$, hydroxy, alkoxy, halo, alkyl, or haloalkyl; and

Y^1 and Y^2 are each independently hydrogen or alkyl,

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I), which is

2-Pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-Pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide,

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2,3-dimethyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-chloro-2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-bromo-indol-1-yl)-amide,

3-Oxo-4-[(2-phenyl-pyrimidine-5-carbonyl)-amino]-piperazine-1-carboxylic acid benzyl ester,

2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-(3-dimethylsulfamoyl-5-fluoro-indol-1-yl)amide,

2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-(3-dimethylsulfamoyl-5-fluoroindol-1-yl)amide,

2-(3-Fluorophenyl)pyrimidine-5-carboxylicacid-[5-fluoro-3-(morpholine-4-sulfonyl)indol-1-yl] amide,

2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3- (morpholine-4-sulfonyl) indol-1-yl] amide,

2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-sulfamoylindol-1-yl)amide,

2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-methylsulfamoyl)indol-1-yl)amide,

2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-(2-morpholin-4-ylethylsulfamoyl)indol-1-yl)amide,

2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3-methylsulfamoyl)indol-1-yl)amide,

2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-{5-fluoro-[(3-tetrahydropyran-4-ylmethyl)sulfamoyl]indol-1-yl}amide,

2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3-(2-morpholin-4-ylethylsulfamoyl)indol-1-yl)amide,

2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide,

2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide,

2-(Pyridin-2-yl)-pyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide,

2-(Pyridin-2-yl)-4-methylpyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide,

2-Phenyl-pyrimidine-5-carboxylic acid [6-(4-fluoro-phenyl)-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl]-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid[5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1-yl]-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1 yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-cyano-5-fluoro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(1H-tetrazol-5-yl)-indol-1-yl]-amide,

2- Phenyl-pyrimidine-5-carboxylic acid [1,2,4] triazol-4-ylamide,

2-phenyl-pyrimidine-5-carboxylic acid piperidin-1-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-(2-fluoro-phenyl)-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-ethyl-N'-tolyl-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid (3-oxo-morpholin-4-yl)-amide,

2-(5-Methyl-[1,2,4]oxadiazol-3-yl)-pyrimidine-5-carboxylic acid morpholin-4-ylamide,

2-Benzoyl-pyrimidine-5-carboxylic acid morpholin-4-ylamide,

2-Benzoyl-pyrimidine-5-carboxylic acid [4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-methyl-N'-[5-trifluoromethyl-pyridin-2-yl]-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-methyl-N'-[4-trifluoromethyl-pyridin-2-yl]-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-pyridin-2-yl-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-(2-chloro-phenyl)-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-(2-oxo-piperidin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-cyclohexyl-N'-methyl-hydrazide,

2-Phenyoxy-pyrimidine-5-carboxylic acid N'-morpholin-4-yl-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (2,6-dimethyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (6-tert-butyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-tert-butyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide,

3-{2,4-Dioxo-3-[(2-pheyl-pyrimidine-5-carbonyl)-amino]-1,2,3,4-tetrahydro-pyrimidin-5-yl}-propionic acid methyl ester,

3-{2,4-Dioxo-3-[(2-pheyl-pyrimidine-5-carbonyl)-amino]-1,2,3,4-tetrahydro-pyrimidin-5-yl}-propionic acid,

2-Phenyl-pyrimidine-5-carboxylic acid (4-methyl-piperazin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid morpholin-4-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid ((s)-2-methoxymethyl)-pyrrolidin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid ((R)-2-methoxymethyl)-pyrrolidin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (5-bromo-2, 4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (3-isopropyl-5-oxo-1,5-dihydro-[1,2,4]triazol-4-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid pyrrol-1-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid (5-morpholin-4-ylmethyl-2-oxo-oxazolidin-3-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (4-cyclopentyl-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (2-oxo-oxazolidin-3-yl)-amide,

4-Methyl-2-phenyl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl]-amide,

[N'-(2-Phenyl-pyrimidine-5-carbonyl)-hydrazino]-acetic acid ethyl ester,

2-[N`-(2-Phenyl-pyrimidine-5-carbonyl)-hydrazino]-acetamide,

4-[3-(4-Morpholino)propyl]-1-(2-phenyl-pyrimidine-5-carbonyl)-3-thiosemicarbazide,

2-Phenyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

{4-[2-Phenyl-pyrimidine-5-carbonyl)-amino]-piperazin-1-yl}-acetic acid methyl ester,

2-Phenyl-pyrimidine-5-carboxylic acid (4-cyanomethyl-piperazin-1-yl)-amide,

Acetic acid 2-{4-[(2-phenyl-pyrimidine-5-carbonyl)-amino]-piperazin-1-yl}-ethyl ester,

2-Phenyl-pyrimidine-5-carboxylic acid (4-acetyl-piperazin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-oxo-tetrahydro-furan-3-yl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(2,2,2-trifluoro-acetyl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-methoxy-ethyl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazin-1-yl]-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid piperadin-1-yl-amide,

2-Phenyl-pyrimidine-5-carboxylic acid piperadin-1-yl-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (hexahydro-cyclopenta[c]pyrrol-2-yl)-amide,

4-Methyl-2-phenyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid pyrrolidin-1-yl-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (2,6-dimethyl-piperadin-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (4-cyclopentyl-piperazin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-methyl-N'-pyridin-2-yl-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid indol-1-yl-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid indol-1-yl-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid indol-1-ylamide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid indol-1-ylamide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-methanesulfonyl-indol-1-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide,

2-Pyridin-3-yl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl-4-methyl)-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,
2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,
2-Pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridine-1-ylamide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,
4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide,
4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-cyano-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (4-cyano-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [4-(1H-tetrazol-5-yl)-indol-1-yl]-amide,
1-{[2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-4-carboxylic acid methyl ester,
1-{[2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-4-carboxylic acid,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-cyanomethyl-indol-1-yl)-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methoxy-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(1H-tetrazol-5-ylmethyl)-indol-1-yl]-amide,
2-(2-Phenyl-pyrimidine-5-carbonyl)-1-hydrazinecarboxamide,
2-(2-Phenyl-pyrimidine-5-carbonyl)-1-hydrazine-1-carbothioamide,
2-Phenyl-pyrimidine-5-carboxylic acid (2,4-dioxo-imidazolidin-1-yl)-amide,
2-Phenyl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-Phenyl-pyrimidine-5-carboxylic acid N'-phenyl-hydrazide,

Pyridine-2-carboxylic acid N'-(2-phenyl-pyrimidine-5-carbonyl)-hydrazide,
4-[N'-(2-Phenyl-pyrimidine-5-carbonyl)-hydrazino]-benzenesulfonamide,
3-Hydroxy-benzoic acid N'-(2-phenyl-pyrimidine-5-carbonyl)-hydrazide,
Benzo[1,3]dioxo-5-carboxylic acid N'-(phenyl-pyrimidine-5-carbonyl)-hydrazide,
3,4-Dimethoxy-benzoic acid N'-(phenyl-pyrimidine-5-carbonyl)-hydrazide,
2-Phenyl-pyrimidine-5-carboxylic acid N'-methyl-N'-phenyl-hydrazide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-indol-1-yl)-amide,
2-(3-Methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-(2-Methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-(4-Methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-(3-Hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-(2-Hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-(4-Hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,
2-Thiazol-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,
[2,2']Bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylicacid(3chloro-5-fluoro-indol-1-yl)-amide,
5-Fluoro-1-{[2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indole-3-carboxylic acid amide,
2-{5-Fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indol-3-yl}-2-methyl-propionic acid,
2-(5-Fluoro-1-{[2-(3-fluoro-phenyl) -4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-3-yl)-2-methyl-propionic acid,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3- (3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3- (2-pyridin-3-yl-ethyl)-indol-1-yl]- amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-formyl-indol-1-yl)-amide,

5-Fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indole-3-carboxylic acid,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-hydroxymethyl-indol-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-2-methyl-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid *N',N'*-diphenyl-hydrazide
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (7-fluoro-3-methyl-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-3-methyl-indol-1-yl)-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3c] pyridin-1-yl)-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-5-trifluoromethyl-indol-1-yl)-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3c]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-nitro-indol-1-yl)-amide,

2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-amino-indol-1-yl)-amide,

2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-(dimethanesulfonyl)-amino-indol-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-benzoylamino-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-indol-1-yl]-amide,

2-Pyridin-2-yl-4-trifluoromethyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-1,4-benzoxazin-4-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-1,4-benzoxazin-4-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (2-cyclopropyl-5-fluoro-indol-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (2-cyclopropyl-5-fluoro-indol-1-yl)-amide,

2-Pyrimidin-2-yl-4-methyl-pyrimidine-5-carboxylic acid (5-methoxyl-indol-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(1-oxy-pyridin-2-yl)-pyrimidin-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-(3-Difluoromethyl-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide, or

2-(3-Trifluoromethyl-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Another particular embodiment of the invention is a compound of formula (I), which is:

2-Phenyl-pyrimidine-5-carboxylic acid (4-benzyl-piperazin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid piperazin-1-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid (4-methanesulfonyl-piperazin-1-yl)-amide,

2-(2-Methyl-thiazol-4-yl)-pyrimidine-5-carboxylic acid morpholin-4-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(1-methyl-1H-imidazole-2-carbonyl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(1-methyl-1H-imidazole-4-carbonyl)-piperazin-1-yl]-amide,

4-[(2-Phenyl-pyrimidine-5-carbonyl)-amino]-piperazine-1-carboxylic acid tert-butyl ester,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(4-trifluoromethyl-phenoxy)-piperidin-1-yl]-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid [4-(4-trifluoromethyl-phenoxy)-piperidin-1-yl]-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid morpholin-4-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid indol-1-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid (4-methoxy-piperidin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-benzo[1,4]oxazin-4-yl)-amide,
2-Phenyl-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-benzo[1,4]oxazin-4-yl)-amide,
1-{[2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-3-(2-morpholin-4-yl-ethyl)-1H-indole-6-carboxylic acid methyl ester,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(tetrahydro-pyran-4-yl)-indol-1-yl]-amide,
N-methyl-N-(5-fluoro)-indol-3-ylsulfonyl N`-[2-(3-fluoro)-phenyl-pyrimidine-5-carbonyl]-hydrazide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(tetrahydro-pyran-4-yl)-indol-1-yl]-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,
4-Methyl-2-(1-oxy)-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[3,2-c]pyridin-1-ylamide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethy l-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[3,2-c]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-(4-chloro -thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[3,2-c]pyridin-1-ylamide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-(4-Methyl-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-3-oxo-2,3-dihydro-indazol-1-yl)amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid(5-fluoro-indol-1-yl)amide)amide,

6-(4-Chloro-thiazol-2-yl)-2-methyl-N-pyrrolo[2,3-c]pyridin-1-yl-nicotinamide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid(5-methyl-4-oxo-4,5-dihydro-pyrrolo[3,2-c]pyridin-1-yl)amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (5-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (5-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluo ro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluo ro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluo ro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-

ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-difluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo [3,2-b]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo [3,2-b]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrro lo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-2,2-diuoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-c] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrro lo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo [2,3-c]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo [2,3-c]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo [2,3-b]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo [2,3-b]pyridin-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-trifluoro methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-difluorom ethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoro

methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoro
methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoro
methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-indol-1-yl)-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (3-difluoromethyl-indol-1-yl)-amide, or
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-indol-1-yl)-amide,
or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

It is to be understood that this invention covers all appropriate combinations of the particular embodiments referred thereto.

The present invention also includes within its scope a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of the invention, in admixture with a pharmaceutically acceptable carrier.

Compounds of the present invention are PGDS inhibitors and thus, are useful for treating allergic and/or inflammatory disorders, particularly disorders such as allergic rhinitis, asthma and/or chronic obstructive pulmonary disease (COPD). Accordingly, another invention herein is directed to a method of treating a patient suffering from allergic rhinitis, asthma, and/or chronic obstructive pulmonary disease (COPD) comprising administering to the patient a

pharmaceutically effective amount of compound of formula (I), or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

References herein directed to treating should be understood to include prophylactic therapy to inhibit PGDS, as well as to treat an established acute or chronic or physiological conditions associated with PGDS to essentially cure a patient suffering therefrom, or ameliorate the physiological conditions associated therewith. Physiological conditions discussed herein include some, but not all, of the possible clinical situations where an anti- allergic rhinitis and/or asthma treatment is warranted. Those experienced in this field are well aware of the circumstances requiring treatment.

In practice, the compound of the present invention may be administered in pharmaceutically acceptable dosage form to humans and other mammals by topical or systemic administration, including oral, inhalational, rectal, nasal, buccal, sublingual, vaginal, colonic, parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), intracisternal and intraperitoneal. It will be appreciated that the particular route may vary with for example the physiological condition of the recipient.

"Pharmaceutically acceptable dosage forms" refers to dosage forms of the compound of the invention, and includes, for example, tablets, dragées, powders, elixirs, syrups, liquid preparations, including suspensions, sprays, inhalants tablets, lozenges, emulsions, solutions, granules, capsules and suppositories, as well as liquid preparations for injections, including liposome preparations. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, latest edition.

A particular aspect of the invention provides for the compound of the invention to be administered in the form of a pharmaceutical composition.

Pharmaceutically acceptable carriers include at least one component selected from the group comprising pharmaceutically acceptable carriers, diluents, coatings, adjuvants, excipients, or vehicles, such as preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, emulsion stabilizing agents, suspending agents, isotonic agents, sweetening agents, flavoring agents, perfuming agents, coloring agents, antibacterial agents, antifungal agents,

other therapeutic agents, lubricating agents, adsorption delaying or promoting agents, and dispensing agents, depending on the nature of the mode of administration and dosage forms.

Exemplary suspending agents include ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances.

Exemplary antibacterial and antifungal agents for the prevention of the action of microorganisms include parabens, chlorobutanol, phenol, sorbic acid, and the like.

Exemplary isotonic agents include sugars, sodium chloride, and the like.

Exemplary adsorption delaying agents to prolong absorption include aluminum monostearate and gelatin.

Exemplary adsorption promoting agents to enhance absorption include dimethyl sulfoxide and related analogs.

Exemplary diluents, solvents, vehicles, solubilizing agents, emulsifiers and emulsion stabilizers, include water, chloroform, sucrose, ethanol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, tetrahydrofurfuryl alcohol, benzyl benzoate, polyols, propylene glycol, 1,3-butylene glycol, glycerol, polyethylene glycols, dimethylformamide, Tween® 60, Span® 60, cetostearyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate, fatty acid esters of sorbitan, vegetable oils (such as cottonseed oil, groundnut oil, olive oil, castor oil and sesame oil) and injectable organic esters such as ethyl oleate, and the like, or suitable mixtures of these substances.

Exemplary excipients include lactose, milk sugar, sodium citrate, calcium carbonate and dicalcium phosphate.

Exemplary disintegrating agents include starch, alginic acids and certain complex silicates. Exemplary lubricants include magnesium stearate, sodium lauryl sulfate, talc, as well as high molecular weight polyethylene glycols.

The choice of pharmaceutical acceptable carrier is generally determined in accordance with the chemical properties of the active compound such as solubility, the particular mode of administration and the provisions to be observed in pharmaceutical practice.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as a solid dosage form, such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, or as a powder or granules; as a liquid dosage form such as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

"Solid dosage form" means the dosage form of the compound of the invention is solid form, for example capsules, tablets, pills, powders, dragées or granules. In such solid dosage forms, the compound of the invention is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or: (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, (j) opacifying agents, (k) buffering agents, and agents which release the compound of the invention in a certain part of the intestinal tract in a delayed manner.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants

such as magnesium stearate, sodium lauryl sulfate and talc may be used. A mixture of the powdered compounds moistened with an inert liquid diluent may be molded in a suitable machine to make molded tablets. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Solid compositions may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols, and the like.

If desired, and for more effective distribution, the compound can be microencapsulated in, or attached to, a slow release or targeted delivery systems such as a biocompatible, biodegradable polymer matrices (e.g., poly(d,l-lactide co-glycolide)), liposomes, and microspheres and subcutaneously or intramuscularly injected by a technique called subcutaneous or intramuscular depot to provide continuous slow release of the compound(s) for a period of 2 weeks or longer. The compounds may be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

"Liquid dosage form" means the dose of the active compound to be administered to the patient is in liquid form, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compound, the liquid dosage forms may contain inert diluents commonly used in the art, such solvents, solubilizing agents and emulsifiers.

When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension.

Pharmaceutical compositions suitable for topical administration mean formulations that are in a form suitable to be administered topically to a patient. The formulation may be presented as a topical ointment, salves, powders, sprays and inhalants, gels (water or alcohol based), creams, as is generally known in the art, or incorporated into a matrix base for application in a patch, which would allow a controlled release of compound through the transdermal barrier. When formulated in an ointment, the active ingredients may be employed with either a

paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. Formulations suitable for topical administration in the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The oily phase of the emulsion pharmaceutical composition may be constituted from known ingredients, in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. In a particular embodiment, a hydrophilic emulsifier is included together with a lipophilic emulsifier that acts as a stabilizer. Together, the emulsifier(s) with, or without, stabilizer(s) make up the emulsifying wax, and together with the oil and fat make up the emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

If desired, the aqueous phase of the cream base may include, for example, a least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as, propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound that enhances absorption, or penetration of the active ingredient through the skin, or other affected areas.

The choice of suitable oils or fats for a composition is based on achieving the desired properties. Thus a cream should particularly be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Pharmaceutical compositions suitable for rectal or vaginal administrations mean formulations that are in a form suitable to be administered rectally or vaginally to a patient and containing at least one compound of the invention. Suppositories are a particular form for such formulations that can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Pharmaceutical composition administered by injection may be by transmuscular, intravenous, intraperitoneal, and/or subcutaneous injection. The compositions of the present invention are formulated in liquid solutions, in particular in physiologically compatible buffers such as Hank's solution or Ringer's solution. In addition, the compositions may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms are also included. The formulations are sterile and include emulsions, suspensions, aqueous and non-aqueous injection solutions, which may contain suspending agents and thickening agents and anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic, and have a suitably adjusted pH, with the blood of the intended recipient.

Pharmaceutical composition of the present invention suitable for nasal or inhalational administration means compositions that are in a form suitable to be administered nasally or by inhalation to a patient. The composition may contain a carrier, in a powder form, having a particle size for example in the range 1 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc.). Suitable compositions wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Compositions suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents. Inhalational therapy is readily administered by metered dose inhalers or any suitable dry powder inhaler, such as the Eclipse, Spinhaler®, or Ultrahaler® as described in patent application WO2004/026380, and US Patent No. 5,176,132.

Actual dosage levels of active ingredient(s) in the compositions of the invention may be varied so as to obtain an amount of active ingredient(s) that is (are) effective to obtain a desired therapeutic response for a particular composition and method of administration for a patient. A selected dosage level for any particular patient therefore depends upon a variety of factors including the desired therapeutic effect, on the route of administration, on the desired duration of treatment, the etiology and severity of the disease, the patient's condition, weight, sex, diet and age, the type and potency of each active ingredient, rates of absorption, metabolism and/or excretion and other factors.

Total daily dose of the compound of this invention administered to a patient in single or divided doses may be in amounts, for example, of from about 0.001 to about 100 mg/kg body weight daily and particularly 0.01 to 10 mg/kg/day. For example, in an adult, the doses are generally from about 0.01 to about 100, particularly about 0.01 to about 10, mg/kg body weight per day by inhalation, from about 0.01 to about 100, particularly 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.01 to about 50, particularly 0.01 to 10, mg/kg body weight per day by intravenous administration. The percentage of active ingredient in a composition may be varied, though it should constitute a proportion such that a suitable dosage shall be obtained. Dosage unit compositions may contain such amounts or such submultiples thereof as may be used to make up the daily dose. Obviously, several unit dosage forms may be administered at about the same time. A dosage may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much lower maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

The formulations can be prepared in unit dosage form by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the pharmaceutically active ingredient with the carrier that constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

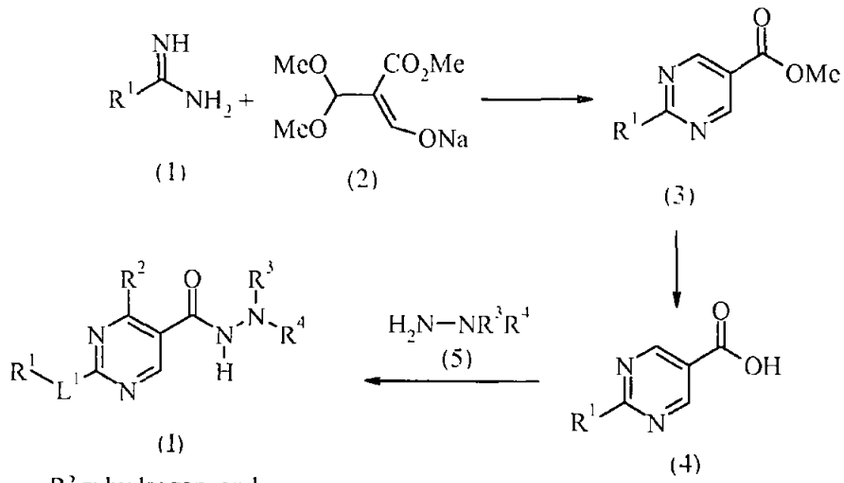
The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Compounds of the invention may be prepared by the application or adaptation of known methods, by which is a meant method used heretofore or described in the literature, for example those described by R.C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc., 1999.

A compound of formula (I), wherein R^2 is hydrogen, L^1 is a bond, –NH-C(=O)- or (C_1-C_2)-alkylene optionally substituted one or more times by halo, and R^1, R^3 and R^4 are as defined herein, may be prepared, as shown in Scheme I below, by (i) reacting a corresponding amidine compound of formula (1), with a reagent of formula (2) to provide a compound of formula (3), (ii) hydrolyzing the compound offormula (3) to provide a compound of formula (4), and (iii) coupling the compound of (4) with a corresponding compound of formula (5).

Scheme I

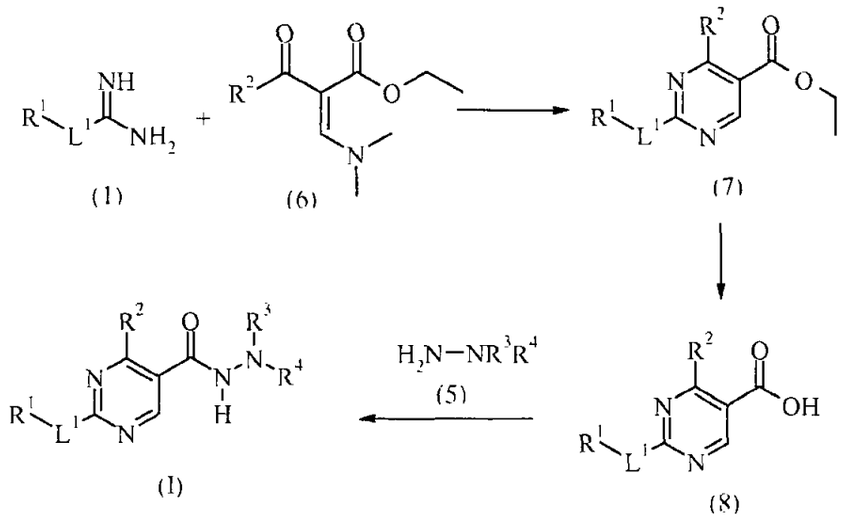


R^2 = hydrogen, and
L^1 is a bond, -NH-C(=O)- or (C_1-C_2)-alkylene optionally substituted one or more times by halo

The first step reaction may conveniently be carried out, for example, at a temperature about 100°C, in an inert solvent, such as DMF. The second step reaction may conveniently be carried out, for example, at room temperature, in the presence of an inorganic base, such as LiOH, KOH or NaOH, in a solvent, such as THF, MeOH, water, or a mixture thereof. The third step reaction may conveniently be carried out, for example, at about a temperature about room temperature to 100°C, in the presence of a coupling agent, such as HCTU, HOTT, PyBrOP, DMTMM, or HATU with HOAt, and a base, such as DIPEA or Et_3N, in an inert solvent, such as DMF. The third step reaction may conveniently be carried out, for example, at about a temperature about 0°C to room temperature, by first reacting the compound of formula (4) with oxalyl chloride, and then adding the compound of formula (5) and a base such as DIPEA, Et_3N, K_2CO_3 or Na_2CO_3, in an inert solvent, such as DCM or DMF.

A compound of formula (I), wherein R^2 is (C_1-C_4)-alkyl optionally substituted one or more times by halo, L^1 is a bond, –NH-C(=O)- or (C_1-C_2)-alkylene optionally substituted one or more times by halo, and R^1, R^3 and R^4 are as defined herein,may also be prepared, as shown in Scheme II below, by (i) reacting a corresponding amidine compound of formula (1), with a reagent of formula (6) to provide a compound of formula (7), (ii) hydrolyzing the compound of formula (7) to provide a compound of fommula (8), and (iii) coupling the compound of formula (8) with a corresponding compound of formula (5).

Scheme II



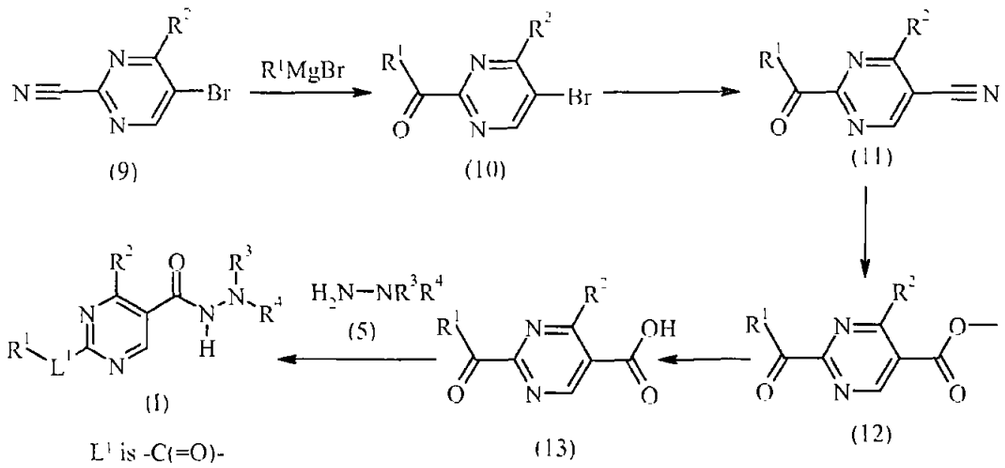
R^2 = (C_1-C_4)-alkyl optionally substituted one or more times by halo, and
L^1 is a bond, -NH-C(=O)- or (C_1-C_2)-alkylene optionally substituted one or more times by halo

The first step reaction may conveniently be carried out, for example, at a temperature about 100°C, in the presence of sodium metal, in a solvent, such as EtOH. The second step reaction may conveniently be carried out, for example, at room temperature, in the presence of an inorganic base, such as LiOH, KOH or NaOH, in a solvent, such as THF, MeOH, water, or a mixture thereof. The third step reaction may conveniently be carried out, for example, at about a temperature about room temperature to 100°C, in the presence of a coupling agent, such as HCTU, HOTT, PyBrOP, DMTMM, or HATU with HOAt, and a base, such as DIPEA or Et_3N, in an inert solvent, such as DMF. The third step reaction may conveniently be carried out, for example, at about a temperature about 0°C to room temperature, by first reacting the compound of formula (8) with oxalyl chloride, and then adding the compound of formula (5) and a base such as DIPEA, Et_3N, K_2CO_3 or Na_2CO_3, in an inert solvent, such as DCM or DMF.

A compound of formula (I), wherein L^1 is -C(=O)-, and R^1, R^2, R^3 and R^4 are as defined herein,may be prepared, as shown in Scheme III below, by (1) reacting a corresponding compound of formula (9), with a Grignard reagent of formula R^1MgBr to provide a compound of formula (10), (2) converting the compound of formula (10) into a compound of fomrmula

(11), and (3) hydrolyzing the compound of formula (11) to provide a compound of formula (12), (4) hydrokyzing the compound of formula (12) to provide a compound of formula (13) and (5) coupling the compound of formula (13) with a corresponding compound of formula (5).

Scheme III

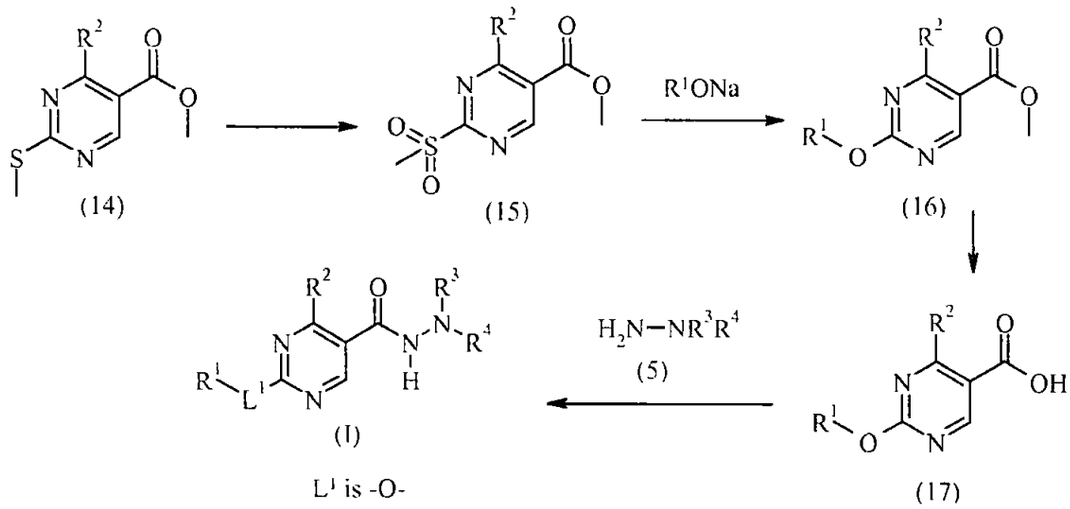


The first step reaction may conveniently be carried out, for example, at a temperature about room temperature to 50°C, in an inert solvent, such as Et_2O. The second step reaction may conveniently be carried out, for example, at a temperature about 150°C, in the presence of potassium hexacyanoferrate(II) trihydrate, palladium (II) acetate and a base such as Na_2CO_3 or K_2CO_3, in an inert solvent, such as dimethylacetamide or DMF. The third step reaction may conveniently be carried out, for example, at about a temperature about 0°C to room temperature, in the presence of an inorganic base such as KOH, NaOH or LiOH, in a solvent, such as MeOH, or a mixture of MeOH and water. The fourth step reaction may conveniently be carried out, for example, at room temperature, in the presence of an inorganic base, such as LiOH, KOH or NaOH, in a solvent, such as THF, MeOH, water, or a mixture thereof. The fifth step reaction may conveniently be carried out, for example, at about a temperature about room temperature to 100°C, in the presence of a coupling agent, such as HCTU, HOTT, PyBrOP, DMTMM, or HATU with HOAt, and a base, such as DIPEA or Et_3N, in an inert solvent, such as DMF. The third step reaction may conveniently be carried out, for example, at about a temperature about 0°C to room temperature, by first reacting the compound of

formula (4) with oxalyl chloride, and then adding the compound of formula (5) and a base such as DIPEA, Et_3N, K_2CO_3 or Na_2CO_3, in an inert solvent, such as DCM or DMF.

A compound of formula (I), wherein L^1 is -O-, and R^1, R^2, R^3 and R^4 are as defined herein,may be prepared, as shown in Scheme IV below, by (i) oxidizing a compound of formula (14) to provide a compound of formula (15), (ii) reacting the compound of formula (15) with a corresponding compound having formula R^1ONa to provide a compound of fomrmula (16), (iii) hydrolyzing the compound of formula (16) to provide a compound of formula (17), and (iv) coupling the compound of formula (17) with a corresponding compound of formula (5).

Scheme IV



The first step oxidation reaction may conveniently be carried out, for example, at room temperature, in the presence of MCPBA and $Na_2S_2O_3$, in an inert solvent, such as DCM. The second step reaction may conveniently be carried out, for example, in a microwave heated at a temperature about 100°C, in an inert solvent, such as NMP. The third step reaction may conveniently be carried out, for example, at about a temperature about 0°C to room temperature, in the presence of an inorganic base such as KOH, NaOH or LiOH, in a solvent, such as THF, MeOH, or a mixture thereof. The fourth step reaction may conveniently be carried out, for example, at about a temperature about room temperature to 100°C, in the presence of a coupling agent, such as HCTU, HOTT, PyBrOP, DMTMM, or HATU with

HOAt, and a base, such as DIPEA or Et_3N, in an inert solvent, such as DMF. The third step reaction may conveniently be carried out, for example, at about a temperature about 0°C to room temperature, by first reacting the compound of formula (17) with oxalyl chloride, and then adding the compound of formula (5) and a base such as DIPEA, Et_3N, K_2CO_3 or Na_2CO_3, in an inert solvent, such as DCM or DMF.

Compounds of the invention may also be prepared by interconversion of other compounds of the invention.

It will be appreciated that compounds of the present invention may contain asymmetric centers. These asymmetric centers may independently be in either the R or S configuration. It will be apparent to those skilled in the art that certain compounds of the invention may also exhibit geometrical isomerism. It is to be understood that the present invention includes individual geometrical isomers and stereoisomers and mixtures thereof, including racemic mixtures, of compounds of Formula (I) hereinabove. Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates.

The compounds of the invention, their methods or preparation and their biological activity will appear more clearly from the examination of the following examples that are presented as an illustration only and are not to be considered as limiting the invention in its scope. Compounds of the invention are identified, for example, by the following analytical methods.

Mass Spectra (MS) are recorded using a Micromass LCT mass spectrometer. The method is positive electrospray ionization, scanning mass m/z from 100 to 1000.

300MHz ^1H nuclear magnetic resonance spectra (^1H NMR) are recorded at ambient temperature using a Varian Mercury (300 MHz) spectrometer with an ASW 5 mm probe. In the ^1H NMR chemical shifts (δ) are indicated in parts per million (ppm) with reference to tetramethylsilane (TMS) as the internal standard.

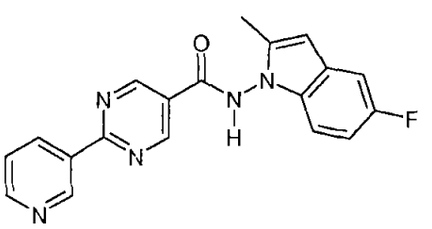
As used in the examples and preparations that follow, as well as the rest of the application, the terms used therein shall have the meanings indicated: "kg" = kilograms, "g" = grams, "mg" = milligrams, "μg" = micrograms, "mol" = moles, "mmol" = millimoles, "M" = molar, "mM" = millimolar, "μM" = micromolar, "nM" = nanomolar, "L" = liters, "mL" or "ml" = milliliters, "μL" = microliters, "°C" = degrees Celsius, "mp" or "m.p." = melting point, "bp" or "b.p." = boiling point, "mm of Hg" = pressure in millimeters of mercury, "cm" = centimeters, "nm" = nanometers, "abs." = absolute, "conc." = concentrated, "c" = concentration in g/mL, "rt" = room temperature, "TLC" = thin layer chromatography, "HPLC" = high performance liquid chromatography, "i.p." = intraperitoneally, "i.v." = intravenously, "s" = singlet, "d" = doublet; "t" = triplet; "q" = quartet; "m" = multiplet, "dd" = doublet of doublets; "br" = broad, "LC" = liquid chromatograph, "MS" = mass spectrograph, "ESI/MS" = electrospray ionization/mass spectrograph, "R_T" = retention time, "M" = molecular ion, "PSI" = pounds per square inch, "DMSO" = dimethyl sulfoxide, "DMF" = N,N-dimethylformamide, "DCM" = dichloromethane, "HCl" = hydrochloric acid, "SPA" = Scintillation Proximity Assay, "EtOAc" = ethyl acetate, "PBS"= Phosphate Buffered Saline, "IUPAC" = International Union of Pure and Applied Chemistry, "MHz" = megahertz, "MeOH " = methanol, "N" = normality, "THF" = tetrahydrofuran, "min" = minute(s), "N_2" = nitrogen gas, "MeCN" or "CH_3CN" = acetonitrile, "Et_2O" = ethyl ether, "TFA" = trifluoroacetic acid, "~" = approximately, "$MgSO_4$" = magnesium sulfate, "Na_2SO_4" = sodium sulfate, "$NaHCO_3$" = sodium bicarbonate, "Na_2CO_3" = sodium carbonate, "MCPBA" = 3-Chloroperoxybenzoic acid, "NMP" = N-methylpyrrolidone, "PS-DCC" = polymer supported-dicyclohexylcarbodiimde, "LiOH" = Lithium hydroxide, "PS-trisamine" = polymer supported-trisamine, "PGH2" = prostaglandin H2, "PGD2" = prostaglandin D2; "PGE2" = prostaglandin E2, "hPGDS" = Hematopoietic PGD2 Synthase, "GSH" = glutathione (reduced), "EIA" = Enzyme immunoassay, "KH_2PO_4" = potassium phosphate, monobasic, "K_2HPO_4" = potassium phosphate, dibasic, "$FeCl_2$" = ferrous chloride, "MOX" = methoxylamine; "EtOH" = ethanol, "DMSO" = dimethylsulfoxide, "Ag_2O" = silver(I) oxide, "HATU" = *O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate, "HOAt" = 1-hydroxy-7-azabenzotriazole, "DIPEA" = *N*,*N*-diisopropylethylamine, "HOTT" = *S*-(1-Oxido-2-pyridyl)-*N*,*N*,*N*',*N*'-tetramethylthiuronium hexafluorophosphate, "HCTU" = *N*,*N*,*N*',*N*'-tetramethyl-*O*-(6-chloro-1*H*-benzotriazol-1-yl)uronium hexafluorophosphate., "PyBrOP" = bromo-*tris*-pyrrolidinophosphonium hexafluorophosphate, "LiAlH4" = lithium aluminum hydride, "PyAOP" = (7-azabenzotriazol-1-yloxy)-tripyrrolidinophosphonium

hexafluorophosphate, "TBTU" = O-benzotriazol-1-yl-N,N,N,N,-tetramethyluronium tetrafluoroborate, "NaHMDS" = sodium bis(trimethylsilyl)amide, "NMP" = N-methyl-2-pyrrolidinone, "HOSA" = hydroxylamine-O-sulfonic acid, "DMTMM" = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, "$TMSN_3$" = trimethylsily azide, "TBAF" = tetrabutylammonium fluoride, "TFAA" = trifluoro acetic anhydride.

EXAMPLES

Example 1

2-Pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide



Step 1: A solution of potassium *tert*-butoxide (1.84 g, 16.43 mmol) and 5-fluoro-2-methylindole (1.21 g, 8.09 mmol) in DMF (20 mL) is stirred under N_2 at rt for 60 min. A solution of monochloroamine in ether (65 mL, 9.75 mmol) is added *via* an addition funnel over 10 min. The resulting mixture is stirred at 23°C for 2 hours, and then concentrated *in vacuo*. The residue is partitioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% EtOAc in heptane to afford 5-fluoro-2-methyl-indol-1-ylamine (290 mg, 22%) as a solid. MS: 165 (M+H); ^1H NMR (300MHz, $CDCl_3$): δ 7.24-7.19 (m, 1H), 7.12 (dd, 1H), 6.92 (dt, 1H), 6.12 (s, 1H), 4.23 (br s, 2 H), 2.39 (s, 3H).

Step 2: A 250 mL, three-neck, round-bottom flask equipped with a magnetic stirrer and a reflux condenser is purged with N_2. The flask is charged sequentially with methyl 3,3-dimethoxypropionate (5.22 g, 35.3 mmol), anhydrous 1,2-dimethoxyethane (25 mL), anhydrous methyl formate (5 mL), 60% sodium hydride (1.7 g, 42.5 mmol), and the mixture warmed to 40 – 50°C until evolution of hydrogen gas stops. The reaction mixture is cooled in an ice/water bath and slowly allowed to reach room temperature overnight with stirring. Anhydrous ether (25 mL) is added, and the resulting suspension is filtered under N_2, washed

with anhydrous ether (10 mL), and vacuum dried for 2 hours to yield sodium salt of 2-dimethoxymethyl-3-hydroxy-acrylicacid methyl ester (3.51 g, 50%) as a powder. ^{1}H NMR (CD_3OD): δ 3.33 (s, 6H), 3.60 (s, 3H), 5.31 (s, 1H), 8.89 (s, 1H). (see: P. Zhichkin, D.J. Fairfax, S.A. Eisenbeis, Synthesis, 2002, 720-722.)

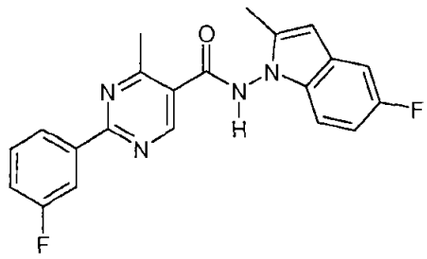
Step 3: To a solution of nicotinamidine hydrochloride (1 g, 6.35 mmol) in anhydrous DMF (12 mL) is added sodium salt of 2-dimethoxymethyl-3-hydroxy-acrylicacid methyl ester (1.46 g, 7.36 mmol) and the reaction mixture is heated at 100°C under N_2 for 3 hours. After this time the reaction is cooled to room temperature and water (48 mL) is added. The precipitate is collected by filtration, washed with water and vacuum dried to afford 2-pyridin-3-yl-pyrimidine-5-carboxylic acid methyl ester (0.7 g, 51%). MS: 216 (M+H).

Step 4: A solution of 2-pyridin-3-yl-pyrimidine-5-carboxylic acid methyl ester (0.73 g, 3.32 mmol) and 1M aqueous LiOH (3.32 mL) in MeOH (5 mL) is stirred at rt overnight. The MeOH is removed *in vacuo*, and the aqueous solution is treated with 3 N aqueous HCl to adjust the pH ~ 2-3. The solid is filtered off and washed with water and dried in vacuum to yield 2-pyridin-3-yl-pyrimidine-5-carboxylic acid (0.2 g, 30%) as a solid. MS: 202 (M+H).

Step 5: A solution of 2-pyridin-3-yl-pyrimidine-5-carboxylic acid (506 mg, 2.13 mmol), HCTU (970 mg, 2.34 mmol), and DIPEA (1 mL, 5.72 mmol) in DMF (10 mL) is stirred at rt under N_2 for 10 min. 5-Fluoro-2-methyl-indol-1-ylamine (311 mg, 1.89 mmol) is added. The resulting mixture is stirred at 75°C overnight. The mixture is cooled and portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 45% EtOAc in heptane to afford 2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide (300 mg, 46%) as a solid. MS: 348 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 12.02 (s, 1H), 9.60 (d, 1H), 9.49 (s, 2H), 8.82-8.76 (m, 2H), 7.64 (dd, 1H), 7.39 (dd, 1H), 7.29 (dd, 1H), 6.94 (dt, 1H), 6.35 (s, 1H), 2.33 (s, 3H).

Example 2

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)amide



Step 1: Na^0 (0.66 g, 28.6 mmol) is added to anhydrous EtOH (100 mL) and stirred at rt for 15 min. 3-Fluorobenzamidine hydrochloride (4.87 g, 27.8 mmol) is added and the solution is stirred for 15 min. 2-Dimethylaminomethylene-3-oxo-butyric acid ethyl ester (5.3 g, 28.6 mmol,) is added and the reaction mixture is heated at reflux under N_2 for 1 hours. The reaction is cooled to rt and concentrated *in vacuo*. The residue is dissolved in EtOAc (300 mL), washed with brine (2x100 mL), dried (Na_2SO_4), filtered, and concentrated to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid ethyl ester (6.8 g, 99%). MS: 261 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (t, J = 7.0 Hz, 3H), 2.92 (s, 3H), 4.42 (q, J = 7.0 Hz, 2H), 7.24 (m, 1H), 7.45 (m, 1H), 8.27 (m, 1H), 8.37 (m, 1H), 9.21 (s, 1H).

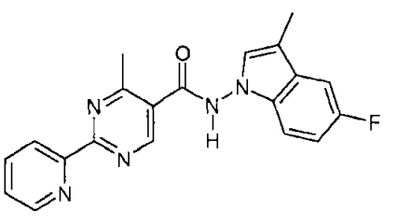
Step 2: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid ethyl ester (6.7 g, 27.2 mmol) and NaOH (2.1 g, 54.4 mmol) in a 1:1:1 solution of THF, MeOH and water (300 mL) is heated at reflux for 45 min. The THF/MeOH is evaporated, and the aqueous solution is treated with 3 N HCl to adjust the pH to between 2 and 3. The solid is filtered off, washed with water and dried *in vacuo* to yield 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5.4 g, 91%) as a solid. MS: 233 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.85 (s, 3H), 7.24 (m, 1H), 7.50 (m, 1H), 8.17 (m, 1H), 8.32 (m, 1H), 9.20 (s, 1H).

Step 3: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (340 mg, 1.46 mmol, prepared according to the general procedure described in Example 1, steps 3 and 4), HOAt (248 mg, 1.82 mmol), and HATU (645 mg, 1.70 mmol) in DMF (15 mL) is stirred at rt under N_2 for 20 min. 5-Fluoro-2-methyl-indol-1-ylamine (237 mg, 1.44 mmol) and DIPEA (380 μL, 2.18 mmol) are added. The resulting mixture is stirred at 80°C overnight. The mixture is cooled and portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 20% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid

(5-fluoro-2-methyl-indol-1-yl)amide (300 mg, 55%) as a solid. MS: 379 (M+H). ^{1}H NMR (300MHz, CD_3OD): δ 9.14 (s, 1H), 8.38-8.20 (m, 3H), 7.56-7.52 (m, 1H), 7.30-7.27 (m, 2H), 7.19-7.16 (m, 1H), 6.96-6.90 (m, 1H), 6.32 (s, 1H), 2.83 (s, 3H), 2.42 (s, 3H).

Example 3

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)amide



Step 1: A suspension of NaH (2.01 g, 50.3 mmol, 60% in mineral oil) in DMF (45 mL) at 0°C is treated with 5-fluoro-3-methyl-1H-indole (500 mg, 3.55 mmol), and the mixture is stirred at 0°C for 1 h. NH_2OSO_3H (1.9 g, 16.75 mmol) is added portion wise, and the mixture is then warmed to rt and stirred for 2 h. The mixture is quenched with MeOH, diluted with water, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated to afford 5-fluoro-3-methyl-indol-1-ylamine. MS: 165 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.22 (s, 3H), 6.86 (m, 1H), 6.99 (s, 1H), 7.08 (m, 1H), 7.36 (m, 1H).

Step 2: Na^0 (31.7 mmol) is added to anhydrous EtOH (100 mL) and stirred at rt for 15 min. Pyridine-2-carboxamidine hydrochloride (31.7 mmol) is added and the solution is stirred for 15 min. 2-Dimethylaminomethylene-3-oxo-butyric acid ethyl ester (31.7mmol) is added and the reaction mixture is heated at reflux under N_2 for 1 h. The reaction is cooled to rt and concentrated *in vacuo*. The residue is dissolved in EtOAc (200 mL), washed with brine (2x100 mL), dried (Na_2SO_4), filtered, and concentrated to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid ethyl ester (6.77 g, 88%). MS: 261 (M+H); ^{1}H ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, 3H), 2.97 (s, 3H), 4.44 (q, 2H), 7.44 (m, 1H), 7.91 (m, 1H), 8.60 (m, 1H), 8.90 (m, 1H), 9.31 (s, 1H).

Step 3: A solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid ethyl ester (26.7 mmol) and LiOH (53.4 mmol) in a 1:1:1 solution of THF, MeOH and water (200 mL) is stirre at rt overnight. The THF/MeOH is evaporated, and the aqueous solution is treated with 10% aqueous HCl to adjust the pH to between 1.5 and 2.5. The solid is filtered off, washed with water and dried *in vacuo* to yield 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5.50

g, 96%) as a solid. MS: 233 (M+H); ^{1}H ^{1}H NMR (300 MHz, CD_3OD): δ = 2.93(s, 3H), 7.59 (m, 1H), 8.05 (t, 1H), 8.62 (d, 1H), 8.76 (d, 1H), 9.28 (s, 1H).

Step 4, Method A:

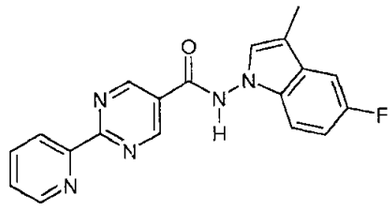
A solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (335 mg, 1.56 mmol), HOTT (638 mg, 1.72 mmol), and DIPEA) (700 μL, 4.01 mmol in DMF (6 mL) is stirred stirred at rt under N_2 for 20 min. 5-Fluoro-3-methyl-indol-1-ylamine (241 mg, 1.47 mmol) is added. The resulting mixture is stirred at rt overnight. The mixture is portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 60% EtOAc in heptane to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)amide (193 mg, 36%) as a solid. MS: 362 (M+H). ^{1}H NMR (300MHz, $CDCl_3$): δ 10.41 (s, 1H), 8.84 (s, 1H), 8.55 (s, 1H), 8.48-8.45 (m, 1H), 7.86 (t, 1H), 7.40-7.36 (m, 1H), 7.24-7.20 (m, 2H), 7.05-7.01 (m, 2H), 2.82 (s, 3H), 2.32 (s, 3H).

Step 4, Method B:

5-Fluoro-3-methyl-indol-1-ylamine (10.6 mmol) is treated with 4-methyl-2-pyridin-2-ylpyrimidine-5-carboxylic acid (2.75 g, 12.8 mmol) in DMF (75 mL) and the mixture is stirred at rt for 10 min. The mixture is then treated with 2,4-dimethoxy-6-(4-methylmorpholin-4-yl)-[1,3,5]triazine chloride (3.82 g, 13.85 mmol) and stirred at 60°C for 1 h. The mixture is concentrated *in vacuo*. The residue is diluted with Et_2O (50 mL) and 10% $NaHCO_3$ (50 mL), and the mixture is stirred at rt for 20 min. The resulting solid is filtered, washed, and dried to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)amide (3.2 g, 83%). The solid is crystallized with MeOH:water (4:1) to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)amide as a crystal. MS: 362 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H), 2.78 (s, 3H), 7.06 (m, 1H), 7.34 (m, 1H), 7.37 (s, 1H), 7.44 (m, 1H), 7.59 (m, 1H), 8.05 (m, 1H), 8.45 (m, 1H), 8.80 (m, 1H), 9.25 (s, 1H). IC_{50} = 7 nM.

Example 4

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide



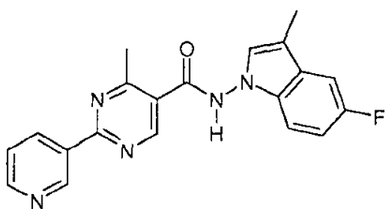
Step 1: Following the procedures similar to those of Example 1, step 3, but substituting pyridine-2-carboxamidine hydrochloride nicotinamidine hydrochloride, there is prepared 2-pyridin-2-yl-pyrimidine-5-carboxylic acid methyl ester.

Step 2: Following the procedures similar to those of Example 2, step 1, but substituting 2-pyridin-2-yl-pyrimidine-5-carboxylic acid methyl ester for 2-pyridin-3-yl-pyrimidine-5-carboxylic acid methyl ester, there is prepared 2-pyridin-2-yl-pyrimidine-5-carboxylic acid.

Step 3: A solution of 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (209 mg, 0.88 mmol), HOTT (435 mg, 1.17 mmol), and DIPEA (400 µL, 2.29 mmol) in DMF (10 mL) is stirred at rt under N_2 for 20 min. 5-Fluoro-3-methyl-indol-1-ylamine (125 mg, 0.76 mmol) is added. The resulting mixture is stirred at rt overnight. The mixture is portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 70% EtOAc in heptane to afford 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide (180 mg, 68%) as a solid. MS: 348 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 12.12 (s, 1H), 9.47 (s, 2H), 8.82 (d, 1H), 8.51 (d, 1H), 8.05 (td, 1H), 7.62 (dd, 1H), 7.42 (dd, 1H), 7.35 (dd, 1H), 7.33 (s, 1H), 7.03 (td, 1H), 2.27 (s, 3H).

Example 5

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide



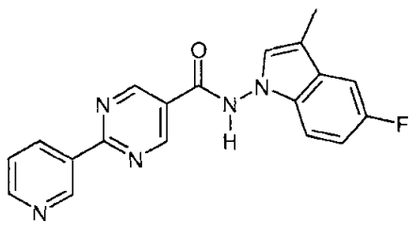
Step 1: Following the procedures similar to those of Example 2, step 1, but substituting nicotinamidine hydrochloride for 3-fluorobenzamidine hydrochloride, there is prepared 2-pyridin-3-yl-4-methyl-pyrimidine-5-carboxylic acid ethyl ester.

Step 2: Following the procedures similar to those of Example 2, step 1, but substituting 2-pyridin-3-yl-4-methyl-pyrimidine-5-carboxylic acid ethyl ester for 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid ethyl ester, there is prepared 4-methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid.

Step 3: A solution of 4-methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (502 mg, 2.33 mmol), HCTU (1.054 g, 2.55 mmol). and DIPEA (1.10 mL, 6.30 mmol) in DMF (10 mL) is stirred at rt under N_2 for 10 min. 5-Fluoro-3-methyl-indol-1-ylamine (341 mg, 2.08 mmol) is added. The resulting mixture is stirred at rt overnight. The mixture is portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is triturated in ether (4 times) to afford 4-methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide (160 mg, 21%) as a solid. MS: 362 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 11.86 (s, 1H), 9.58 (s, 1H), 9.24 (s, 1H), 8.79-8.78 (m, 1H), 8.74 (td, 1H), 7.62 (dd, 1H), 7.44 (dd, 1H), 7.37-7.36 (m, 2H), 7.06 (td, 1H), 2.78 (s, 3H), 2.27 (s, 3H).

Example 6

2-Pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide

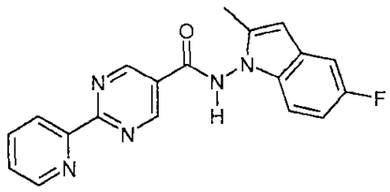


A solution of 2-pyridin-3-yl-pyrimidine-5-carboxylic acid (664 mg, 2.79 mmol), HCTU (1.27 g, 3.07 mmol), and DIPEA (1.4 mL, 8.02 mmol) in DMF (15 mL) is stirred at rt under N_2 for 10 min. 5-fluoro-3-methyl-indol-1-ylamine (491 mg, 2.55 mmol) is added. The resulting mixture is stirred at rt overnight. The mixture is portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is triturated in ether (3 times) and

methanol to afford 2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide (375 mg, 42%) as a solid. MS: 348 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 12.10 (s, 1H), 9.61-9.60 (m, 1H), 9.45 (s, 2H), 8.81-8.80 (m, 1H), 8.77 (dt, 1H), 7.64 (dd, 1H), 7.41 (dd, 1H), 7.35 (dd, 1H), 7.32 (s, 1H), 7.03 (td, 1H), 2.27 (s, 3H). IC_{50} = 10 nM.

Example 7

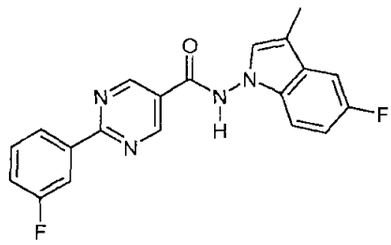
2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide



A solution of 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (485 mg, 2.04 mmol), HCTU (909 mg, 2.2 mmol), and DIPEA (1 mL, 5.72 mmol) in DMF (15 mL) is stirred at rt under N_2 for 10 min. 5-Fluoro-2-methyl-indol-1-ylamine (299 mg, 1.82 mmol) is added. The resulting mixture is stirred at rt overnight. The mixture is portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 70% EtOAc in heptane to afford 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide (112 mg, 18%) as a solid. MS: 348 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 12.03 (s, 1H), 9.51 (s, 2H), 8.83 (d, 1H), 8.50 (d, 1H), 8.05 (dt, 1H), 7.62 (dd, 1H), 7.39 (dd, 1H), 7.28 (dd, 1H), 6.94 (dt, 1H), 6.35 (s, 1H), 2.33 (s, 3H).

Example 8

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide



Step 1: To a solution of 3-fluoro-benzamidine hydrochloride (4 g, 22.6mmol) in anhydrous DMF (35 mL) is added sodium 3,3-dimethoxy-2-carbomethoxyprop-1-en-1-oxide (4.99g,

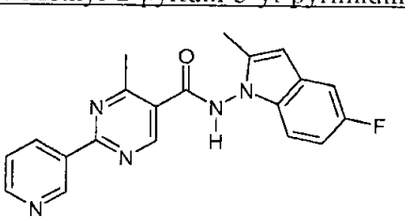
25.2mmol). The reaction mixture is heated at 100°C under N_2 for 3 h and then cooled to rt. Water (150 mL) is added and the mixture is extracted with EtOAc. The organic layer is washed with brine, dried ($MgSO_4$) filtered and concentrated in vacuo to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid methyl ester (1.76 g, 34%). MS: 233 (M+H).

Step 2: To a solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid methyl ester (1.76 g, 7.58 mmol) in anhydrous MeOH (35 mL) is added LiOH (0.38g, 15.9mmol) and the reaction mixture is stirred at rt overnight. The mixture is concentrated *in vacuo* and the residue is partitionned between EtOAc and 3 N aqueous HCl (7.6 mL). The mixture is extracted with EtOAc and the organic layer is washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (1.62 g, 98%) as a solid. MS: 219 (M+H).

Step 3: A solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (372 mg, 1.7 mmol), HCTU (757 mg, 1.83 mmol), and DIPEA (780 µL, 4.47 mmol) in DMF (10 mL) is stirred at rt under N_2 for 10 min. 5-Fluoro-3-methyl-indol-1-ylamine (250 mg, 1.52 mmol) is added. The resulting mixture is stirred at rt overnight. The mixture is portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is triturated in ether to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide (332 mg, 60%) as a solid. MS: 365 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 12.08 (s, 1H), 9.43 (s, 2H), 8.36 (d, 1H), 8.20 (dt, 1H), 7.70-7.62 (m, 1H), 7.48 (dt, 1H), 7.40 (dd, 1H), 7.35 (dd, 1H), 7.32 (s, 1H), 7.03 (dt, 1H), 2.27 (s, 3H).

Example 9

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide

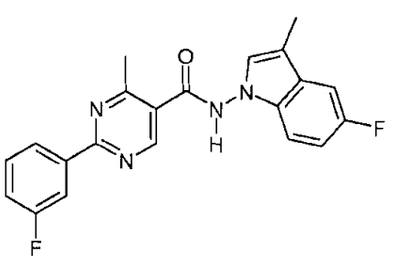


A solution of 4-methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (504 mg, 2.34 mmol), HCTU (1.06 g, 2.55 mmol), and DIPEA (1.1 mL, 6.30 mmol) in DMF (15 mL) is stirred at rt under N_2 for 10 min. 5-Fluoro-2-methyl-indol-1-ylamine (346 mg, 2.11 mmol) is added. The

resulting mixture is stirred at rt overnight. The mixture is portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 70% EtOAc in heptane to afford 4-methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide (82 mg, 11%) as a solid. MS: 362 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 11.80 (s, 1H), 9.59 (d, 1H), 9.29 (s, 1H), 8.80-8.73 (m, 2H), 7.63 (dd, 1H), 7.22 (dd, 1H), 7.28 (dd, 1H), 6.97 (dt, 1H), 6.35 (s, 1H), 2.79 (s, 3H), 2.37 (s, 3H).

Example 10

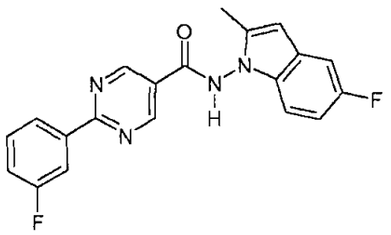
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide



A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (645 mg, 2.78 mmol), HCTU (1.25 g, 3.02 mmol), and DIPEA (1.35 mL, 7.73 mmol) in DMF (15 mL) is stirred at rt under N_2 for 10 min. 5-Fluoro-3-methyl-indol-1-ylamine (380 mg, 2.31 mmol) is added. The resulting mixture is stirred at rt overnight. The mixture is portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is triturated in ether to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide (533 mg, 61%) as a solid. MS: 379 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 11.84 (s, 1H), 9.21 (s, 1H), 8.32 (d, 1H), 8.17-8.15 (m, 1H), 7.66-7.61 (m, 1H), 7.47-41 (m, 2H), 7.36-7.34 (m, 2H), 7.05 (dt, 1H), 2.76 (s, 3H), 2.26 (s, 3H). IC_{50} = 6 nM.

Example 11

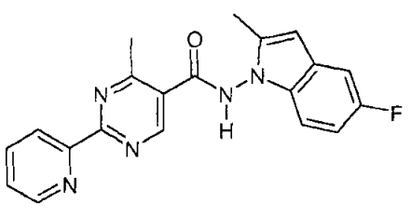
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)amide



A solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (389 mg, 1.78 mmol), HOAt (290 mg, 2.13 mmol), and HATU (811 mg, 2.13 mmol) in DMF (20 mL) is stirred at rt under N_2 for 20 min. 5-Fluoro-2-methyl-indol-1-ylamine (290 mg, 1.77 mmol) and DIPEA (450 μL, 2.58 mmol) are added. The resulting mixture is stirred at 80°C overnight. The mixture is cooled and portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 25% DCM in heptane to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1 yl)amide (300 mg, 47%) as a solid. MS: 365 (M+H). ^{1}H NMR (300MHz, $CDCl_3$): δ 9.23 (s, 1H), 8.76 (s, 1H), 8.35-8.22 (m, 2H), 7.54-7.45 (m, 1H), 7.19-6.86 (m, 5H), 6.25 (s, 1H), 2.29 (s, 3H).

Example 12

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide

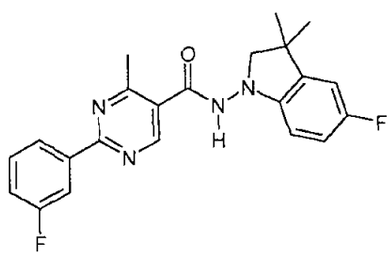


A solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (810 mg, 3.76 mmol), PyBrOP (1.76 g, 3.78 mmol), and DIPEA (1.9 mL, 10.89 mmol) in DMF (15 mL) is stirred at rt under N_2 for 10 min. 5-Fluoro-2-methyl-indol-1-ylamine (560 mg, 3.41 mmol) is added. The resulting mixture is stirred at rt overnight. The mixture is portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 3% MeOH in DCM to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide (174 mg, 14%) as a solid. MS: 362 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 11.82 (s, 1H), 9.30 (d, 1H), 8.81 (d, 1H),

8.46 (d, 1H), 8.03 (dt, 1H), 7.59 (dd, 1H), 7.43 (dd, 1H), 7.29 (dd, 1H), 6.98 (dt, 1H), 6.35 (s, 1H), 2.79 (s, 3H), 2.38 (s, 3H). IC_{50} = 8 nM.

Example 13

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide



Step 1: Isoamyl nitrite (3.4 mL, 25.42 mmol) is added to a solution of 5-fluoro-3,3-dimethyl-2,3-dihydro-1H-indole (3.75 g, 22.69 mmol) in DCM. The mixture is refluxed overnight. The mixture is cooled and portioned between DCM and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 5-fluoro-3,3-dimethyl-1-nitroso-2,3-dihydro-1H-indole (4.23 g, 96%) as a solid. MS: 195 (M+H). ^{1}H NMR (300MHz, CD_3Cl)): δ 7.77 (dd, 1H), 7.08-6.98 (m, 2H), 3.94 (s, 2H), 1.39 (s, 6H).

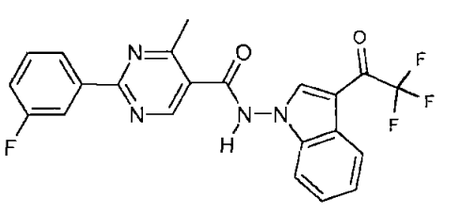
Step 2: To a solution of 5-fluoro-3,3-dimethyl-1-nitroso-2,3-dihydro-1H-indole (4.03 g, 20.75 mmol) in THF (70 mL) at 0°C is added a solution of $LiAlH_4$ (40 mL, 40 mmol) in THF dropwise. The mixture is allowed to warm to rt and stirred overnight. The mixture is quenched with a saturated aqueous solution of Rochelle's Salt. The resulting mixture is stirred until a slurry is obtained. The organic phase is separated, washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 25% EtOAc in heptane to afford 5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-ylamine (3.51 g, 94%) as an oil. MS: 181 (M+H). ^{1}H NMR (300MHz, CD_3Cl)): δ 6.85-6.78 (m, 1H), 6.75-6.68 (m, 2H), 3.44 (br s, 2H), 3.14 (s, 2H), 1.28 (s, 6H).

Step 3: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (348 mg, 1.5 mmol), HOTT (618 mg, 1.66 mmol), and DIPEA (700 µL, 4.01 mmol) in DMF (10 mL) is stirred at rt under N_2 for 10 min. 5-Fluoro-3,3-dimethyl-2,3-dihydro-indol-1-ylamine (239

mg, 1.33 mmol) is added. The resulting mixture is stirred at 80°C overnight. The mixture is cooled and portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 15% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide (416 mg, 80%) as a solid. MS: 395 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 10.43 (s, 1H), 8.99 (s, 1H), 8.28 (d, 1H), 8.15-8.11 (m, 1H), 7.66-7.58 (m, 1H), 7.46-7.39 (m, 1H), 7.06 (dd, 1H), 6.95-6.88 (m, 1H), 6.75-6.71 (m, 1H), 3.51 (s, 2H), 2.68 (s, 3H), 1.33 (s, 6H).

Example 14

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-amide

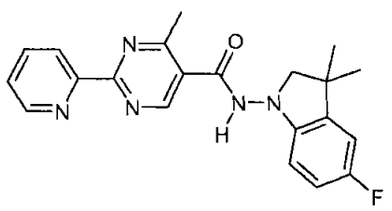


Step 1: Following procedures similar to those of Example 1, step 1, but substituting 3-(2,2,2-trifluoro-acetyl)indole for 5-fluoro-2-methylindole, 1-(1-amino-1H-indol-3-yl)-2,2,2-trifluoro-ethanone is prepared.

Step 2: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (360 mg, 1.55 mmol), HOTT (628 mg, 1.69 mmol), and DIPEA (740 µL, 4.24 mmol) in DMF (10 mL) is stirred at rt under N_2 for 10 min. 1-(1-Amino-1H-indol-3-yl)-2,2,2-trifluoro-ethanone (322 mg, 1.4 mmol) is added. The resulting mixture is stirred at 80°C overnight. The mixture is cooled and portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by HPLC reverse phase column chromatography eluting with a mobile phase of 0.1% TFA/water through 100% MeCN in a 30 min. ramp to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-amide (71 mg, 11%) as a solid. MS: 443 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 12.56 (s, 1H), 9.32 (s, 1H), 8.90 (d, 1H), 8.35 (d, 1H), 8.30-8.27 (m, 1H), 8.22-8.17 (m, 1H), 7.75-72 (m, 1H), 7.69-7.62 (m, 1H), 7.52-7.44 (m, 3H), 2.81 (s, 3H).

Example 15

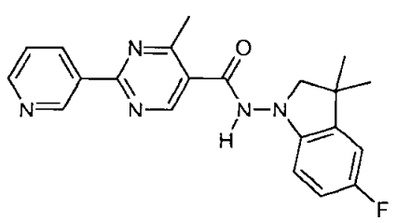
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide



A solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (685 mg, 3.18 mmol), HOTT (1.29 g, 3.48 mmol), and DIPEA (1.6 mL, 9.16 mmol) in DMF (15 mL) is stirred at rt under N_2 for 10 min. 5-Fluoro-3,3-dimethyl-2,3-dihydro-indol-1-ylamine (542 mg, 3.01 mmol) is added. The resulting mixture is stirred at 80°C overnight. The mixture is cooled and portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 2% MeOH in DCM to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide (585 mg, 52%) as a solid. MS: 378 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 10.46 (s, 1H), 9.02 (s, 1H), 8.78 (d, 1H), 8.42 (d, 1H), 8.00 (dt, 1H), 7.56 (dd, 1H), 7.06 (dd, 1H), 6.92 (dt, 1H), 6.76-6.72 (m, 1H), 3.32 (s, 2H), 2.70 (s, 3H), 1.33 (s, 6H).

Example 16

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide

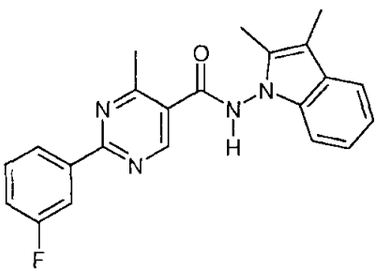


A solution of 4-methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (706 mg, 3.28 mmol), HOTT (1.34 g, 3.6 mmol), and DIPEA (1.65 mL, 9.45 mmol) in DMF (15 mL) is stirred at rt under N_2 for 10 min. 5-Fluoro-3,3-dimethyl-2,3-dihydro-indol-1-ylamine (560 mg, 3.11 mmol) is added. The resulting mixture is stirred at 80°C overnight. The mixture is cooled and portioned between EtOAc and water. The organic phase is separated, washed with saturated

aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 35% EtOAc in heptane to afford 4-methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide (617 mg, 53%) as a solid. MS: 378 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 10.44 (s, 1H), 9.55-9.54 (m, 1H), 9.01 (s, 1H), 8.77-8.75 (m, 1H), 8.72-8.68 (m, 1H), 7.60 (dd, 1H), 7.06 (dd, 1H), 6.96-6.88 (m, 1H), 6.76-6.72 (m, 1H), 3.51 (s, 2H), 2.70 (s, 3H), 1.33 (s, 6H).

Example 17

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2,3-dimethyl-indol-1-yl)-amide

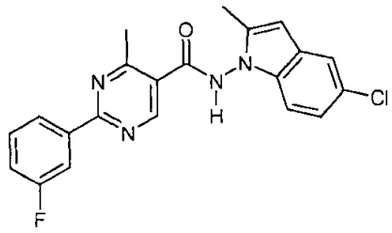


Step 1: Following procedures similar to those of Example 1, step 1, but substituting 2,3-dimethylindole for 5-fluoro-2-methylindole, there is prepared 2,3-dimethyl-indol-1-ylamine as a solid. MS: 161 (M+H). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.48-7.45 (m, 1H), 7.33-7.30 (m, 1H), 7.19-7.13 (m, 1H), 7.10-7.05 (m, 1 H), 4.40 (br s, 2H), 2.37 (s, 3H), 2.23 (s, 3H).

Step 2: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (764 mg, 3.29 mmol), HOTT (1.33 g, 3.58 mmol), and DIPEA (1.65 mL, 9.45 mmol) in DMF (15 mL) is stirred at rt under N_2 for 10 min. 2,3-Dimethyl-indol-1-ylamine (497 mg, 3.1 mmol) is added. The resulting mixture is stirred at 80°C overnight. The mixture is cooled and portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 20% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2,3-dimethyl-indol-1-yl)-amide (568 mg, 49%) as a solid. MS: 375 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 11.68 (s, 1H), 9.24 (s, 1H), 8.33 (d, 1H), 8.20-8.15 (m, 1H), 7.69-7.61 (m, 1H), 7.50-7.43 (m, 2H), 7.37 (d, 1H), 7.17-7.05 (m, 2H), 2.78 (s, 3H), 2.30 (s, 3H), 2.24 (s, 3H).

Example 18

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-chloro-2-methyl-indol-1-yl)-amide

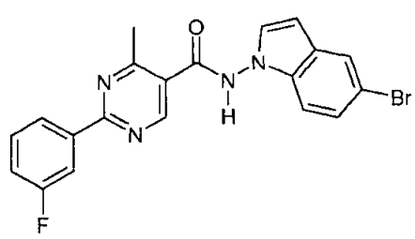


Step 1: Following procedures similar to those of Example 1, step 1, but substituting 5-chloro-2-methylindole for 5-fluoro-2-methylindole, there is prepared 5-chloro-2-methyl-indol-1-ylamine as a solid. MS: 181 (M+H). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.46-7.43 (m, 1H), 7.27-7.24 (m, 1H), 7.12-7.09 (m, 1H), 6.10 (s, 1 H), 4.44 (br s, 2H), 2.44-2.43 (m, 3H).

Step 2: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (379 mg, 1.63 mmol), HOTT (662 mg, 1.78 mmol), and DIPEA (800 μL, 4.58 mmol) in DMF (10 mL) is stirred at rt under N_2 for 10 min. 5-Chloro-2-methyl-indol-1-ylamine (274 mg, 1.52 mmol) is added. The resulting mixture is stirred at 80°C overnight. The mixture is cooled and portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is triturated in ether to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-chloro-2-methyl-indol-1-yl)-amide (93 mg, 16%) as a solid. MS: 395 (M+H). ^{1}H NMR (300MHz, DMSO-d_6): δ 11.83 (s, 1H), 9.27 (s, 1H), 8.33 (d, 1H), 8.20-8.15 (m, 1H), 7.69-7.61 (m, 1H), 7.56 (d, 1H), 7.50-7.43 (m, 2H), 6.36 (s, 1H), 2.78 (s, 3H), 2.37 (s, 3H).

Example 19

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-bromo-indol-1-yl)-amide



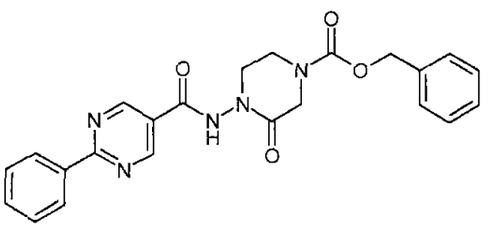
Step 1: Following procedures similar to those of Example 1, step 1, but substituting 5-bromoindole for 5-fluoro-2-methylindole, there is prepared 5-bromoindol-1-ylamine as a

solid. MS: 211 (M+H). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.71-7.70 (m, 1H), 7.29-7.28 (m, 2H), 7.13 (d, 1H), 6.32-6.31 (m, 1 H), 4.73 (br s, 2H).

Step 2: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (596 mg, 2.57 mmol), PyAOP (2.63 mmol), and DIPEA (830 µL, 4.75 mmol) in DCM (20 mL) is stirred at rt under N_2 for 10 min. 5-Bromoindol-1-ylamine (500 mg, 2.37 mmol) is added. The resulting mixture is stirred at rt overnight. The mixture is portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 2% MeOH in DCM to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-bromo-indol-1-yl)-amide (246 mg, 24%) as a solid. MS: 425 (M) & 427 (M+2). ^{1}H NMR (300MHz, DMSO-d_6): δ 12.02 (s, 1H), 9.24 (s, 1H), 8.34 (d, 1H), 8.20-8.15 (m, 1H), 7.84 (d, 1H), 7.68-7.61 (m, 1H), 7.59 (d, 1H), 7.50-7.43 (m, 2H), 7.35 (dd, 1H), 6.57 (dd, 1H), 2.78 (s, 3H).

Example 20

3-Oxo-4-[(2-phenyl-pyrimidine-5-carbonyl)-amino]-piperazine-1-carboxylic acid benzyl ester



Step 1: Following the procedures described in M. A. Brook, T. H. Chan *Synthesis* **1983**, (3), 201-204, there is prepared benzyloxycarbonylamino-acetic acid ethyl ester (95%). MS: 238 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.41 (m, 5H), 5.20-5.37 (br s, 1H), 5.13 (s, 2H), 4.21 (q, J=7.0 Hz, 2H), 3.96 (br d, J=5.3 Hz, 2H), 1.27 (t, J=7.1 Hz, 3H).

Step 2: Following the procedures described in P. Shenbagamurthi, H. A. Smith, J. M. Becker, F. Naider *J. Med Chem.* **1986**, *29* (5), 802-809; R. K. Olsen *J. Org. Chem.* **1970**, *35* (6), 1912-1915, there is prepared (allyl-benzyloxycarbonyl-amino)-acetic acid ethyl ester as a liquid (92%): MS: 278 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.41 (m, 5H), 5.70-5.88 (m, 1H), 5.06-5.25 (m, 4H), 4.02-4.23 (m, 2H), 3.81-4.02 (m, 4H), 1.10-1.30 (m, 3H).

Step 3: To a 0°C solution of AD-mix-β (2.54 g) in a mixture of *t*-butanol (10 mL) and water (12 mL) is added a solution of (allyl-benzyloxycarbonyl-amino)-acetic acid ethyl ester (0.52 g, 1.91 mmol) in *t*-butanol (2.00 mL). The reaction mixture is allowed to gradually warm to ambient temperature over 2 h, and stirred at rt for 20 h. Excess oxidant is quenched by the addition of Na_2SO_3 (2.58 g, 20.44 mmol) and the mixture is stirred vigorously for 4 h. The mixture is extracted with EtOAc (50 mL) and the organic phase is washed with satuated aqueous NaCl (2 x 30 mL). The organic solution is dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue is purified by silica gel chromatography (1:1:1 of EtOAc:DCM :heptane to 50:50 DCM:EtOAc gradient elution) to afford [benzyloxycarbonyl-(2,3-dihydroxy-propyl)-amino]-acetic acid ethyl ester as an oil (0.276 g, 46%). MS: 312 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.40 (m, 5H), 5.05-5.18 (m, 2H), 3.95-4.25 (m, 4H), 3.80-3.95 (m, 1H), 3.20-3.80 (m, 11H), 1.11-1.35 (m, 3H). (See H. Takahata, H. Ouchi, M. Ichinose, H. Nemoto *Org. Lett.* **2002**, *4* (20), 3459-3462 and supplementary material; J. Gonzalez, C. Aurigemma, L. Truesdale *Org. Synth.* **2002**, *79*, 93-102).

Step 4: To a solution of [benzyloxycarbonyl-(2,3-dihydroxy-propyl)-amino]-acetic acid ethyl ester (1.98 g, 6.37 mmol) in DCM (30 mL) is added $NaIO_4$-impregnated silica (13.04 g). The slurry is stirred rapidly for 4.5 h, and then filtered through a coarse porosity sintered glass funnel. The filtrate is concentrated to afford [benzyloxycarbonyl-(2-oxo-ethyl)-amino]-acetic acid ethyl ester (1.65 g, 92%). MS: 280 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60-9.68 (m, 1H), 7.26-7.40 (m, 5H), 510-5.19 (m, 2H), 4.00-4.22 (m, 6H), 1.18-1.30 (m, 3H). (see Y.-L. Zhong, T. K. M. Shing *J. Org. Chem.* **1997**, *62* (8), 2622-2624).

Step 5: N-Aminophthalimide (0.55 g, 3.4 mmol) is added to a solution of benzyloxycarbonyl-(2-oxo-ethyl)-amino]-acetic acid ethyl ester (0.72, 2.6 mmol) in 1,4-dioxane (10 mL), and the mixture is heated to reflux under N_2 for 15 h. The reaction mixture is cooled to rt and filtered through diatomaceous earth. The filtrate is concentrated. The residue is re-dissolved in $CHCl_3$ (30 mL) and filtered again through diatomaceous earth. This filtrate is concentrated to afford (benzyloxycarbonyl-{2-[(E)-1,3-dioxo-1,3-dihydro-isoindol-2-ylimino]ethyl}-amino)-acetic acid ethyl ester (~ 100%). MS: 424 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77-8.88 (n, 1H), 7.80-7.93 (m, 2H), 7.67-7.80 (m, 2H), 7.23-7.40 (m, 5H), 5.09-5.21 (m, 2H), 4.25-4.45 (m, 2H), 3.97-4.25 (m, 4H), 1.12-1.32 (m, 3H).

Step 6: A solution of (benzyloxycarbonyl-{2-[(E)-1,3-dioxo-1,3-dihydro-isoindol-2-ylimino]ethyl}-amino)-acetic acid ethyl ester (7.7 mmol) in CH_3CN (65 mL) is treated with sodium cyanoborohydride (1.92 g, 30.5 mmol), and acetic acid (6.8 mL, 118.8 mmol) is added with stirring under N_2. After 5.5 h, the reaction solution is diluted with EtOAc (150 mL) and washed with saturated aqueous $KHCO_3$ (3 x 50 mL) and saturated aqueous NaCl (50 mL). The organic phase is dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue is purified by silica gel chromatography (75:25 to 50:50 heptane:ethyl acetate gradient elution) to afford {benzyloxycarbonyl-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylamino)-ethyl]-amino}-acetic acid ethyl ester as an oil (2.66 g, 81%). MS: 426 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-7.91 (m, 2H), 7.69-7.79 (m, 2H), 7.17-7.39 (m, 5H), 5.04-5.21 (m, 2H), 4.87-5.04 (m, 1H), 4.04-4.23 (m, 4H), 3.48-3.59 (m, 2H), 3.18-3.38 (m, 2H), 1.10-1.30 (m, 3H).

Step 7: A solution of {benzyloxycarbonyl-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylamino)-ethyl]-amino}-acetic acid ethyl ester (0.22 g, 0.52 mmol) in diphenyl ether (3 mL) is heated to reflux for 2 h. Diphenyl ether is removed by vacuum distillation and the residue is purified by flash silica gel chromatography (2:1:1 to 1:1:1 heptane:DCM:EtOAc gradient elution) to afford 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-oxo-piperazine-1-carboxylic acid benzyl ester as a solid (0.126 g, 64%). MS: 380 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.95 (m, 2H), 7.75-7.86 (m, 2H), 7.24-7.42 (m, 5H), 5.20 (s, 2H), 4.42 (s, 2H), 3.90-4.05 (m, 2H), 3.65-3.87 (m, 2H).

Step 8: To a solution of benzamidine hydrochloride hydrate (2 mmol) in anhydrous DMF (4 mL) is added sodium salt of 2-dimethoxymethyl-3-hydroxy-acrylicacid methyl ester (0.46 g, 2.32 mmol) and the reaction mixture heated at 100°C under N2 for 1 hour. The reaction is cooled to rt and water (15 mL) is added. After addition of water, immediate precipitation of the product is observed. The solids are collected by filtration, washed with water (2.5 mL) and vacuum dried to yield 2-phenyl-pyrimidine-5-carboxylic acid methyl ester (0.32 g, 74%). (see: P. Zhichkin, D.J. Fairfax, S.A. Eisenbeis, Synthesis, 2002, 720-722.)

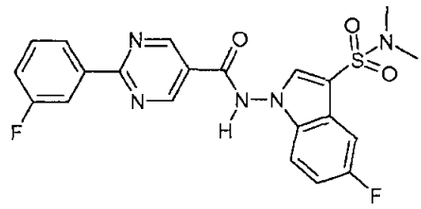
Step 9: A solution of 2-phenyl-pyrimidine-5-carboxylic acid methyl ester (3.15 g) and LiOH (0.71 g) in a mixture of MeOH, THF and water (1:1:1 in volume, 120 mL) is stirred at rt overnight. MeOH and THF are evaporated off to give an aqueous solution. The aqueous solution is acidified with 5% hydrochloric acid to adjust pH to between 2.5 and 3. The

precipitate is filtered off and washed with water, dried *in vacuo* to yield 2.94 g (~100%) of 2-phenyl-pyrimidine-5-carboxylic acid as a solid. MS: 201 (M+H).

Step 10: A solution of 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-oxo-piperazine-1-carboxylic acid benzyl ester (53 mg, 0.14 mmol) in MeOH (10 mL) is treated with anhydrous hydrazine (0.3 mL, 9.56 mmol). The reaction mixture is stirred at reflux under N_2 for 3.5 h. The reaction mixture is concentrated. The residue is dissolved in a mixture of DMF (2 mL) and DCM (2 mL), and treated with 2-phenyl-pyrimidine-5-carbonyl chloride (32 mg, 0.15 mmol). The mixture is stirred under N_2 for 16 h, and then diluted with EtOAc (35 mL). The mixture is washed successively with saturated aqueous $KHCO_3$, (15 mL), water (2 x 15 mL), and saturated aqueous NaCl (15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue is purified by flash silica gel chromatography (80:20 to 0:100 heptane:EtOAc gradient elution) to afford 3-oxo-4-[(2-phenyl-pyrimidine-5-carbonyl)-amino]-piperazine-1-carboxylic acid benzyl ester as an oil (111 mg, 18%). MS: 432 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70-10.10 (br, 1H), 9.06 (s, 2H), 8.46 (dd, J=7.8, 1.7 Hz, 2H), 7.44-7.60 (m, 3H), 7.25-7.40 (m, 5H), 5.18 (s, 2H), 4.36 (s, 2H), 3.93 (t, J=5.1 Hz, 2H), 3.69-3.81 (br s, 2H). IC_{50} = 103.5 nM.

Example 21

2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-(3-dimethylsulfamoyl-5-fluoro-indol-1-yl)amide



Step 1: A solution of 5-fluoroindole (5.4 g) and toluene-4sulponyl chloride (9.12 g) in toluene (300 mL) is treated with a cooled solution of sodium hydroxide pellets (23.2 g) in water (200 mL) followed by the tetrabutylammonium hydrogen sulfate catalyst (400 mg). The mixture is stirred at rt for 24 h. The organic phase is separated, washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford 5-fluoro-1-(toluene-4-sulfonyl)-1H-indole (10.7 g, 78%). MS: 290 (M+H)

Step 2: A solution of 5-fluoro-1-(toluene-4-sulfonyl)indole (5.2 g) in dry CH_3CN (80 mL) is cooled in an ice-bath and treated drop wise with chlorosulfonic acid (12 mL). The reaction mixture is allowed to warm to rt and stirred for 24 h. The reaction mixture is carefully poured onto ice/water (300 mL). The precipitate is collected by filtration and washed with water to afford 5-fluoro-3-chlorosulfonyl-1-(toluene-4-sulfonyl)-1H-indole (6.8 g, 98%) as a solid. MS: 386 (M-H).

Step 3: A solution of 5-fluoro-3-chlorosulfonyl-1-(toluene-4-sulfonyl)indole (2.52 g) in DCM (75 mL) is added to an aqueous solution of dimethylamine (40%, 20 mL) in water (50 mL) and stirred at rt for 20 h. The organic phase is separated, washed with water, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 5-fluoro-1-(toluene-4-sulfonyl)-1H-indole-3-sulpfonic acid dimethylamide (2.55 g, 99%) as a solid. MS: 397 (M+H).

Step 4: A mixture of 5-fluoro-1-(touene-4-sulfonyl)indole-3-sulfonic acid dimethylamide (2.55 g) in MeOH (100 mL) and 5 N KOH (15mL) is heated to reflux for 1.5 hours. The reaction mixture is concentrated *in vacuo*. The residue is diluted with water (50 mL) and acidified to pH ~ 3 with 10 N aqueous HCl. The mixture is extracted with EtOAc. The organic layer is separated, washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo to afford 5-fluoro-1H-indole-3-sulfonic acid dimethylamide (1.35 g, 87%) as a solid. MS: 241 (M-H).

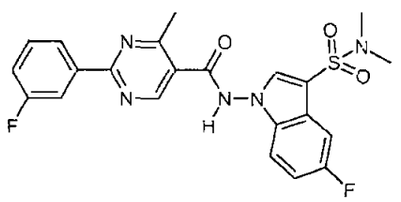
Step 5: A solution of 5-fluoro-1H-indole-3-sulfonic acid dimethylamide (1.24 g) in dry DMF (50 mL) is cooled to 0°C and treated portion wise with 60% MaH oil dispersion (3.07 g). The mixtire is stirred at 0°C for 30 min. Hydroxylamine-O-sulfonic acid (2.9 g) is added portion wise and the mixture is warmed to rt and stirred for 5 h. The reaction mixture is poured onto ice/water and extracted with EtOAc. The organic layer is separated, washed water and brine, dried ($MgSO_4$) filtered and concentrated *in vacuo*. The residue is triturated with ether. The solid is collected by filteration to afford 1-amino-5-fluoro-1H-indole-3-sulfonic acid dimethylamide (0.53 g, 41%). MS: 258 (M+H).

Step 6: A suspension of 2-(3-fluorophenyl)-pyrimidine-5-carboxylic acid (76 mg) in dry DCM (25mL)/dry DMF (2 drops) is treated with oxalyl chloride (0.15mL) and stirred at rt for 3.5 hours. The reaction mixture is concentrated *in vacuo*. The residue is dissolved in toluene (15

mL) and then concentrated *in vacuo*. The residue is dried on high vacuum pump, and then dissolved in EtOAc (7 mL). The solution is added to a mixture of 1-amino-5-fluoro-1H-indole-3-sulfonic acid dimethylamide (100 mg) and Na_2CO_3 (106 mg) in EtOAc (5mL)/water (5mL). The mixture is stirred at rt for 24 h. The organic phase is separated, washed water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 50% EtOAc in heptane to afford 2-(3-fluorophenyl)pyrimidine-5-carboxylic acid-(3-dimethylsulfamoyl-5-fluoroindol-1-yl)amide (100 mg, 62%) as a solid. MS: 458 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.67 (s, 6H), 7.20-7.3 (m, 1H), 7.45-7.55 (m, 1H), 7.57-7.6 (dd, 1H), 7.65-7.75 (m, 2H), 8.2 (d, 1H), 8.38-8.4 (d, 2H), 9.45 (s, 2H), 12.6 (s, 1H).

Example 22

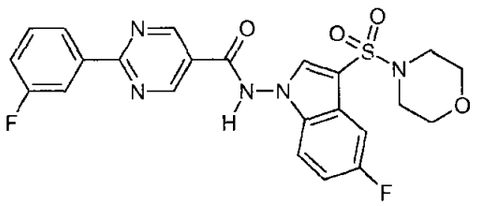
2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-(3-dimethylsulfamoyl-5-fluoroindol-1-yl)amide



A solution of 2-(3-fluorophenyl)-4-methylpyrimidine-5-carboxylic acid (116 mg) and HATU (190 mg) in dry DMF is treated with DIPEA (0.09 mL) and stirred at rt for 40 min. 1-Amino-5-fluoro-1H-indole-3-sulfonic acid dimethylamide (192 mg) is added and the mixture is stirred at rt for 24 h. The mixture is concentrated in vacuo. The residue is dissolved in EtOAc, washed with 2 N aqueous NaOH, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 30% EtOAc/heptane to afford 2-(3-fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-(3-dimethylsulfamoyl-5-fluoroindol-1-yl)amide (85 mg, 40%) as a solid. MS: 472 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.68 (s, 6H), 2.79 (s, 3H), 7.25-7.35 (m, 1H), 7.45-7.55 (m, 1H), 7.57-7.80 (m, 3H), 8.20 (d, 1H), 8.35 (s, 1H), 8.47 (s, 2H), 9.28 (s, 1H), 12.40 (s, 1H).

Example 23

2-(3-Fluorophenyl)pyrimidine-5-carboxylicacid-[5-fluoro-3-(morpholine-4-sulfonyl)indol-1-yl] amide



Step 1: A solution of 5-fluoro-3-chlorosulfonyl-1-(toluene-4-sulfonyl)-1H-indole (1 g) in DCM is added to a solution of morpholine (2.26 mL) in water (50 mL) and stirred at rt for 5 h. The organic phase is separated and washed water, brine and dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 5-fluoro-3-(morpholine-4-sulfonyl)-1-(toluene-4-sulfonyl)-1H-indole (1.3 g, ~ 100%). MS: 439 (M+H).

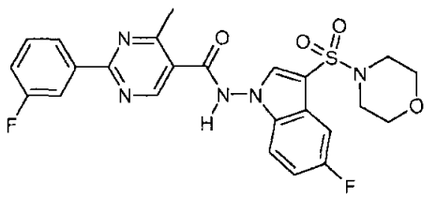
Step 2: A solution of 5-fluoro-3-(morpholine-4-sulfonyl)-1-(toluene-4-sulfonyl)-1H-indole (1.3 g) in MeOH (50 mL)/5 N KOH (3mL) is heated to reflux for 1 h. The reaction mixture is concentrated *in vacuo*. The residue is diluted with water (30 mL) and acidified with 10 N aqueous HCl to pH ~ 4. The mixture is extracted with EtOAc. The organic layer washed with water, brine and dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 5-fluoro-3-(morpholine-4-sulfonyl)-1H-indole (0.8 g, 95%) as a solid. MS: 285 (M+H).

Step 3: Following procedures similar to those of Example 21, step 5, but substituting 5-fluoro-3-(morpholine-4-sulfonyl)-1H-indole for 5-fluoro-1H-indole-3-sulfonic acid dimethylamide, and the product is purified by silica gel chromatography eluting with 20% EtOAc, there is prepared 1-amino-5-fluoro-3-(morpholine-4-sulfonyl)-1H-indole (16%) as a solid. MS: 300 (M+H).

Step 4: Following procedures similar to those of Example 21, step 6, but substituting 1-amino-5-fluoro-3-(morpholine-4-sulfonyl)-1H-indole for 1-amino-5-fluoro-1H-indole-3-sulfonic acid dimethylamide, there is prepared 2-(3-fluorophenyl)pyrimidine-5-carboxylicacid-[5-fluoro-3-(morpholine-4-sulfonyl)indol-1-yl] amide (27%) as a solid. MS: 500 (M+H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.95 (m, 4H), 3.67 (m, 4H), 7.25-7.35 (m, 1H), 7.45-7.55 (m, 1H), 7.57-7.60 (dd, 1H), 7.62-7.72 (q, 1H), 7.75-7.80 (q, 1H), 8.20 (d, 1H), 8.35-8.40 (d, 1H), 8.41 (s, 1H), 9.45 (s, 2H), 12.6 (s, 1H).

Example 24

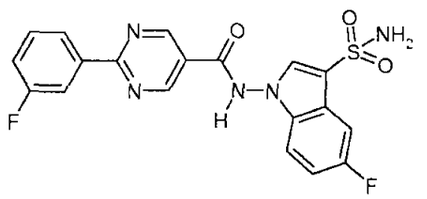
2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3- (morpholine-4-sulfonyl) indol-1-yl] amide



Following procedures similar to those of Example 22, but substituting 1-amino-5-fluoro-3-(morpholine-4-sulfonyl)-1H-indole for 1-amino-5-fluoro-1H-indole-3-sulfonic acid dimethylamide, there is prepared 2-(3-fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3-(morpholine-4-sulfonyl)indol-1-yl] amide (48%) as a solid. MS: 512 (M-H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.80 (s, 3H), 2.95 (m, 4H), 3.67 (m, 4H), 7.25-7.35 (m, 1H), 7.45-7.55 (m, 1H), 7.57-7.60 (m, 1H), 7.62-7.72 (m, 1H), 7.75-7.80 (m, 1H), 8.15-8.20 (d, 1H), 8.30-8.35 (d, 1H), 8.45 (s, 1H), 9.30 (s, 1H), 12.4 (s, 1H).

Example 25

2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-sulfamoylindol-1-yl)amide



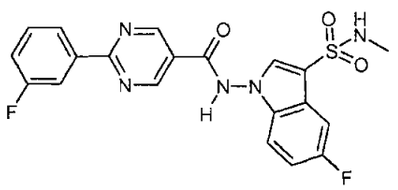
Step 1: A solution of 2-(3-fluorophenyl)pyrimidine-5-carboxylic acid-(5-fluoroindol-1-yl)amide (0.35 g,) in dry CH_3CN (20 mL) is treated with chlorosulfonic acid (0.5 mL) and stirred at rt for 24 h. Thereaction mixture is poured onto ice/water (150 mL) and extracted with EtOAc. The organic layer is washed with water, brine and dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 5-fluoro-1-{[2-(3-fluorophenyl)pyrimidine-5-carbonyl]amino}-1H-indole-3-sulfonyl chloride (0.43 g, 95%). MS: 449 (M+H).

Step 2: A solution of 5-fluoro-1-{[2-(3-fluorophenyl)pyrimidine-5-carbonyl]amino}-1H-indole-3-sulfonyl chloride (0.14 g) in DCM (20 mL) is treated with a solution of aqueous ammonia solution (28%-5 mL) in water (15 mL) and stirred at rt for 24 h. The reaction mixture is acidified with 10 N aqueous HCl to pH ~ 3 and extracted with DCM. The organic layer is washed with water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 50% EtOAc in heptane to afford

2-(3-fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-sulfamoylindol-1-yl)amide (10 mg, 8%) as a solid. MS: 430 (M+H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.20-7.30 (m, 1H), 7.40-7.50 (m, 2H), 7.60-7.72 (m, 2H), 8.10 (s, 1H), 8.19-8.22 (d, 1H), 8.33-8.37 (d, 1H), 9.44 (s, 1H), 12.45 (s, 1H).

Example 26

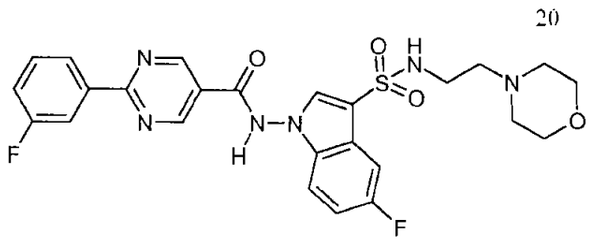
2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-methylsulfamoyl)indol-1-yl)amide



Following procedures similar to those of Example 25, but substituting 40% aqueous methylamine for aqueous ammonia solution, there is prepared 2-(3-fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-methylsulfamoyl)indol-1-yl)amide (60%) as a solid. MS: 444 (M+H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.45 (d, 3H), 7.20-7.30 (m, 1H), 7.40-7.50 (m, 2H), 7.60-7.70 (m, 3H), 8.19-8.22 (d, 1H), 8.24 (s, 1H), 8.34-8.37 (d, 1H), 9.44 (s, 1H), 12.50 (s, 1H).

Example 27

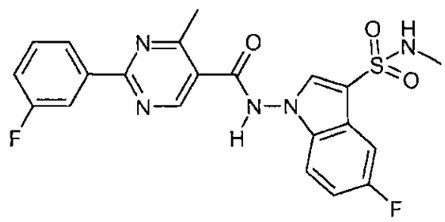
2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-(2-morpholin-4-ylethylsulfamoyl)indol-1-yl)amide



Following procedures similar to those of Example 25, but substituting an aqueous solution of 2-(morpholin-4-yl) ethylamine for the aqueous ammonia solution, there is prepared 2-(3-fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-(2-morpholin-4-ylethylsulfamoyl)indol-1-yl)amide (35%). MS: 543 (M+H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.20-2.38 (m, 6H), 2.89-2.95 (q, 2H), 3.40-3.50 (s, 4H), 7.20-7.30 (m, 1H), 7.42-7.55 (m, 2H), 7.63-7.70(m, 3H), 8.19-8.22 (d, 1H), 8.26 (s, 1H), 8.34-8.37 (d, 1H), 9.44 (s, 2H), 12.40-12.60 (s, 1H).

Example 28

2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3-methylsulfamoyl)indol-1-yl)amide



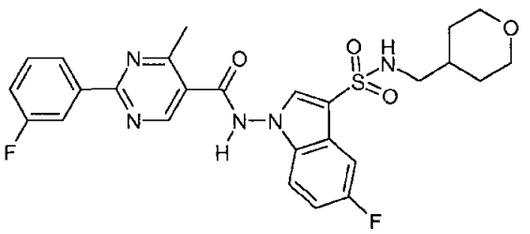
Step 1: A solution 2-(3-fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-(5-fluoroindol-1-yl)amide (1 g, 2.75 mmol) in dry CH_3CN is cooled to 0°C and treated drop wise with chlorosulfonic acid (0.55 mL) and stirred for 2hours.The precipitated solid is filtered off and washed with ether to afford 5-fluoro-1-{[2-(3-fluorophenyl)-4-methylpyrimidine-5-carbonyl]amino}-1H-indole-3-sulfonic acid (1.06 g, 87%) as an off-white solid. MS: 443 (MH-).

Step 2: To a suspension of 5-fluoro-1-{[2-(3-fluorophenyl)-4-methylpyrimidine-5-carbonyl]amino}-1H-indole-3-sulfonic acid (1.06 g) in DCM (60 mL) at 0°C is added dry DMF (10 drops). Oxalyl chloride (1.05 mL) is added drop wise and the mixture is stirred at 0°C for 3 h. The mixture is filtered and the collected solid is washed with ether to afford 5-fluoro-1-{[2-(3-fluorophenyl)-4-methylpyrimidine-5-carbonyl] amino}-1H-indole-3-sulfonyl chloride (0.94 g). MS: 461 (M-H)

Step 3: Following procedures similar to those of Example 25, step 2, but substituting 40% aqueous methylamine for the aqueous ammonia solution, and substituting 5-fluoro-1-{[2-(3-fluorophenyl)-4-methylpyrimidine-5-carbonyl] amino}-1H-indole-3-sulfonyl chloride for 5-fluoro-1-{[2-(3-fluorophenyl)pyrimidine-5-carbonyl]amino}-1H-indole-3-sulfonyl chloride, there is prepared 2-(3-fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3-methylsulfamoyl)indol-1-yl)amide (40 mg, 35%) as a solid. MS: 456 (M-H): ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.45 (d, 3H), 2.80 (s, 3H), 7.20-7.30 (m, 1H), 7.40-7.50 (m, 2H), 7.60-7.70 (m, 3H), 8.17-8.20 (d, 1H), 8.30-8.35 (d, 2H), 9.28 (s, 1H), 12.30 (s, 1H).

Example 29

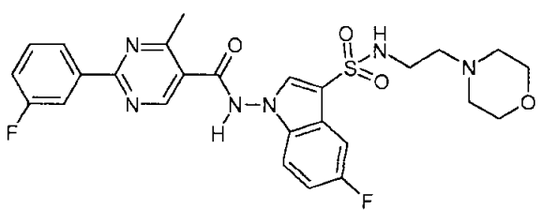
2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-{5-fluoro-[(3-tetrahydropyran-4-ylmethyl)sulfamoyl]indol-1-yl}amide



Following procedures similar to those of Example 25, step 2, but substituting an aqueous solution of 4-aminomethyltetrahydropyran for the aqueous ammonia solution, and substituting 5-fluoro-1-{[2-(3-fluorophenyl)-4-methylpyrimidine-5-carbonyl] amino}-1H-indole-3-sulfonyl chloride for 5-fluoro-1-{[2-(3-fluorophenyl)pyrimidine-5-carbonyl]amino}-1H-indole-3-sulfonyl chloride, there is prepared 2-(3-fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-{5-fluoro-[(3-tetrahydropyran-4-ylmethyl)sulfamoyl]indol-1-yl}amide as a solid. MS: 542 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00-1.15, (m, 2H), 1.50-1.70, (m, 3H), 2.60-2.70, (t, 2H), 2.80, (s, 1H), 3.1-3.2, (t, 2H), 3.70-3.80, (dd, 2H), 7.20-7.30, (m, 1H), 7.40-7.50, (m, 1H), 7.60-7.70, (m, 4H), 8.16-8.20, (d, 1H), 8.28-8.34 (d, 2H), 9.28, (s, 1H), 12.25, (s, 1H).

Example 30

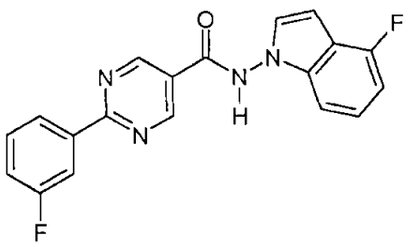
2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3-(2-morpholin-4-ylethylsulfamoyl)indol-1-yl)amide



Following procedures similar to those of Example 25, step 2, but substituting an aqueous solution of 2-(morpholin-4-yl) ethylamine for the aqueous ammonia solution, and substituting 5-fluoro-1-{[2-(3-fluorophenyl)-4-methylpyrimidine-5-carbonyl] amino}-1H-indole-3-sulfonyl chloride for 5-fluoro-1-{[2-(3-fluorophenyl)pyrimidine-5-carbonyl]amino}-1H-indole-3-sulfonyl chloride, there is prepared 2-(3-fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3-(2-morpholin-4-ylethylsulfamoyl)indol-1-yl)amide (58%) MS: 557 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.20-2.30 (s, 4H), 2.30-2.40 (t, 2H), 2.80 (s, 3H), 2.89-2.95 (q, 2H), 3.40-3.50 (s, 4H), 7.20-7.30 (m, 1H), 7.42-7.55 (m, 2H), 7.63-7.70(m, 3H), 8.17-8.20 (d, 1H), 8.32-8.35 (d, 2H), 9.28 (s, 2H), 12.25-12.30 (s, 1H).

Example 31

2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide

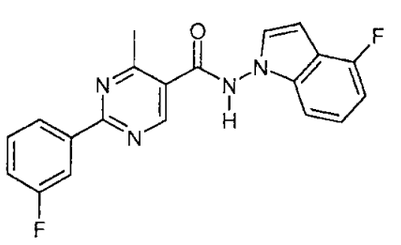


Step 1: The crude product of 1-amino-4-fluoroindole is prepared according to the procedures described in J.Hymes et al., J.O.C., (2004), 69, 1368-1371. The crude product is then purified by silica gel chromatography eluting with 30% DCM in heptane to afford 1-amino-4-fluoroindole (43%). MS: 151 (M+H).

Step 2: A solution of 2-(3-fluorophenyl)-pyrimidine-5-carboxylic acid (0.33 g), HATU (0.67 g) and hydroxyazabenzotriazole (0.26 g) in dry DMF (15 mL) is stirred at rt for 30 min under N_2. A solution of 1-amino-4-fluoroindole (0.24 g) in dry DMF (5 mL) is added followed by the addition of DIPEA (0.39 mL). The mixture is stirred at 80°C for 24 h, cooled to rt, and then concentrated in vacuo. The residue is dissolved in EtOAc and washed with water, brine and dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 60% DCM/heptane to afford 2-(3-fluorophenyl)pyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide (0.24 g, 53%) as a solid. MS: 351 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.64 (d, 1H), 6.89-6.92 (q, 1H), 7.15-7.22 (m, 1H), 7.31-7.33 (d, 1H), 7.46-7.52 (m, 1H), 7.56 (d, 1H), 7.63-7.70 (q, 1H), 8.18-8.23 (d, 1H), 8.34-8.37 (d, 1H), 9.45 (s, 2H), 12.30 (s, 1H). IC_{50} = 11 nM.

Example 32

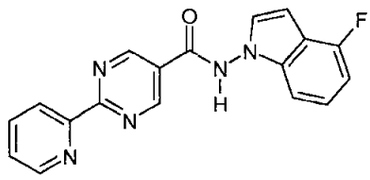
2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide



Following procedures similar to those of Example 31, step 2, but substituting 2-(3-fluorophenyl)-4-methylpyrimidine-5-carboxylic acid for 2-(3-fluorophenyl)-pyrimidine-5-carboxylic acid, there is prepared 2-(3-fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide (63%) as a solid. MS: 365 (M-H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.75 (σ, 3H), 6.61 (d, 1H), 6.86-6.92 (q, 1H), 7.15-7.22 (m, 1H), 7.30-7.32 (d, 1H), 7.40-7.46 (m, 1H), 7.56-7.65 (m, 2H), 8.13-8.16 (d, 1H), 8.28-8.31 (d, 1H), 9.21 (s, 1H), 12.05 (s, 1H).

Example 33

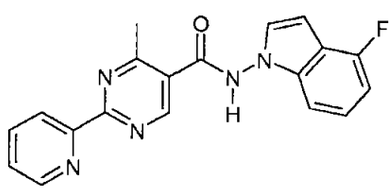
2-(Pyridin-2-yl)-pyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide



A suspension of 2-(pyridine-2-yl)-pyrimidine-5-carbonyl chloride (0.44 g) in EtOAc (20 mL) is added portion wise to a mixture of 1-amino-4-fluoroindole (0.30 g) and K_2CO_3 (0.276 g) in EtOAc (10 mL) / water (20 mL) and the resulting mixture is stirred at rt for 24 h. The aqueous phase is separated and extracted twice with EtOAc. The combined organic layer is washed with water and brine, dried ($MgSO_4$), filtered and concentration *in vacuo*. The residue is purified by silica gel chromatography eluting with EtOAc to afford 2-(pyridin-2-yl)pyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide (0.115 g, 17%) as a solid. MS: 334 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.65 (d, 1H), 6.89-6.95 (q, 1H), 7.16-7.23 (m, 1H), 7.32-7.35 (d, 1H), 7.57 (d, 1H), 7.57-7.64 (m, 1H), 8.02-8.08 (t, 1H), 8.50-8.52 (d, 1H), 8.82-8.83 (d, 1H), 9.49 (s, 2H), 12.30 (s, 1H).

Example 34

2-(Pyridin-2-yl)-4-methylpyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide

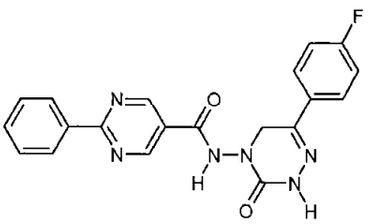


A solution of 2-(pyridine-2-yl)-4-methylpyrimidine-5-carboxylic acid (0.11 g) and HATU (0.19 g) in dry DMF (7mL) is treated with DIPEA (0.09 mL) and stirred at rt under N_2 for 30

min. 1-Amino-4-fluoroindole (0.112 g) is added and the mixture is stirred at rt for 24 h. The mixture is concentrated *in vacuo*. The residue is dissolved in EtOAc, washed with water and brine and dried ($MgSO_4$), filtered, and concentration *in vacuo*. The residue is purified by silica gel chromatography eluting with 75% EtOAc to afford 2-(pyridin-2-yl)-4-methylpyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide (0.085gms, 50%). MS: 348 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.82 (s, 3H), 6.65 (d, 1H), 6.93-6.97 (q, 1H), 7.19-7.26 (m, 1H), 7.35-7.38 (d, 1H), 7.62 (d, 1H), 7.74-7.78 (m, 1H), 8.20-8.25 (t, 1H), 8.58-8.61 (d, 1H), 8.85-8.86 (d, 1H), 9.33 (s, 1H), 12.15 (s, 1H).

Example 35

2-Phenyl-pyrimidine-5-carboxylic acid [6-(4-fluoro-phenyl)-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl]-amide



Step 1: Following procedures described in F. Chau, J.-C. Malanda, and R. Milcent *J. Heterocyclic Chem.* **1997**, *34*, 1603-1606, there is prepared 5-methyl-3H-1,3,4-oxadiazol-2-one (24%). MS: 101 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (br s, 1H), 2.28 (s, 3H).

Step 2: To a solution of 5-methyl-3H-1,3,4-oxadiazol-2-one (2.77 g, 27.7 mmol) in MeOH (25 mL) is added 25 wt % NaOMe solution in methanol (6.4 mL, 27.9 mmol) and the mixture is stirred at rt for 10 min. The mixture is concentrated *in vacuo* and the residue is added to a solution of 2-chloro-4'-fluoroacetophenone (4.71 g, 27.3 mmol) and tetrabutylammonium bromide (0.174 g, 0.54 mmol) in $CHCl_3$ (16 mL). The mixture is heated to reflux for 2.5 h under N_2. The reaction mixture is then allowed to cool and stirred overnight at ambient temperature. The resultant slurry is filtered through qualitative filter paper and the filtrate is concentrated to obtain a liquid. This liquid is further filtered through a pad of silica gel, eluting with 1:1 EtOAc/DCM. The filtrate is concentrated in vacuo to afford 3-[2-(4-fluoro-phenyl)-2-oxo-ethyl]-5-methyl-3H-1,3,4-oxadiazol-2-one (~ 100%). MS: 237 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-8.10 (m, 2H), 7.10-7.22 (m, 2H), 5.08 (s, 2H), 2.29 (s, 3H).

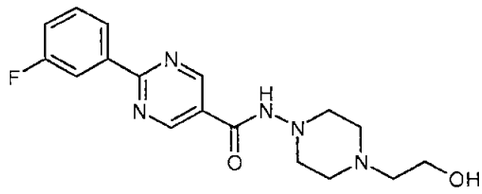
Step 3: To a solution of 3-[2-(4-fluoro-phenyl)-2-oxo-ethyl]-5-methyl-3H-1,3,4-oxadiazol-2-one (2.3 g, 9.7 mmol) in a mixture of 2-propanol (12 mL) and water (0.3 mL) is added hydrzazine monohydrate (0.71 mL, 14.6 mmol). The reaction mixture is heated to reflux under N_2 for 14.5 h, and then a solution of oxalic acid (0.3 g, 3.3 mmol) in 2-propanol (6 mL) is added. The resulting precipitate is removed by filtration. The filtrate is concentrated to ~ 35 mL and then chilled to afford N-[6-(4-fluoro-phenyl)-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl]-acetamide as a crystal that is collected by filtration (0.83 g, 34%). MS: 251 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.37 (s, 1H), 10.16 (s, 1H), 7.65-7.79 (m, 2H), 7.16-7.27 (m, 2H), 4.57 (s, 2H), 1.90 (s, 3H).

Step 4: To a slurry of N-[6-(4-fluoro-phenyl)-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl]-acetamide (0.48 g, 1.9 mmol) in MeOH (5 mL) is added 37% aqueous HCl. The mixture is heated to reflux for 3 h, and then cooled to rt. The mixture is basified with 1 M aqueous NaOH to pH ~ 12. The resulting precipitate is collected by filtration and dried to afford 4-amino-6-(4-fluoro-phenyl)-4,5-dihydro-2H-1,2,4-triazin-3-one (0.35 g, 88%). MS: 209 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.67-7.75 (m, 2H), 7.18-7.29 (m, 2H), 4.75 (s, 2H), 4.45 (s, 2H).

Step 5: To a slurry of 4-amino-6-(4-fluoro-phenyl)-4,5-dihydro-2H-1,2,4-triazin-3-one (0.26 g, 1.23 mmol), 2-phenyl-pyrimidine-5-carboxylic acid (0.25 g, 1.23 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.37 g, 1.94 mmol) in DMF (12 mL) is added Et_3N (0.2 mL, 1.435 mmol) under N_2 and the reaction mixture is stirred at rt for 49 h. The mixture is diluted with EtOAc (120 mL), and washed successively with saturated aqueous NH_4Cl (2 x 50 mL), water (2 x 50 mL), and saturated aqueous NaCl (50 mL). The organic phase is dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue is triturated with EtOH (30 mL) to afford 2-phenyl-pyrimidine-5-carboxylic acid [6-(4-fluoro-phenyl)-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl]-amide (0.12 g, 25%). MS: 391 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.25 (s, 1H), 10.58 (s, 1H), 9.31 (s, 2H), 8.47 (dd, J=7.7, 1.8 Hz, 2 H), 7.70-7.86 (m, 2 H), 7.49-7.67 (m, 3H), 7.18-7.34 (m, 2H), 4.77.

Example 36

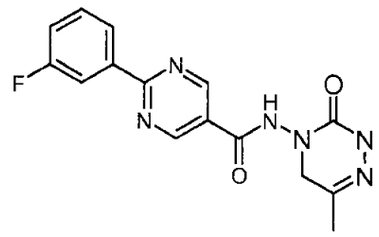
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide



To a solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (0.28 g, 1.4 mmol) in anhydrous DCM (10 mL) at 0°C is added the oxalyl chloride (0.18 mL, 1.4 mmol) followed by the addition of DMF (0.11 mL). The mixture is stirred at 0°C for 30 min, and then allowed to warm up to rt and stirred for 30 min. The mixture is concentrated *in vacuo*. The residue is dissolved in anhydrous DCM (10 mL). 2-(4-Amino-piperazin-1-yl)-ethanol (0.145 g, 1 mmol) is added at rt followed by the addition of NMP (0.19 mL, 2 mmol). The mixture is stirred at rt for 2 h and the mixture is then concentrated *in vacuo*. The residue is triturated in Et_2O and the resulting solid is collected by filtration to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide (0.16 g). MS: 346 (M+H).

Example 37

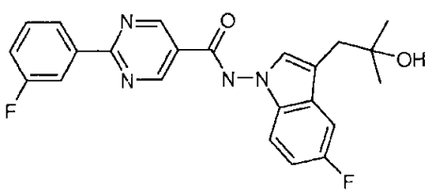
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide



To a solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (0.317 g, 1.45 mmol) in anhydrous DMF (5 mL) is added 4-amino-6-methyl-4,5-dihydro-2H-[1,2,4]triazin-3-one (0.206 g, 1.45 mmol) followed by the addition of DMTMM (0.421 g, 1.52 mmol). The mixture is stirred at rt overnight. The mixture is partitioned between a saturated aqueous $NaHCO_3$solution and EtOAc. The organic phase is separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide (0.306 g) as a solid. MS: 329 (M+H).

Example 38

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid[5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1-yl]-amide



Step 1: A solution of (5-fluoro-1H-indol-3-yl)-acetic acid (1 g, 5.2 mmol) in MeOH (20 mL) is treated with sulfuric acid (20 µL) and stirred at rt for 1 h. This mixture is treated with 10% aqueous $NaHCO_3$ (200 µL) and then concentrated *in vacuo* to afford (5-fluoro-1H-indol-3-yl)-acetic acid methyl ester, which is used in the next step without further purification. MS: 208 (M+H); ^{1}H NMR (300MHz, CD_3OD): δ 3.68 (s, 3H), 3.72 (s, 2H), 6.86 (m, 1H), 7.16 (m, 1H), 7.21 (s, 1H), 7.28 (m, 1H).

Step 2: The above (5-fluoro-1H-indol-3-yl)-acetic acid methyl ester is dissolved in THF (40 mL), cooled to 0°C, and treated with MeMgBr (18.5 mL, 26 mmol, 1.4 M in PhMe/THF (3:1)). The mixture is stirred at rt for 12 h. Additional MeMgBr (5 mL, 7 mmol) is added and the mixture is stirred at rt for 6 h. The mixture is poured onto ice/water, extracted with EtOAc (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 20% - 70% EtOAc in heptane to afford 1-(5-fluoro-1H-indol-3-yl)-2-methyl-propan-2-ol (0.65 g, 60%). MS: 208 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 6H), 2.87 (s, 2H), 6.94 (m, 1H), 7.14 (m, 1H), 7.26-7.30 (m, 2H).

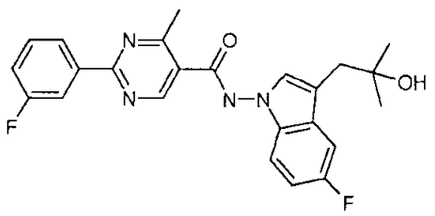
Step 3: A solution of 1-(5-fluoro-1H-indol-3-yl)-2-methyl-propan-2-ol (207 mg, 1 mmol) in DMF (10 mL) is cooled to 0°C, treated with NaH (600 mg, 15 mmol, 60% in mineral oil) and stirred for 30 min. H_2NOSO_3H (565 mg, 5 mmol) is added portion wise, and the mixture is warmed to rt over 2 h. The mixture is diluted with EtOAc (100 mL), quenched with water, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 1-(1-amino-5-fluoroindol-3-yl)-2-methyl-propan-2-ol, which is used in the next step without further purification.

Step 4: A solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (175 mg, 0.8 mmol) in DCM (5 mL) is treated with DMF (20 µL) and ClCOCOCl (348 µL, 4 mmol), and stirred at rt for 3 h. Toluene (10 mL) is added and the mixture is concentrated *in vacuo*. The residue is added to a solution of the above 1-(1-amino-5-fluoroindol-3-yl)-2-methyl-propan-2-ol and Na_2CO_3 (1 g) in EtOAc/H_2O (20 mL, 1:1). The mixture is stirred at rt for 12 h. The mixture

is then diluted with saturated aqueous Na_2CO_3, extracted with EtOAc. The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 30% - 50% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid[5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1-yl]-amide (160 mg, 50%). MS: 423 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (s, 6H), 2.77 (s, 2H), 7.03 (m, 1H), 7.33 (s, 1H), 7.35-7.55 (m, 3H), 7.65 (m, 1H), 8.21 (m, 1H), 8.36 (m, 1H), 9.43 (s, 2H).

Example 39

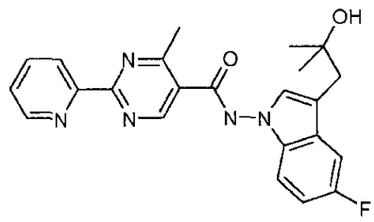
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1-yl]-amide



A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (250 mg, 1.07 mmol) in DCM (10 mL) is cooled to 0°C, treated with DMF (20 µL) and ClCOCOCl (280 µL, 3.21 mmol), and stirred for 20 min. Toluene (10 mL) is added and the mixture is concentrated *in vacuo*. The residue is dissolved in pyridine (10 mL) and treated with DMAP (5 mg) and 1-(1-amino-5-fluoroindol-3-yl)-2-methyl-propan-2-ol (0.72 mmol). The mixture is stirred at rt for 12 h. The mixture is diluted with saturated aqueous Na_2CO_3, extracted with EtOAc. The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 20% - 60% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1-yl]-amide (218 mg, 70%). MS: 437 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (s, 6H), 2.77 (s, 2H), 3.29 (s, 3H), 7.03 (m, 1H), 7.37 (s, 1H), 7.35-7.55 (m, 3H), 7.65 (m, 1H), 8.19 (m, 1H), 8.34 (m, 1H), 9.22 (s, 1H).

Example 40

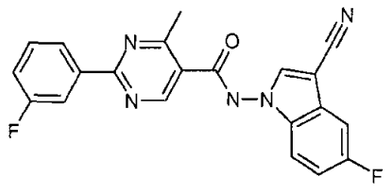
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1 yl]-amide



A solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (748 mg, 3.48 mmol) in DMF (30 mL) is treated with HATU (1.3 g, 3.48 mmol) and DIPEA (1.2 mL, 6.96 mmol), and the mixture is stirred at rt for 30 min. 1-(1-Amino-5-fluoroindol-3-yl)-2-methyl-propan-2-ol (2.9 mmol) is added and the mixture is stirred at 80°C for 12 h. The mixture is diluted with EtOAc, washed with saturated aqueous NH_4Cl and saturated aqueous Na_2CO_3, dried (Na_2SO_4), filtered and concentrated in vacuo to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1 yl]-amide (990 mg, 81%). MS: 420 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.13 (s, 6H), 2.75 (s, 2H), 2.85 (s, 3H), 6.84 (m, 1H), 7.24 (m, 1H), 7.37 (m, 1H), 7.53 (m, 1H), 7.95 (s, 1H), 7.98 (m, 1H), 8.44 (m, 1H), 8.76 (m, 1H), 9.15 (s, 1H).

Example 41

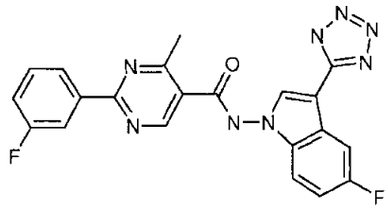
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-cyano-5-fluoro-indol-1-yl)-amide



A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide (300 mg, 0.82 mmol) in THF (8 mL) is cooled to 0°C, treated with chlorosulfonyl isocyanate (86 µL, 0.99 mmol) and the mixture is stirred at rt for 1 h. The mixture is treated with Et_3N (138 µL, 0.99 mmol) and stirred for 1 h. The mixture is diluted with brine, extracted with EtOAc. The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 25% - 35% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-cyano-5-fluoro-indol-1-yl)-amide (120 mg, 38%). MS: 390 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.78 (s, 3H), 7.32 (m, 1H), 7.46 (m, 1H), 7.55 (m, 1H), 7.66 (m, 1H), 7.77 (m, 1H), 8.20 (m, 1H), 8.35 (m, 1H), 8.65 (s, 1H), 9.28 (s, 1H).

Example 42

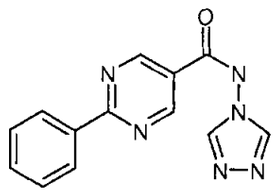
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(1H-tetrazol-5-yl)-indol-1-yl]-amide



A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-cyano-5-fluoro-indol-1-yl)-amide (120 mg, 0.31 mmol), $TMSN_3$ (62 µL, 0.465 mmol), and TBAF (0.155 µL, 0.155 mmol, 1 M in THF) in toluene (3 mL) is heated at 80°C for 18 h. The mixture is cooled, diluted with EtOAc, and washed with 1 M HCl. The organic layer is extracted with Na_2CO_3. The aqueous layer is acidified to pH ~ 3 with 3 N aqueous HCl, extracted with EtOAc The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(1H-tetrazol-5-yl)-indol-1-yl]-amide (100 mg, 75%). MS: 433 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.81 (s, 3H), 7.28 (m, 1H), 7.47 (m, 1H), 7.67 (m, 1H), 7.73 (m, 1H), 8.01 (m, 1H), 8.21 (m, 1H), 8.33 (m, 1H), 8.36 (s, 1H), 9.33 (s, 1H). IC_{50} = 5 nM.

Example 43

2- Phenyl-pyrimidine-5-carboxylic acid [1,2,4] triazol-4-ylamide

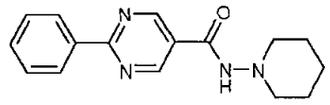


To a solution of 2-phenyl-pyrimidine-5-carboxylic acid (300 mg, 1.5 mmol) in DCM (10 mL) is added 1-[3-(dimethylamino)propyl-3-ethylcarbodiimide (316mg, 1.65 mmol) and N-hydroxybenzotriazole (223 mg, 1.65 mmol) at rt and the mixture is stirred for 10 min. 4-Amino-4H-1,2,4-triazole (252 mg, 3 mmol) is added and the mixture is stirred at rt for 3 days. The resulting precipitate is filtered, washed with DCM and water, and dried in vacuum oven at 40°C overnight to afford 2- phenyl-pyrimidine-5-carboxylic acid [1,2,4] triazol-4-ylamide

(270 mg) as a solid. MS: 267 (M+H); ^{1}H NMR (300 MHz, DMSO): δ = 7.59 (m, 3H), 8.50 (d, 2H), 8.84 (s, 2H), 9.36 (s, 2H). IC_{50} = 262.5 nM.

Example 44

2-phenyl-pyrimidine-5-carboxylic acid piperidin-1-ylamide

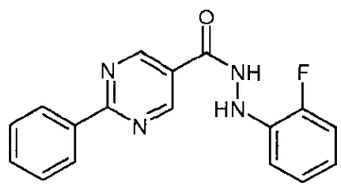


Method A: To a solution of 2-phenyl-pyrimidine-5-carboxylic acid (150 mg, 075 mmol) in DCM (10 mL) is added 1-[3-(dimethylamino)propyl-3-ethylcarbodiimide (158 mg, 0.83 mmol) and N-hydroxybenzotriazole (112 mg, 0.83 mmol) at rt and the mixture is stirred for 10 min. 1-Aminopiperidine (150 mg, 1.5 mmol) is added. The mixture is stirred at rt overnight. The mixture is washed with 2 N aqueous HCl (5 mL), saturated aqueous $NaHCO_3$, (5 mL), and water (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% EtOAc in heptane to afford 2-phenyl-pyrimidine-5-carboxylic acid piperidin-1-ylamide (125 mg) as a solid. MS: 290 (M+H).

Method B: Following procedures similar to those of Example 127 but substituting piperadin-1-ylamine for 3-[3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid piperadin-1-yl-amide (72%) as a solid. MS: 283 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35-1.98 (m, 6H), 2.20-3.60 (m, 4H), 6.60-7.17 (d, N-H), 7.52 (s, 3H), 8.52 (s, 2H), 9.07-9.39 (d, 2H).

Example 45

2-Phenyl-pyrimidine-5-carboxylic acid N'-(2-fluoro-phenyl)-hydrazide

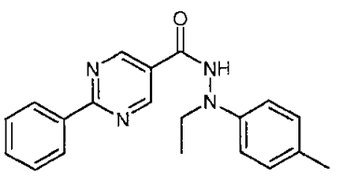


Following procedures similar to those of Example 44, but substituting (2-fluoro-phenyl)-hydrazine for 1-aminopiperidine, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid N'-(2-fluoro-phenyl)-hydrazide as a solid. MS: 309 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68

(broad, 1H), 6.87 (m, 1H), 7.04 (m, 3H), 7.51 (m, 3H), 8.51 (m, 2H), 9.36 (s, 2H), 10.65 (broad, 1H). IC_{50} = 12 nM.

Example 46

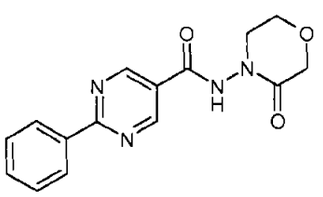
2-Phenyl-pyrimidine-5-carboxylic acid N'-ethyl-N'-tolyl-hydrazide



Following procedures similar to those of Example 44, but substituting N-ethyl-N-para-tolyl-hydrazine for 1-aminopiperidine, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid N'-ethyl-N'-tolyl-hydrazide as a solid. MS: 333 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 1H), 1.11 (t, 2H), 1.28 (t, 3H), 2.28 (d, 3H), 3.46 (q, 1H), 3.65(q, 1H), 6.84 (d, 1H), 6.94(d, 1H), 7.10(t, 2H), 7.52 (m, 3H), 8.47 (m, 2H), 9.12 (s, 1H0, 9.23 (s, 1H).

Example 47

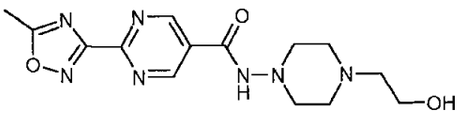
2-Phenyl-pyrimidine-5-carboxylic acid (3-oxo-morpholin-4-yl)-amide



Following procedures similar to those of Example 44, but substituting 4-amino-morpholin-3-one for 1-aminopiperidine, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (3-oxo-morpholin-4-yl)-amide as a solid. MS: 299 (M+H); ^{1}H NMR (300 MHz, DMSO): δ = 3.66 (m, 2H), 4.00 (m, 2H), 4.26 (s, 2H), 7.60 (m, 3H), 8.47 (m, 2H), 9.29(s, 2H), 11.27 (s, 1H). IC_{50} = 55 nM.

Example 48

2-(5-Methyl-[1,2,4]oxadiazol-3-yl)-pyrimidine-5-carboxylic acid [4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide



Step 1: To a solution of 2-methylsulfanyl-pyrimidine-5-carboxylic acid methyl ester 1 (1 g, 5.43 mmol) in DCM (60 mL) is added MCPBA (2.81 g, 16.29 mmol) portion wise at rt. The resulting solution is stirred at rt overnight. A solution of $Na_2S_2O_3$ (1.6 g) in water (60 mL) is added. The mixture is stirred at rt for 20 min. The layer is separated, and the water layer is extracted with DCM (2x20 mL). The combined DCM layer is washed with saturated $NaHCO_3$ (3x20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 2-methanesulfonyl-pyrimidine-5-carboxylic acid methyl ester as a solid (1.05 g, 90%). MS: 217 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.41 (s, 3H), 4.06 (s, 3H), 9.44 (s, 2H).

Step 2: To a solution of 2-methanesulfonyl-pyrimidine-5-carboxylic acid methyl ester 2 (2.5 g, 11.56 mmol) in DCM (30 mL) is added a solution of tetrabutylammonium cyanide (3.1 g, 11.56 mmol) in water (30 mL) slowly at rt. The mixture is stirred for 80 min. The mixture is washed with water (2x20mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by column chromatography eluting with 5-60% EtOAc in heptane to afford 2-cyano-pyrimidine-5-carboxylic acid methyl ester (1.16 g, 61%) as a solid. MS: 164 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.05 (s, 3H), 9.37 (s, 2H).

Step 3: To a solution of 2-cyano-pyrimidine-5-carboxylic acid methyl ester 3 (1 g, 6.13 mmol) in MeOH (20 mL) at rt is added hydroxylamine hydrochloride (0.64g, 9.2mmol) and sodium acetate (0.76 g, 9.2 mmol). The resulting mixture is heated to reflux for 2 hours. The mixture is cooled to rt and concentrated *in vacuo*. Water (30 mL) is added to the residue, and the solid is filtered, and washed with water twice. The solid is dried in vacuum oven overnight to afford 2-(N-hydroxycarbamimidoyl)-pyrimidine-5-carboxylic acid methyl ester (1.09 g, 91%) as a solid. MS: 197 (M+H).

Step 4: To a solution of 2-(N-hydroxycarbamimidoyl)-pyrimidine-5-carboxylic acid methyl ester (900 mg, 4.59 mmol) in pyridine (15 mL) is added acetyl chloride (432 mg, 5.5 mmol) dropwise. The resulting solution is stirred at rt for 1 hour, and heated to reflux for 3h. The solution is cooled to rt and concentrated *in vacuo*. Water (30 mL) is added to the residue, and the mixture is extracted with EtOAc (3x20 mL). The combined organic layer is washed with

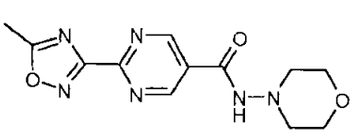
saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 2-(5-methyl-[1,2,3]oxadiazo-3-yl)-pyrimidine-5-carboxylic acid methyl ester (900 mg, 89%) as a solid. MS: 221 (M+H).

Step 5: To a solution of 2-(5-methyl-[1,2,3]oxadiazo-3-yl)-pyrimidine-5-carboxylic acid methyl ester (900 mg) in MeOH (20 mL) is added a solution of LiOH (100 mg) in water (20 mL) at 0°C. The ice-bath is removed, and the mixture is stirred for another 10 min. The solvent is evaporated, and water (20 mL) is added. The water solution is washed with ether (2x20mL), and acidified with 2 N HCl to pH ~ 3. The resulting precipitate is filtered, washed with water and dried in vacuum oven overnight to afford 2-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrimidine-5-carboxylic acid (350 mg, 37%) as a solid. MS: 207 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.73 (s, 3H), 9.39 (s, 2H).

Step 6: Following procedures similar to those of Example 44, but substituting 2-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrimidine-5-carboxylic acid for 2-phenyl-pyriminde-5-carboxylic acid, and substituting 2-(4-amino-piperazin-1-yl)-ethanol for 1-aminopiperidine, there is prepared 2-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrimidine-5-carboxylic acid [4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide as a solid. MS: 334 (M+H). IC_{50} = 461 nM.

Example 49

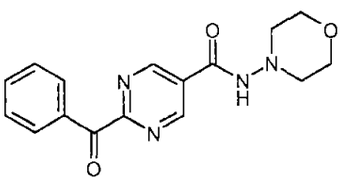
2-(5-Methyl-[1,2,4]oxadiazol-3-yl)-pyrimidine-5-carboxylic acid morpholin-4-ylamide



Following procedures similar to those of Example 44, but substituting 2-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrimidine-5-carboxylic acid for 2-phenyl-pyriminde-5-carboxylic acid, and substituting morpholine-4-ylamine for 1-aminopiperidine, there is prepared 2-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrimidine-5-carboxylic acid morpholin-4-ylamide as a solid. MS: 291 (M+H).

Example 50

2-Benzoyl-pyrimidine-5-carboxylic acid morpholin-4-ylamide



Step 1: 5-Bromo-2-chloropyrimidine (7.51 g, 38.83 mmol) is dissolved in DMSO (20 mL) is added to a mixture of NaCN (1.9 g, 38.83 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.87 g, 7.77 mmol) in DMSO (10 mL) and water (20 mL). The mixture is stirred at rt overnight, and then water (100 mL) is added. The mixture is extracted with ether (3x100 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 5-bromo-pyrimidine-2-carbonitrile (6.28 g, 88%) as a solid. MS: 184 (M+H).

Step 2: 5-Bromo-pyrimidine-2-carbonitrile(2.5 g, 13.59 mmol) is dissolved ether (30 mL), and PhMgBr (3 ether solution, 13.59 mmol, 4.53 mL) is added dropwise at rt. The mixture is heated to reflux for 3 h under N_2, and then cooled to rt. THF (30 mL) is added followed by the addition of 2 N aqueous HCl (10 mL). The resulting solution is stirred at rt for 30 min, and water (30 mL) is added. The aqueous layer is extracted with EtOAc (3x20 mL). The combined organic layer is washed with saturated aqueous $NaHCO_3$ (15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting 70% EtOAc in heptane to afford (5-bromo-pyrimidine-2-yl)-phenyl-methanone (3.01 g, 84%) as a solid. MS: 264 (M+H).

Step 3: (5-Bromo-pyrimidine-2-yl)-phenyl-methanone (1.6 g, 6.08 mmol) is dissolved in dimethylacetamide (20 mL), and potassium hexacyanoferrate(II) trihydrate (0.57 g, 1.34 mmol) is added, followed by Na_2CO_3 (0.64 g, 6.08 mmol), and palladium (II) acetate (68 mg, 0.3 mmol). The mixture is heated to 150°C under N_2 for 3 h, and then cooled to rt. EtOAc (30 mL) is added and the mixture is filtered. The filtrate is washed with water (2 x15 mL) and 5% aqueous NH_4OH (15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 70% EtOAc in heptane to afford 2-benzoyl-pyrimidine-5-carbonitrile (0.53 g, 42%) as a solid. MS: 210 (M+H).

Step 4: 2-Benzoyl-pyrimidine-5-carbonitrile (500 mg, 2.39 mmol) is suspended in MeOH (5 mL), a solution of KOH (148 mg, 2.63 mmol) in water (5 mL) is added in one portion at 0°C. The mixture is stirred at 0°C for 25 min, and then acidified with 2 N aqueous HCl to pH ~ 3.

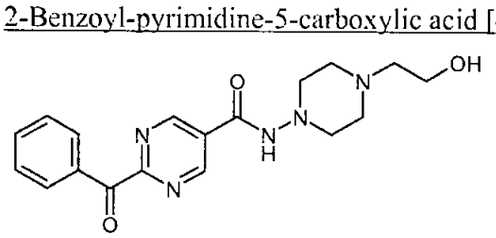
MeOH is evaporated *in vacuo* and the residue is extracted with DCM (2x 5 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 2-benzoyl-pyrimidine-5-carboxylic acid methyl ester (500 mg, 86%) as an oil. MS: 243 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.05 (s, 3H), 7.50 (m, 2H), 7.65 (m, 1H), 8.01 (m, 2H), 9.46 (s, 2H).

Step 5: 2-Benzoyl-pyrimidine-5-carboxylic acid methyl ester (420 mg, 1.73 mmol) is dissolved in THF (5 mL), and a solution of LiOH (46 mg, 1.91 mmol) in water (5 mL) is added in one portion at 0°C. The mixture is stirred at 0°C for 60 min. THF is evaporated *in vacuo*, and the residue is diluted with water (5 mL) and washed with ether (10 mL). The aqueous layer is acidified with 2 N aqueous HCl to pH ~ 3. The resulting precipitate is collected by filtration, washed with water three times, and dried in vacuum oven overnight to afford 2-benzoyl-pyrimidine-5-carboxylic acid (260 mg, 66%). MS: 229 (M+H); ^{1}H NMR (300 MHz, DMSO): δ 7.60 (m, 3H), 7.73 (m, 1H), 7.85 (m, 2H), 9.4 (s, 1H).

Step 6: 2-Benzoyl-pyrimidine-5-carboxylic acid (50 mg, 0.22 mmol) is dissolved in anhydrous DCM (5 mL), and a 2 M oxalyl chloride (0.26 mmol, 0.13 mL) solution in DCM is added at rt followed by one drop of DMF. The mixture is stirred at rt for 2 h, and then concentrated *in vacuo*. The residue is dissolved in DCM (5 mL), and morpholine-4-ylamine (0.24 mmol, 25 mg) is added, followed by DIPEA (0.44 mmol, 57 mg). The reaction mixture is stirred at rt overnight, and then concentrated *in vacuo*. The residue is purified by silica gel column chromatography eluting with 10% MeOH in DCM to afford 2-benzoyl-pyrimidine-5-carboxylic acid morpholin-4-ylamide (42 mg) as a solid. MS: 313 (M+H). IC_{50} = 342 nM.

Example 51

2-Benzoyl-pyrimidine-5-carboxylic acid [4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide

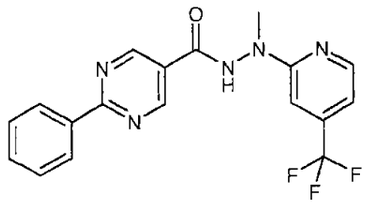


Following procedures similar to those of Example 49, step 6, but substituting 2-(4-amino-piperazin-1-yl)-ethanol for morpholine-4-ylamine, there is prepared 2-benzoyl-pyrimidine-5-

carboxylic acid [4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide as a solid. MS: 356 (M+H). IC_{50} = 665 nM.

Example 52

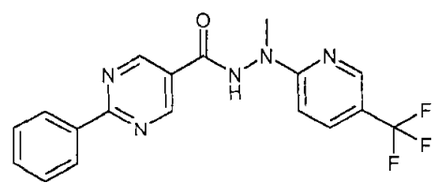
2-Phenyl-pyrimidine-5-carboxylic acid N`-methyl-N`-[5-trifluoromethyl-pyridin-2-yl]-hydrazide



To a solution of 2-phenyl-pyrimidine-5-carboxylic acid (100 mg, 0.52 mmol), 1-hydroxybenzotriazole (77 mg, 0.57 mmol), 1-[3-(dimethylamino)propyl-3-ethylcarbodiimide (111 mg, 0.57mmol) and DIPEA (0.57 mmol) in DCM (5 mL) is added N-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-hydrazine (109 mg, 0.57 mmol). The reaction mixture is stirred at rt for 18 hours and then concentrated. The residue is purified by silica gel chromatography eluting with 10-75% EtOAc in heptane to afford 2-phenyl-pyrimidine-5-carboxylic acid N`-methyl-N`-[5-trifluoromethyl-pyridin-2-yl]-hydrazide as a solid (189mg). MS: 374 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.54 (s, 3H), 6.82 (d, 1H), 7.53-7.59 (m, 3H), 7.74 (d, 1H), 8.45 (d, 2H), 8.53 (d, 2H), 9.25 (s, 2H). IC_{50} = 100 nM.

Example 53

2-Phenyl-pyrimidine-5-carboxylic acid N`-methyl-N`-[4-trifluoromethyl-pyridin-2-yl]-hydrazide

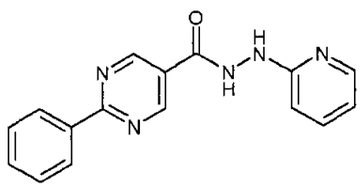


Following procedures similar to those of Example 52, but substituting N-methyl-N-(4-trifluoromethyl-pyridin-2-yl)-hydrazine (109mg, 0.57 mmol) for N-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-hydrazine, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid N`-methyl-N`-[4-trifluoromethyl-pyridin-2-yl]-hydrazide as a solid. MS: 374 (M+H); ^{1}H

NMR (300 MHz, $CDCl_3$): δ 3.54 (s, 3H), 6.95 (m, 2H), 7.50-7.68 (m, 3H), 8.35 (d, 1H), 8.4 (s, 1H), 8.52 (d, 2H), 9.26 (s, 2H).

Example 54

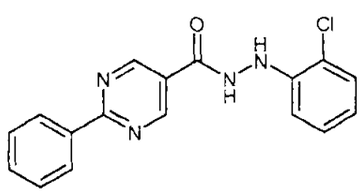
2-Phenyl-pyrimidine-5-carboxylic acid N'-pyridin-2-yl-hydrazide



Following procedures similar to those of Example 52, but substituting 2-hydrazinopyridine (54 mg, 0.52 mmol) for N-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-hydrazine, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid N'-pyridin-2-yl-hydrazide as a solid (56 mg). MS: 292 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.72-6.8 (m, 2H), 7.53-7.62 (m, 4H), 8.09 (m, 2H), 8.48 (d, 2H), 8.62 (s, 1H), 9.34 (s, 2H).

Example 55

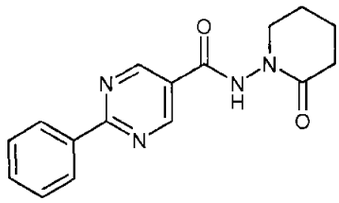
2-Phenyl-pyrimidine-5-carboxylic acid N'-(2-chloro-phenyl)-hydrazide



Following procedures similar to those of Example 52, but substituting 2-chlorophenylhydrazine hydrochloride (93mg, 0.52mmol) for N-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-hydrazine, and using 1.14 mmol of DIPEA, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid N'-(2-chloro-phenyl)-hydrazide as a solid (65mg). MS: 325 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65-6.75 (m, 2H), 6.90-7.05 (m, 2H), 7.25 (t, 1H), 7.39 (d, 1H), 7.58 (m, 3H), 8 (s, 1H), 8.55 (d, 2H), 9.25 (s, 2H).

Example 56

2-Phenyl-pyrimidine-5-carboxylic acid N'-(2-oxo-piperidin-1-yl)-amide

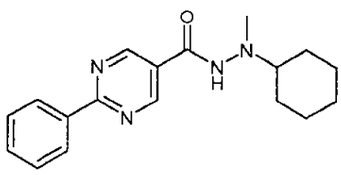


Step 1: A mixture of Methyl-5-bromovalerate(3 g, 15.4 mmol) and hydrazine hydrate (55%, 15.4 mmol) in MeOH (50 mL) is stirred at rt for 18 h. A solution of NaOMe (15.4 mmol) in MeOH (10 mL) is added and the reaction mixture is stirred at rt for 18 h. The reaction mixture is concentrated *in vacuo*. The residue is triturated with cold MeOH and then filtered. The filtrate is concentrated *in vacuo*. The residue is placed on a SCX column (10 g) and the column is washed with MeOH (3x20 mL. The product is eluted with 7 M ammonia in MeOH to afford 1-amino-piperidin-2-one as an oil. MS: 137 (M+Na).

Step 2: To a solution of 2-phenyl-pyrimidine-5-carboxylic acid (100 mg, 0.52 mmol), 1-hydroxybenzotriazole (77 mg, 0.57 mmol), 1-[3-(dimethylamino)propyl-3-ethylcarbodiimide (111 mg, 0.57 mmol) and DIPEA (0.57 mmol) in DCM (5 mL) is added 1-amino-piperidin-2-one (64 mg, 0.57 mmol), and the mixture is stirred at rt for 18 h. DCM (15 mL) is added and the mixture is washed with 0.5 N aqueous HCl (25 mL) and brine, and dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography through eluting with 50-100% EtOAc in heptane to afford 2-phenyl-pyrimidine-5-carboxylic acid N'-(2-oxo-piperidin-1-yl)-amide (20 mg) as a solid. MS: 297 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96-2.10 (m, 4H), 2.60 (t, 2H), 3.77 (t, 2H), 7.51-7.56 (m, 3H), 8.51 (d, 2H), 9.02 (bs, 1H), 9.16 (s, 2H). IC_{50} = 55 nM.

Example 57

2-Phenyl-pyrimidine-5-carboxylic acid N'-cyclohexyl-N'-methyl-hydrazide

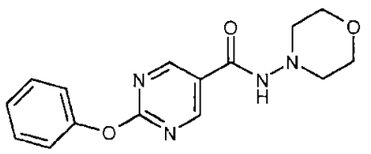


Following procedures similar to those of Example 52, but substituting N-methyl-N-cyclohexyl-hydrazine hydrochloride (72 mg, 0.44 mmol) for N-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-hydrazine, and using 0.88 mmol of DIPEA, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid N'-cyclohexyl-N'-methyl-hydrazide as a solid (40 mg). MS:

311 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.9-1.35 (m, 5H), 1.60-1.95 (m, 6H), 3.25 (s, 3H) 7.53-7.62 (m, 3H), 8.09 (m, 2H), 9.09 (s, 2H). IC_{50} = 146.5 nM.

Example 58

2-Phenyoxy-pyrimidine-5-carboxylic acid N'-morpholin-4-yl-amide



Step 1: To a solution of 2-methylsulfanyl-pyrimidine-5-carboxylic acid methyl ester (1 g, 5.43 mmol) in DCM (60 mL) is added MCPBA (2.81 g, 16.29 mmol) portion wise at rt. The resulting solution is stirred at rt overnight. A solution of $Na_2S_2O_3$ (1.6 g) in water (60 mL) is added. The mixture is stirred at rt for 20 min. The organic layer and aqueous layer are separated, and the aqueous layer is extracted with DCM (2x20 mL). The combined organic layer is washed with saturated aqueous $NaHCO_3$ (3x20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 2-methanesulfonyl-pyrimidine-5-carboxylic acid methyl ester (1.05 g, 90%) as a solid. MS: 217 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.41 (s, 3H), 4.06 (s, 3H), 9.44 (s, 2H).

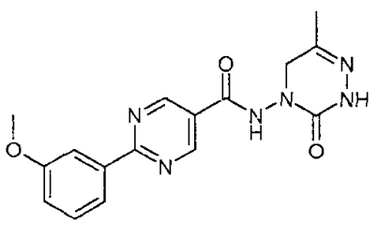
Step 2: To a solution of 2-methanesulfonyl-pyrimidine-5-carboxylic acid methyl ester (0.8 g, 3.7 mmol) in NMP (3 mL) is added sodium phenoxide trihydrate (0.68 g, 4 mmol). The mixture is heated at 100°C in Biotage Microwave for 60 sec. The reaction is poured into water and the precipitate is collted by filtration and dried to afford 2-phenoxy-pyrimidine-5-carboxylic acid methyl ester (0.56g, 66%) as a solid. MS: 231 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.75 (s, 3H), 7.19-7.33 (m, 3H), 7.46 (t, 2H) 9.10 (s, 2H).

Step 3: To a solution of 2-phenoxy-pyrimidine-5-carboxylic acid methyl ester (0.5 g, 2.17 mmol) in THF (10 mL) and water (5 mL) is added LiOH (105 mg, 4.35 mmol). The reaction is stirred at 0°C for 1 h. The THF is evaporated and the aqueous reissue is washed with ether, acidified with 2 M aqueous HCl. The resulting precipitate is filtered and dried to afford 2-phenoxy-pyrimidine-5-carboxylic acid (0.34g, 73%) as a solid. MS: 217 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20-7.35 (m, 3H), 7.47 (t, 2H) 9.16 (s, 2H).

Step 4: To a solution of 2-phenoxy-pyrimidine-5-carboxylic acid (60 mg, 0.28 mmol) in DCM (5 mL) is added oxalyl chloride (2M in DCM, 0.15 mL, 0.29 mmol) and 1 drop of DMF. The reaction is stirred at rt for 1 h and concentrated *in vacuo*. The residue is dissolved in DCM (3 mL), and DIPEA (53 µL, 0.3 mmol) and 4-amino-morpholine (30 µL, 0.3 mmol) is added. The reaction is stirred at rt for 18 h and then water and DCM are added. The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 20-100% EtOAc in heptane to afford 2-phenyoxy-pyrimidine-5-carboxylic acid N'-morpholin-4-yl-amide (20 mg) as a solid. MS: 301 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.85-3.05 (m, 4H), 3.75-3.95 (m, 4H), 7.18-7.35 (m, 3H), 7.45 (t, 2H), 8.95 (s, 2H). IC_{50} = 227 nM.

Example 59

2-(3-Methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide



Step 1: 2-Methylsulfanyl-pyrimidine-5-carboxylicacid methyl ester (323 mg, 1.75 mmol), Copper(I)thiophene-2-carboxylate (501 mg, 2.63 mmol), tetrakis(triphenylphosphine) palladium(0) (202 mg, 0.175 mmol) and 3-methoxyphenylboronic acid (400 mg, 2.63 mmol) are taken in a glass tube, evacuated, refilled with N_2, added anhydrous THF (6 mL) and is heated overnight at 85°C after closing with a cap. The reaction is cooled to rt, diluted with EtOAc and ammonium hydroxide is added. The organic layer is seperated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by flash silica gel chromatography to afford 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester (152 mg) as a powder. MS: 245 (M+H); ^{1}H NMR ($CDCl_3$): δ 4.00 (s, 3H), 4.82 (d, 2H), 7.55 (m, 2H), 8.46 (m, 1H), 8.53 (s, 1H), 9.33 (s, 2H).

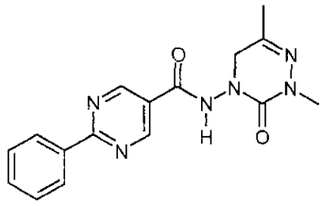
Step 2: A mixture of 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester (145 mg, 0.59 mmol), lithium hydroxide monohydrate (49.5 mg, 1.18 mmol), MeOH (1.5 mL), water (1.5 mL) and THF (1.5 ml) is stirred at rt for 3.5 hrs. Ther eaction mixture is

concentrated, and water (1 mL) and 1 N aqueous HCl (1.2 mL) are added. The precipitated product is filtered and dried to afford 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid (140 mg). MS: 231 (M+H); ^{1}H NMR (DMSO-d6): δ 4.62 (s, 3H), 7.54 (m, 2H), 8.14 (s, 1H), 8.34 (m, 1H), 8.46 (s, 1H), 9.30 (s, 2H).

Step 3: A mixture of 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid (135 mg, 0.58 mmol), 4-amino-6-methyl-4,5-dihydro-2H-[1,2,4]triazin-3-one (76 mg, 0.58 mmol), DMTMM (171 mg, 0.6 mmol) and DMF (3 mL) is stirred at rt for 2 days. Water (3 ml) is added, and the precipitated product is filtered, washed with water and dried to afford 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide (127 mg). MS: 341 (M+H); ^{1}H NMR (DMSO-d_6): δ 1.91 (s, 3H), 4.23 (s, 3H), 4.62 (s, 2H), 7.53 (m, 2H), 8.34 (m, 1H), 8.46 (s, 1H), 9.27 (s, 2H), 9.97 (s, 1H), 11.08 (s, 1H). IC_{50} = 174.5 nM.

Example 60

2-Phenyl-pyrimidine-5-carboxylic acid (2,6-dimethyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide



Step 1: To a solution of 5-methyl-3H-1,3,4-oxadiazol-2-one (5.509 g, 55.0 mmol) in MeOH (40 mL) is added 25wt % NaOMe solution in methanol (12.7 mL, 58.8 mmol). The mixture is stirred at rt for 15 min and then concentrated *in vacuo*. The residue is added to a solution of tetrabutylammonium bromide (0.358 g, 1.08 mmol) and chloro-acetone (4.6 ml, 54.9 mmol) in $CHCl_3$ (33 mL), and the mixture is heated to reflux for 5 h under N_2. The mixture is cooled to rt and stirred overnight. The resulting slurry is filtered, and the filtrate is concentrated *in vacuo*. The residue is purified on a pad of silica gel, eluting with 2:1:1 / heptane:EtOAc:DCM to afford 5-methyl-3-(2-oxo-propyl)-3H-1,3,4-oxadiazol-2-one (7.32 g, 86%) as a crystalline solid. MS: 157 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (s, 2H), 2.27 (s, 3H), 2.21 (s, 3H).

Step 2: To a solution of 5-methyl-3-(2-oxo-propyl)-3H-1,3,4-oxadiazol-2-one (1.518 g, 9.72

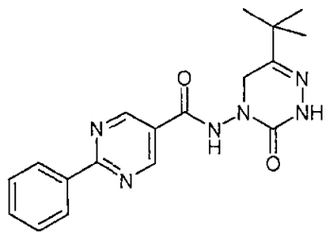
mmol) in a mixture of 2-propanol (8.8 mL) and water (0.22 mL) is added methyl hydrazine (0.79 mL, 14.6 mmol). The reaction mixture is heated to reflux under N_2 for 4 h, and then a solution of oxalic acid (0.273 g, 2.92 mmol) in 2-propanol (4 mL) is added. The resulting precipitate is removed by filtration. The filtrate is concentrated *in vacuo* and the residue dissolved in 2-propanol (25 mL). The solution is chilled and Et_2O is added. The precipitate is collected by filtration and dried to afford N-(2,6-dimethyl-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl)-acetamide (0.96 g, 54%) as a crystalline solid. MS: 185 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (s, 1H), 4.18 (s, 2H), 3.28 (s, 3H), 2.02 (s, 3H), 1.95 (s, 2H).

Step 3: To a slurry of N-(2,6-dimethyl-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl)-acetamide (0.34 g, 1.846 mmol) in MeOH (3 mL) is added concentrated HCl (0.25 mL, 2.9 mmol). The mixture is heated to reflux for 3 h. The mixture is then chilled to 0°C, adjusted to pH ~ 12 with 1 M aqueous NaOH (2.9 mL) and concentrated *in vacuo*. CH_3CN is added to the residue with stirring and the mixture is filtered. The filtrate is concentrated *in vacuo*. CH_3CN is added to the residue with stirring and the mixture is filtered. The filtrate is concentrated *in vacuo* to afford 4-amino-2,6-dimethyl-4,5-dihydro-2H-1,2,4-triazin-3-one (~100%)). MS: 143 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.6-3.6 (broad peak, 2H), 4.02 (s, 2H), 3.29 (s, 3H), 1.95 (s, 3H).

Step 4: To a solution of 4-amino-2,6-dimethyl-4,5-dihydro-2H-1,2,4-triazin-3-one (0.219g, 1.58 mmol) and 2-phenyl-pyrimidine-5-carboxylic acid (0.317 g, 1.58 mmol) in dry DMF (10 mL) under N_2 is added DMTMM (0.46 g, 1.66 mmol). The mixture is stirred at rt for 22 h, then diluted with EtOAc (70 mL), and washed successively with saturated aqueous $NaHCO_3$ solution (2x10 mL) and brine (10 mL). The organic phase is dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with heptane:EtOAc gradient to afford 2-phenyl-pyrimidine-5-carboxylic acid (2,6-dimethyl-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl)-amide as a solid (0.28 g, 55%). MS: 325 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.24 (s, 2H), 8.45 (dd, J=7.7, 2.0 Hz, 2 H), 7.52-7.62 (m, 3H), 4.25 (s, 2H), 3.18 (s, 3H), 1.95 (s, 3H).

Example 61

2-Phenyl-pyrimidine-5-carboxylic acid (6-tert-butyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide



Step 1: To a solution of 5-methyl-3H-1,3,4-oxadiazol-2-one (1.01 g, 10.09 mmol) in MeOH (8 mL) is added 25 wt % NaOMe solution in methanol (2.32 mL, 10.8 mmol). The mixture is stirred at rt for15 min and then concentrated *in vacuo*. The residue is added to a solution of tetrabutylammonium bromide (0.07 g, 0.22 mmol) and 1-chloropinacolone (1.35 mL, 10.07 mmol), in $CHCl_3$ (7 mL), and the mixture is heated to reflux for 5 h under N_2. The mixture is cooled to rt and stirred over the weekend at rt. The resulting slurry is filtered, and the filtrate is concentrated *in vacuo* to afford 3-(3,3-dimethyl-2-oxo-butyl)-3H-1,3,4-oxadiazol-2-one (1.876 g, 94%) as an oil. MS: 199 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (s, 2H), 2.26 (s, 3H), 1.23 (s, 9H).

Step 2: To a solution of 3-(3,3-dimethyl-2-oxo-butyl)-3H-1,3,4-oxadiazol-2-one (0.91 g, 4.59 mmol) in a mixture of 2-propanol (4 mL) and water (0.1 mL) is added hydrazine monohydrate (0.34 mL, 6.89 mmol). The reaction mixture is heated to reflux under nitrogen for 5 h, then a solution of oxalic acid (0.13 g, 1.38 mmol) in 2-propanol (5 mL) is added to the hot solution. The resulting precipitate is removed hot by filtration. The filtrate is concentrated *in vacuo* and the residue is purified on a pad of silica gel, eluting with heptane:EtOAc gradient to afford N-(6-tert-butyl-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl)-acetamide (0.546 g, 56%) as a solid. MS: 213 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.29 (s, 1H), 7.64 (s, 1H), 4.22 (s, 2H), 2.04 (s, 3H), 1.15 (s, 9H).

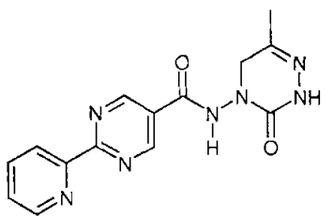
Step 3: To a slurry of N-(6-tert-butyl-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl)-acetamide (0.51 g, 2.40 mmol) in MeOH (5 mL) is added concentrated HCl (0.33 mL, 3.84 mmol). The mixture is heated to reflux for 3 h. The mixture is then chilled to 0°C and basified with 1 M aqueous NaOH (2.9 mL) to pH ~ 12, and concentrated *in vacuo*. EtOH is added to the residue with stirring and the mixture is filtered. The filtrate is concentrated *in vacuo*. CH_3CN is added to the residue with stirring and the mixture is filtered. The filtrate is concentrated *in vacuo* to afford 4-amino-6-tert-butyl-4,5-dihydro-2H-1,2,4-triazin-3-one (0.354 g, 84%) as a solid. MS: 171 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.49 (br s, 1H), 4.22 (br s, 2H),

4.06 (s, 2H), 1.15 (s, 9H).

Step 4: Following the procedure similar to those of Example 60, step 4, but substituting 4-amino-6-tert-butyl-4,5-dihydro-2H-1,2,4-triazin-3-one for 4-amino-2,6-dimethyl-4,5-dihydro-2H-1,2,4-triazin-3-one, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (6-tert-butyl-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl)-amide (74%) as a solid. MS: 353 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.09 (s, 1H), 10.03 (s, 1H), 9.27 (s, 2H), 8.45 (dd, J=7.7, 2.0 Hz, 2 H), 7.52-7.60 (m, 3H), 4.29 (s, 2H), 1.13 (s, 9H).

Example 62

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide



Step 1: To a solution of 5-methyl-3-(2-oxo-propyl)-3H-1,3,4-oxadiazol-2-one (2.052 g, 13.14 mmol) in a mixture of 2-propanol (12 mL) and water (0.3 mL) is added hydrazine monohydrate (0.96 mL, 19.8 mmol). The mixture is stirred at rt under N_2 for 15 h, and then heated to reflux for 7 h. A solution of oxalic acid (0.363 g, 4.032 mmol) in 2-propanol (6 mL) is added to the warm reaction solution. The resulting precipitate is removed by filtration through a coarse porosity sintered glass funnel, and the filtrate is concentrated *in vacuo* to approximately 10 mL in total volume. The concentrated solution is chilled to -12°C , and the resulting crystals are collected by filtration and dried to afford N-(6-methyl-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl)-acetamide (1.562 g, 70%). MS: 171 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.57 (br s, 1H), 4.20 (s, 2H), 2.04 (s, 3H), 1.95 (s, 3H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1), 9.74 (s, 1), 4.04 (s, 2), 1.84 (s, 6).

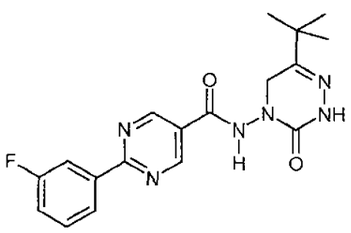
Step 2: Following the procedure similar to those of Example 35, step 4, but substituting N-(6-methyl-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl)-acetamide for N-[6-(4-fluoro-phenyl)-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl]-acetamide, there is prepared 4-amino-6-methyl-4,5-dihydro-2H-1,2,4-triazin-3-one (92%) as a solid. MS: 129 (M+H); ^{1}H NMR (300 MHz,

CD_3CN) δ 8.25 (br s, 1H), 4.26 (br s, 2H), 3.96 (s, 2H), 1.85 (s, 3H).

Step 3: To a solution of 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (0.152 g, 0.75 mmol), in dry DCM (3 mL) and DMF (0.9 μL) in a dry flask under N_2 is added oxalyl chloride (74 μL, 0.86 mmol). The reaction mixture is stirred at rt for 1 h. The solvent is evaporated and toluene is added and evaporated three times. The residue is dissolved in dry DCM (3 mL), and a solution of 4-amino-6-methyl-4,5-dihydro-2H-1,2,4-triazin-3-one (0.77 g, 0.6 mmol) in DCM (5 mL) is added followed by the addition of DIPEA (0.14 mL, 0.79 mmol). The mixture is stirred at rt overnight, and then concentrated *in vacuo*. The residue is diluted with water and adjusted to pH ~ 8.5 with saturated aqueous $NaHCO_3$ solution. The resulting precipitate is filtered to afford 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)amide (0.043 g, 23%). MS: 312 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.11 (s, 1H), 9.95 (s, 1H), 9.31 (s, 2H), 8.78 (d, 1H), 8.45 (d, 1H), 8.01 (tr, 1H), 7.58 (dd, 1H), 4.22 (2, 2H), 1.91 (s, 3H).

Example 63

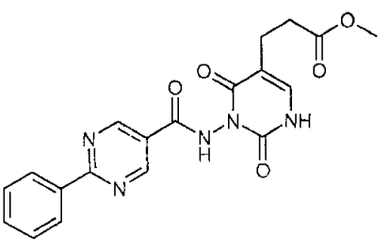
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-tert-butyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide



Following the procedure similar to those of Example 62, step 3, but substituting 2-(3-Fluoro-phenyl)-pyrimidine-5-carbonyl chloride for 2-pyridin-2-yl-pyrimidine-5-carbonyl chloride, substituting 4-amino-6-tert-butyl-4,5-dihydro-2H-1,2,4-triazin-3-one for 4-amino-6-methyl-4,5-dihydro-2H-1,2,4-triazin-3-one, and substituting Et_3N for DIPEA, there is prepared 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-tert-butyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide (0.067 g, 61%). MS: 371 (M+H); ^{1}H NMR (300 MHz, CD_3OD) δ 9.26 (s, 2H), 8.35 (d, J=8.1 Hz, 1H), 8.21 (d, J=10.3 Hz), 7.55 (q, J=10.3 Hz, 1 H), 7.30 (tr, J=8.2 Hz, 1H), 4.37 (s, 2H), 1.19 (s, 9H).

Example 64

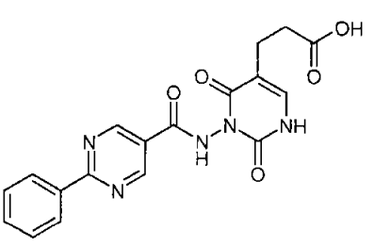
3-{2,4-Dioxo-3-[(2-pheyl-pyrimidine-5-carbonyl)-amino]-1,2,3,4-tetrahydro-pyrimidin-5-yl}-propionic acid methyl ester



A mixture of 2-phenyl-pyrimidine-5-carboxylic acid (1.17 mmol), 1-hydroxybenzotriazole (1.99 mmol), and PS-DCC (1.21 mmol/g, 2.34 mmol in DMF (8 mL) is shaken at rt for 60 min. 3-{3-Amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester (1.17 mmol) is added and the mixture is shaken at rt for 2-4 days. Polymer supported-trisamine (PS-trisamine) (4.08 mmol/g, 3.51 mmol) is added and the mixture is continually shaken at rt for 18 hours. The solid is filtered and washed with MeOH. The filtrate is concentrated. The residue is purified by silica gel chromatography eluting with 10-60% EtOAc in hexanes to afford 3-{2,4-dioxo-3-[(2-pheyl-pyrimidine-5-carbonyl)-amino]-1,2,3,4-tetrahydro-pyrimidin-5-yl-propionic acid methyl ester (115 mg, 25%) as a solid. MS: 397 (M+H) 397; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57-2.76 (m, 2H), 2.80-3.00 (m, 2H), 3.64 (s, 3H), 5.30 (br. N-H), 7.37-7.55 (m, 3H), 8.35 (d, 2H), 9.26 (s, 2H).

Example 65

3-{2,4-Dioxo-3-[(2-pheyl-pyrimidine-5-carbonyl)-amino]-1,2,3,4-tetrahydro-pyrimidin-5-yl}-propionic acid

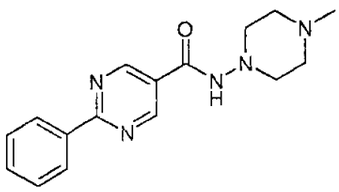


3-{2,4-Dioxo-3-[(2-pheyl-pyrimidine-5-carbonyl)-amino]-1,2,3,4-tetrahydro-pyrimidin-5-yl}-propionic acid methyl ester (0.22 mol) is hydrolyzed by LiOH (0.88 mol) in MeOH/water/THF (1:1:1) at rt overnight. MeOH and THF are evaporated *in vacuo*. The residue is acidified by 5% aqueous HCl. The resulting precipitate is collected and dried to afford 3-{2,4-dioxo-3-[(2-pheyl-pyrimidine-5-carbonyl)-amino]-1,2,3,4-tetrahydro-pyrimidin-5-yl}-propionic acid (40 mg, 48%). MS: 383 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.68-

2.77 (m, 2H), 2.98-2.90 (m, 2H), 5.49 (s. N-H), 7.48-7.60 (m, 3H), 8.41-8.56 (m, 2H), 9.32 (s, 2H).

Example 66

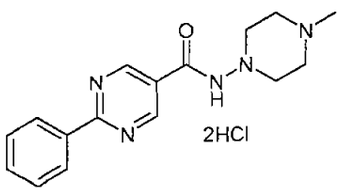
2-Phenyl-pyrimidine-5-carboxylic acid (4-methyl-piperazin-1-yl)-amide



Following procedures similar to those of Example 64 but substituting 4-methyl-piperazin-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (4-methyl-piperazin-1-yl)-amide.

Example 67

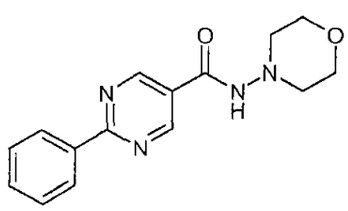
2-Phenyl-pyrimidine-5-carboxylic acid (4-methyl-piperazin-1-yl)-amide dihydrochloride



2-Phenyl-pyrimidine-5-carboxylic acid (4-methyl-piperazin-1-yl)-amide is dissolved in HCl methanol solution and evaporated methanol to dryness to afford 2-phenyl-pyrimidine-5-carboxylic acid (4-methyl-piperazin-1-yl)-amide dihydrochloride as a solid. MS: 298 (M+H).

Example 68

2-Phenyl-pyrimidine-5-carboxylic acid morpholin-4-ylamide

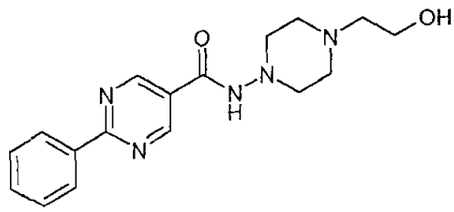


Following procedures similar to those of Example 64 but substituting 4-aminomorpholine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid morpholin-4-ylamide (71%) as a solid. MS:

285 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.90-3.00 (m, 2H), 3.80-3.85 (m, 2H), 7.44-7.58 (m, 3H), 8.45-8.53 (m, 2H), 9.18 (s, 2H).

Example 69

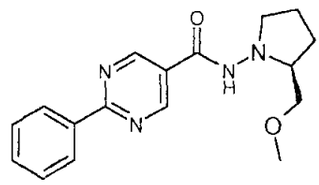
2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide



Following procedures similar to those of Example 64 but substituting 2-(4-amino-piperazin-1-yl)-ethanol for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic [4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide (25%) as a solid. MS: 328 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.65 (t, 2H), 2.80 (br, 2H), 3.04 (br, 2H), 3.73 (t, 2H), 7.24-7.34 (m, H), 7.47-7.57 (m, 3H), 7.62-7.73 (m, H), 8.43-8.52 (m, 2H), 9.18 (s, 2H).

Example 70

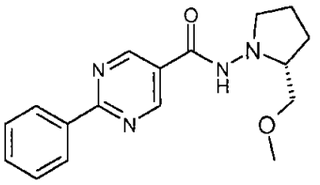
2-Phenyl-pyrimidine-5-carboxylic acid ((s)-2-methoxymethyl)-pyrrolidin-1-yl]-amide



Following procedures similar to those of Example 64 but substituting (S)-2-methoxymethyl-pyrrolidin-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2 -phenyl-pyrimidine-5-carboxylic acid ((s)-2-methoxymethyl)-pyrrolidin-1-yl]-amide (63%) as a solid. MS: 313 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57-2.15 (m, 4H), 2.70-3.70 (m, 8H), 6.93 (br, 0.4N-H), 7.81 (br, 0.6N-H), 7.50 (m, 3H), 8.48 (m, 2H), 9.10-9.38 (d, 2H).

Example 71

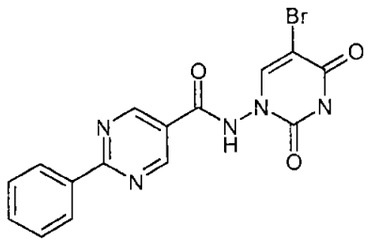
2-Phenyl-pyrimidine-5-carboxylic acid ((R)-2-methoxymethyl)-pyrrolidin-1-yl]-amide



Following procedures similar to those of Example 64 but substituting (R)-2-methoxymethyl-pyrrolidin-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid ((R)-2-methoxymethyl)-pyrrolidin-1-yl]-amide (66%) as a solid. MS: 313 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57-2.15 (m, 4H), 2.71-3.63 (m, 8H), 6.93 (br, 0.4N-H), 7.71 (br, 0.6N-H), 7.50 (m, 3H), 8.50 (m, 2H), 9.10-9.38 (d, 2H).

Example 72

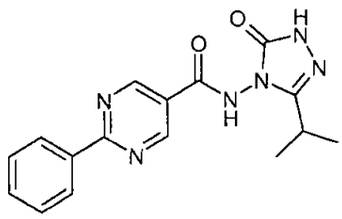
2-Phenyl-pyrimidine-5-carboxylic acid (5-bromo-2, 4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-amide



Following procedures similar to those of Example 64 but substituting 5-bromo-2, 4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (5-bromo-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-amide (34%) as a solid. MS: 389 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 7.49-7.62 (m, 3H), 7.98 (br, 3H), 8.23 (s, H), 8.54 (d, 2H), 9.29 (s, 2H). IC_{50} = 107.5 nM.

Example 73

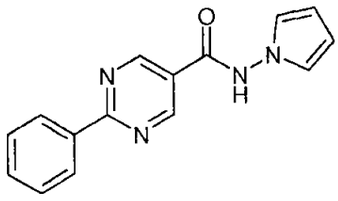
2-Phenyl-pyrimidine-5-carboxylic acid (3-isopropyl-5-oxo-1,5-dihydro-[1,2,4]triazol-4-yl)-amide



Following procedures similar to those of Example 64 but substituting 3-isopropyl-5-oxo-1,5-dihydro(1,2,4)-triazol-4-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (3-isopropyl-5-oxo-1,5-dihydro-[1,2,4]triazol-4-yl)-amide (25%) as a solid. MS: 325 (M+H).

Example 74

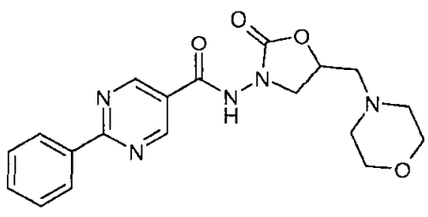
2-Phenyl-pyrimidine-5-carboxylic acid pyrrol-1-ylamide



Following procedures similar to those of Example 64 but substituting pyrrol-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid pyrrol-1-ylamide (62%) as a solid. MS: 265 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.25 (d, 2H), 6.76 (d, 2H), 7.48-7.63 (m, 3H), 8.52 (d, 2H), 8.95-9.60 (br, 2H).

Example 75

2-Phenyl-pyrimidine-5-carboxylic acid (5-morpholin-4-ylmethyl-2-oxo-oxazolidin-3-yl)-amide

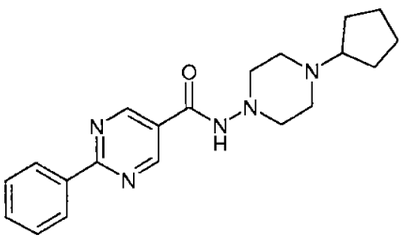


Following procedures similar to those of Example 64 but substituting 5-morpholin-4-ylmethyl-2-oxo-oxazolidin-3-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (5-

morpholin-4-ylmethyl-2-oxo-oxazolidin-3-yl)-amide (51%) as a solid. MS: 384 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.50-2.95 (m, 6H), 3.64-3.85 (m, 5H), 3.98 (t, H), 4.88 (m, H), 7.48-7.60 (m, 3H), 8.49 (d, 2H), 9.16 (s, 2H), 9.37 (br. N-H). IC_{50} = 20 nM.

Example 76

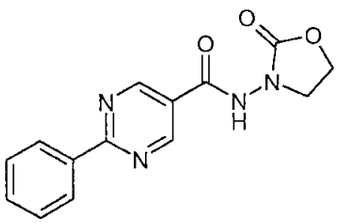
2-Phenyl-pyrimidine-5-carboxylic acid (4-cyclopentyl-piperazin-1-yl]-amide



Following procedures similar to those of Example 64 but substituting 4-cyclopentyl-piperazin-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (4-cyclopentyl-piperazin-1-yl]-amide (67%) as a solid. MS: 352 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25-2.00 (m, 8H), 2.00-3.35 (m, 9H), 6.70-7.40 (m, N-H), 7.40-7.60 (m, 3H), 8.50 (s, 2H), 8.86-9.38 (m,2H).

Example 77

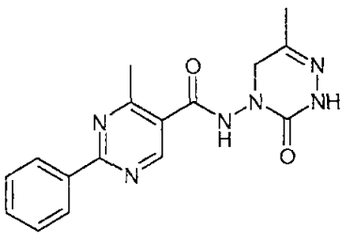
2-Phenyl-pyrimidine-5-carboxylic acid (2-oxo-oxazolidin-3-yl)-amide



Following procedures similar to those of Example 64 but substituting 2-oxo-oxazolidin-3-ylamine hydrochloride for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (2-oxo-oxazolidin-3-yl)-amide (18%) as a solid. MS: 285 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 3.94 (t, 2H), 4.55 (t, 2H), 7.46-7.62 (m, 3H), 8.53 (d, 2H), 9.30 (d, 2H). IC_{50} = 49 nM.

Example 78

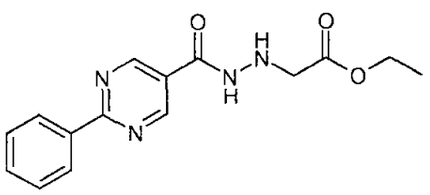
4-Methyl-2-phenyl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl]-amide



Following procedures similar to those of Example 64 but substituting 6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 4-methyl-2-phenyl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl]-amide (87%) as a solid. MS: 325 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (s, 3H), 3.72 (s, 3H), 4.30 (s, 2H), 7.34-7.58 (m, 4H), 7.72 (br, H), 8.92 (br, H), 8.43 (d, 2H), 8.87 (s, H), 9.46 (br, H).

Example 79

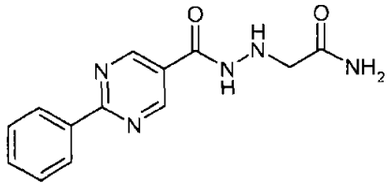
[N'-(2-Phenyl-pyrimidine-5-carbonyl)-hydrazino]-acetic acid ethyl ester



Et_3N (13.15 mmol) is added to a stirred solution of 2-phenyl-pyrimidine-5-carboxylic acid chloride (5.26 mmol) and hydrazine-acetic acid ethyl ester hydrochloride (5 mmol) in DCM (30 mL) at rt, and the mixture is stirred at rt for 5 h. The mixture is quenched with water and extracted with EtOAc (60 mL). The organic layer is washed with water (20 mL) and brine(15 mL), dried, filtered and concentrated *in vacuo*. The residue is purified by silical gel chromatography eluting with 5-50% EtOAc in heptane to afford [N'-(2-phenyl-pyrimidine-5-carbonyl)-hydrazino]-acetic acid ethyl ester (256 mg, 16%) as a solid. MS: 301 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 4.20-4.40 (m, 4H), 4.56 (s, 2H), 7.54 (m, 3H), 8.53 (m, 2H), 9.24 (s, 2H).

Example 80

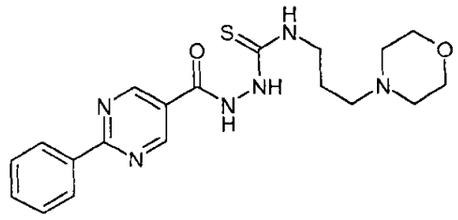
2-[N'-(2-Phenyl-pyrimidine-5-carbonyl)-hydrazino]-acetamide



A mixture of [N'-(2-phenyl-pyrimidine-5-carbonyl)-hydrazino]-acetic acid ethyl ester (0.37 mmol) in 25% ammonia solution (25 mL) is stirred at rt over night. The solid is collected by filtration and dried to afford 2-[N'-(2-phenyl-pyrimidine-5-carbonyl)-hydrazino]-acetamide (46%). MS: 272 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 4.45 (s, 2H), 7.45-7.56 (m, 3H), 8.40-8.50 (m, 2H), 9.18 (s, 2H).

Example 81

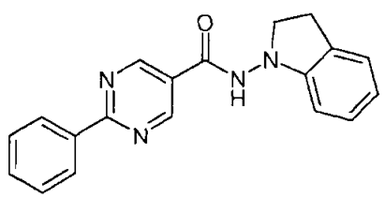
4-[3-(4-Morpholino)propyl]-1-(2-phenyl-pyrimidine-5-carbonyl)-3-thiosemicarbazide



Following procedures similar to those of Example 64 but substituting 4-[3-(4-morpholino)-propyl]-3-thiosemicarbazide for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 4-[3-(4-morpholino)propyl]-1-(2-phenyl-pyrimidine-5-carbonyl)-3-thiosemicarbazide (32%) as a solid. MS: 401 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 1.67-1.97 (m, 2H), 2.27-2.84 (m, 6H), 3.40-3.86 (m, 6H), 7.34-7.59 (m, 3H), 8.33-8.57 (m, 2H), 9.24 (s, 2H).

Example 82

2-Phenyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide

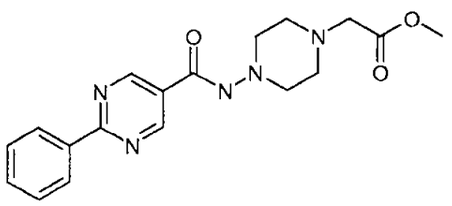


Oxalyl chloride in DCM (2 M, 1.5 mL) is added to a solution of 2-phenyl-pyrimidine-5-carboxylic acid (200 mg, 2 mmol) in DCM (20 mL) and stirred at rt for 2 h. The reaction

solution is concentrated *in vacuo*. The residue is dissolved in DCM (20 mL). N-amino-indoline (268 mg, 2 mmol) and triethylamine (404 mg, 4 mmol) are added and stirred at rt overnight. The mixture is concentrated *in vacuo* and the residue is purified by silica gel column chromatography eluting with 0-40% EtOAc in heptane to afford 2-phenyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide (195 mg, 31%) as a solid. MS: 317 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 3.07 (t, 2H), 3.77 (t, 2H), 6.76 (m, H), 6.82-6.95 (m, H) 7.09-7.24 (m, 2H), 7.54-7.63 (m, 3H), 8.52 (d, 2H), 9.28 (s, 2H) and 2-phenyl-pyrimidine-5-carboxylic acid (indol-1-yl)-amide (10 mg, 2%). MS: 315 (M+H). IC_{50} = 2 nM.

Example 83

{4-[2-Phenyl-pyrimidine-5-carbonyl)-amino]-piperazin-1-yl}-acetic acid methyl ester



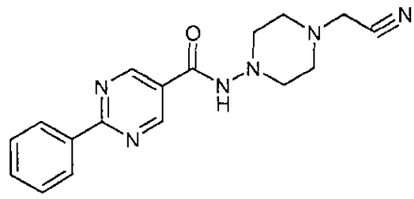
Step 1: Following procedures similar to those of Example 64 but substituting piperazin-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid piperazin-1-yl-amide.

Step 2: Phenyl-pyrimidine-5-carboxylic acid piperazin-1-yl-amide is dissolved in HCl methanol solution and evaporated methanol to dryness to afford 2-phenyl-pyrimidine-5-carboxylic acid piperazin-1-yl)-amide dihydrochloride as a solid.

Step 3: A suspended solution of 2-phenyl-pyrimidine-5-carboxylic acid piperazin-1-ylamide dihydrochloride (0.5 mmol), methyl bromoacetate (0.5 mmol) and Na_2CO_3 (2.5 mmol) in wet THF (20 mL) is stirred at rt for 20 h. The mixture is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 1-5% methanol in DCM to afford {4-[2-phenyl-pyrimidine-5-carbonyl)-amino]-piperazin-1-yl}-acetic acid methyl ester (135 mg, 76%) as a solid. MS: 356 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60-3.18 (m, 8H), 3.18-3.35 (d, 2H), 3.74 (s, 3H), 6.67 (br, 0.5 N-H) 7.03 (br, 0.5 N-H), 7.46-7.60 (m, 3H), 8.50 (d, 2H), 9.21 (d, 2H).

Example 84

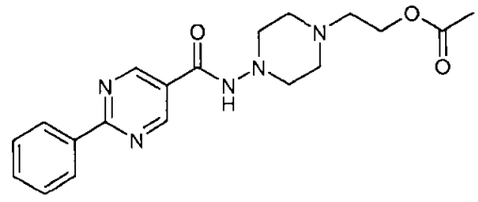
2-Phenyl-pyrimidine-5-carboxylic acid (4-cyanomethyl-piperazin-1-yl)-amide



A solution of 2-phenyl-pyrimidine-5-carboxylic acid piperazin-1-ylamide dihydrochloride (0.29 mmol), bromoacetonitrile (0.29 mmol) and Na_2CO_3 (1.46 mmol) in wet THF (8 mL) is stirred at rt overnight. The reaction mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 1-2% methanol in DCM to afford 2-phenyl-pyrimidine-5-carboxylic acid (4-cyanomethyl-piperazin-1-yl)-amide (38 mg, 40%) as a solid. MS: 323 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60-3.30 (m, 8H), 3.55 (s, 2H), 6.63 (br, 0.5 N-H), 7.14 (br, 0.5 N-H), 7.52 (s, 3H), 8.53 (d, 2H), 9.06-9.38 (m, 2H).

Example 85

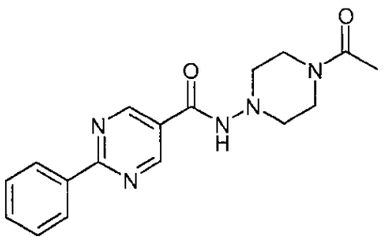
Acetic acid 2-{4-[(2-phenyl-pyrimidine-5-carbonyl)-amino]-piperazin-1-yl}-ethyl ester



A solution of 2-phenyl-pyrimidine-5-carboxylic [4-(2-hydroxy-ethyl)-piperazin-1-y]-amide (0.21 mmol), acetyl chloride(1.06 mmol) in pyridine (4 mL) is stirred at 80°C overnight. The reaction mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is dissolved in EtOAc (10 mL), washed with water (10 mL), 10% Na_2CO_3 (10 mL) and brine (10mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-5% methanol in DCM to afford 2-{4-[(2-phenyl-pyrimidine-5-carbonyl)-amino]-piperazin-1-yl)-ethyl ester (12 mg, 15%) as a solid. MS: 370 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (s, 3H), 2.42-3.20 (m, 8H), 3.20-3.80 (m, 3H), 4.10-4.52 (m, 2H) 7.42-7.65 (m, 3H), 8.52 (m, 2H), 9.07-9.38 (d, 2H).

Example 86

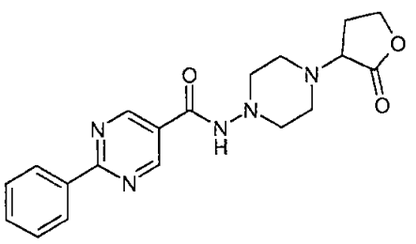
2-Phenyl-pyrimidine-5-carboxylic acid (4-acetyl-piperazin-1-yl)-amide



A solution of 2-phenyl-pyrimidine-5-carboxylic acid piperazin-1-ylamide dihydrochloride (0.43 mmol), acetyl chloride (1.28 mmol) and Et_3N (1.72 mmol) in DMF (8 mL) is stirred at rt overnight. mixture is concentrated *in vacuo*. The residue is dissolved in EtOAc (15 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is triturated with ether to afford 2-phenyl-pyrimidine-5-carboxylic acid (4-acetyl-piperazin-1-yl)-amide (98 mg, 71%) as a solid. MS: 326 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.92-3.10 (m, 4H), 3.40-4.10 (m, 4H), 7.43-7.60 (m, 3H), 7.75 (br, N-H), 8.52 (m, 2H), 9.11-9.38 (br, 2H).

Example 87

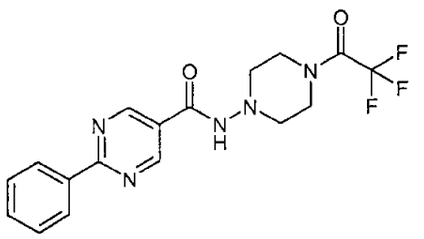
2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-oxo-tetrahydro-furan-3-yl)-piperazin-1-yl]-amide



A solution of 2-phenyl-pyrimidine-5-carboxylic acid piperazin-1-ylamide dihydrochloride (0.45 mmol) and bromo-dihydro-furan-2-one (1.8 mmol) in DMF (10 mL) is stirred under N_2 at 0°C for 15 min, then NaH (60%, 1.8 mmol) is added and the mixture is warmed to rt and stirred overnight. The mixture is quenched with water, and extracted with EtOAC. The organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-2% methanol in DCM to afford give 2-phenyl-pyrimidine-5-carboxylic acid [4-(2-oxo-tetrahydro-furan-3-yl)-piperazin-1-yl]-amide (120 mg, 73%) as a solid. MS: 368 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 2H), 2.50-3.30 (m, 8H), 3.42-3.70 (m, H), 4.17-4.50 (m, 2H), 7.34-7.68 (m, 3H), 8.50 (d, 2H), 9.06-9.38 (d, 2H). IC_{50} = 26 nM.

Example 88

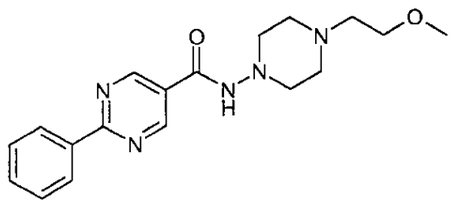
2-Phenyl-pyrimidine-5-carboxylic acid [4-(2,2,2-trifluoro-acetyl)-piperazin-1-yl]-amide



A solution of 2-phenyl-pyrimidine-5-carboxylic acid piperazin-1-ylamide dihydrochloride (0.36 mmol), trifluoroacetic anhydride (1.08 mmol) and Et_3N (1.44 mmol) in DMF (8 mL) is stirred under N_2 at rt overnight. The reaction mixture is concentrated *in vauo*. The residue is dissolved in EtOAc (15 mL), washed with water (10 ml) and brine (15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is triturated with ether to give 2-phenyl-pyrimidine-5-carboxylic acid [4-(2,2,2-trifluoro-acetyl)-piperazin-1-yl]-amide (136 mg, ~ 100%) as a solid. MS: 380 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95-3.40 (s, 4H), 3.60-4.10 (m, 4H), 7.41-7.68 (m, 3H), 8.52 (d, 2H), 9.03-9.40 (br, 2H). IC_{50} = 57 nM.

Example 89

2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-methoxy-ethyl)-piperazin-1-yl]-amide

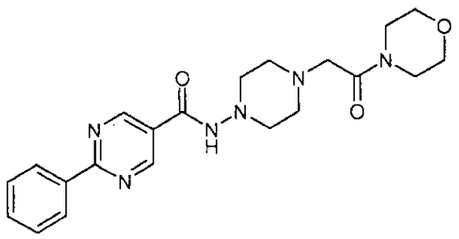


Step 1: To a suspended solution of 2-phenyl-pyrimidine-5-carboxylic acid [4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide (0.83 mmol) in DCM (8 mL) under N_2 are added a solution of Et_3N (2.67 mmol) in DCM (1 mL), a solution of N,N-dimethyl-4-aminopyridine (0.2 mmol) in DCM (1 mL) and a solution of di-tert-butyl dicarbonate (1.48 mmol) in DCM (1 mL) at rt. The resulting mixture is stirred at rt for 3 h, and then concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 6% ethanol in EtOAc to afford [4-(2-methoxy-ethyl)-piperazin-1-yl]-(2-phenyl-pyrimidine-5-carbonyl)-carbamic acid tert-butyl ester (70 mg, 20%) as a solid. MS: 428 (M+H).

Step 2: A solution of [4-(2-methoxy-ethyl)-piperazin-1-yl]-(2-phenyl-pyrimidine-5-carbonyl)-carbamic acid tert-butyl ester (0.21 mmol), NaH (60%, 0.66 mmol) and iodomethane (0.63 mmol) in DMF (8 mL) is stirred under N_2 at rt overnight. The reaction mixture is quenched with water, and extracted with EtOAc. The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-2% methanol in DCM to afford 2-phenyl-pyrimidine-5-carboxylic acid [4-(2-methoxy-ethyl)-piperazin-1-yl]-amide (32 mg, 44%) as a solid. MS: 342 (M+H).

Example 90

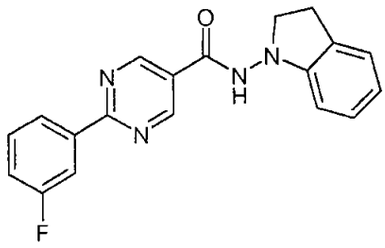
2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazin-1-yl]-amide



A solution of 2-phenyl-pyrimidine-5-carboxylic acid piperazin-1-ylamide dihydrochloride (0.43 mmol) and NaH (60%, 2.15 mmol) in DMF (10 mL) is stirred under N_2 at rt for 20 min. 2-Chloro-1-morpholin-4-yl-ethanone (0.65 mmol)) is added and the reaction mixture is stirred at rt overnight. The reaction mixture is quenched with water, and extracted with EtOAc. The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-4% methanol in DCM to afford 2-phenyl-pyrimidine-5-carboxylic acid [4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazin-1-yl]-amide (24 mg, 14%) as a solid. MS: 411 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.85-3.10 (m, 2H), 3.60-4.00 (m, 12H), 4.46 (d, 2H), 4.84 (s, 2H), 7.44-7.62 (m, 3H), 8.34-8.58 (m, 2H), 9.20-9.38 (d, 2H). IC_{50} = 831.5 nM.

Example 91

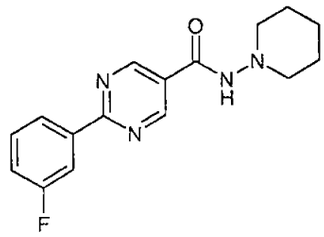
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide



Following procedures similar to those of Example 64 but substituting 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid for 2-phenyl-4-yl-pyrimidine-5-carboxylic acid, and substituting 2,3-dihydro-indol-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide (83%) as a solid. MS: 335 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 2H), 3.70 (s, 2H), 6.53-7.34 (m, 5H), 7.45 (s, H), 8.00-8.38 (m, 2H), 9.20 (s, 2H). IC_{50} = 3 nM.

Example 92

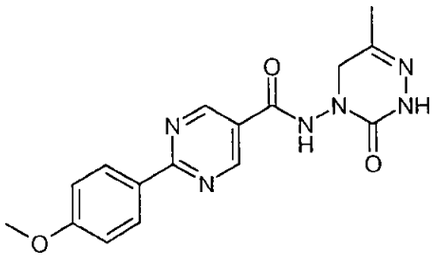
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid piperadin-1-yl-amide



Following procedures similar to those of Example 64 but substituting 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid for 2-phenyl-4-yl-pyrimidine-5-carboxylic acid, and substituting piperadin-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid piperadin-1-yl-amide (71%) as a solid. MS: 301 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20-2.00 (m, 6H), 2.20-3.60 (m, 4H), 6.97-7.30 (m, H), 7.34-7.56 (m, H), 8.06-8.38 (m, 2H), 9.00-9.38 (d, 2H). IC_{50} = 19.5 nM.

Example 93

2-(4-Methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,



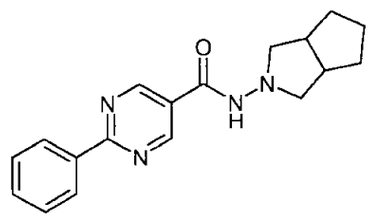
Step 1: Following the procedures similar to those of Example 59, step 1, but substituting 4-methoxyphenylboronic acid for 3-methoxyphenylboronic acid, there is prepared 2-(4-methoxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester.

Step 2: Following the procedures similar to those of Example 59, step 2, but substituting 2-(4-methoxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester for 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester, there is prepared 2-(4-methoxy-phenyl)-pyrimidine-5-carboxylic acid.

Step 3: Following the procedures similar to those of Example 59, step 3, but substituting 2-(4-methoxy-phenyl)-pyrimidine-5-carboxylic acid for 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid, there is prepared 2-(4-methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide. MS: 341 (M+H); ^{1}H NMR (DMSO-d_6): δ 1.91 (s, 3H), 3.86 (s, 3H), 4.22 (s, 2H), 7.12 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 8.42 (d, J = 8.6 Hz, 1H), 9.21 (s, 2H), 9.95 (s, 1H), 11.02 (s, 1H).

Example 94

2-Phenyl-pyrimidine-5-carboxylic acid (hexahydro-cyclopenta[c]pyrrol-2-yl)-amide

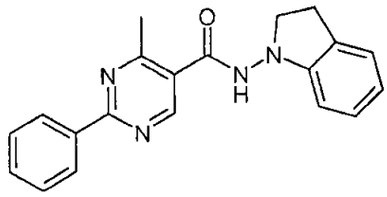


Following procedures similar to those of Example 64 but substituting hexahydro-cyclopenta[c]pyrrol-2-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (hexahydro-cyclopenta[c]pyrrol-2-yl)-amide (39%) as a solid. MS: 309 (M+H); ^{1}H NMR

(300 MHz, $CDCl_3$): δ 1.20-1.90 (m, 6H), 2.40-3.50 (m, 6H), 6.94 (s, N-H), 7.52 (s, 3H), 8.50 (s, 2H), 9.08-9.38 (d, 2H).

Example 95

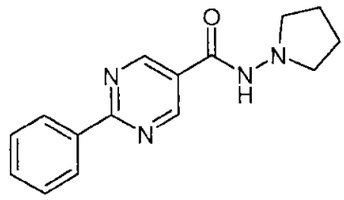
4-Methyl-2-phenyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide



Following procedures similar to those of Example 64 but substituting 4-methyl-2-phenyl-pyrimidine-5-carboxylic acid chloride for 2-phenyl-4-yl-pyrimidine-5-carboxylic acid, and substituting 2,3-dihydro-indol-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared there is prepared 4-methyl-2-phenyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide (80%) as a solid. MS: 331 (M+H); ^1H NMR (300 MHz, $CDCl_3$): δ 2.69 (s, 3H), 2.74-3.10 (m, 2H), 3.64 (t, 2H), 6.58-6.97 (m, 2H), 7.03-7.30 (m, 2H), 7.49 (s, 3H), 7.96 (s, N-H), 8.44 (s, 2H), 8.72 (d, 2H). IC_{50} = 5.5 nM.

Example 96

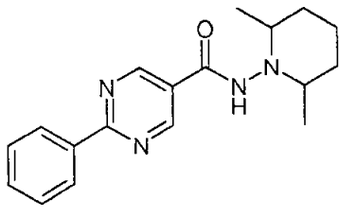
2-Phenyl-pyrimidine-5-carboxylic acid pyrrolidin-1-yl-amide



Following procedures similar to those of Example 64 but substituting pyrrolidin-1-ylamine hydrochloride for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid pyrrolidin-1-yl-amide (67%) as a solid. MS: 269 (M+H); ^1H NMR (300 MHz, $CDCl_3$): δ 1.70-2.20 (m, 4H), 2.70-3.46 (m, 4H), 7.55 (s, 3H), 8.42-8.67(m, 2H), 9.14-9.49(t, 2H).

Example 97

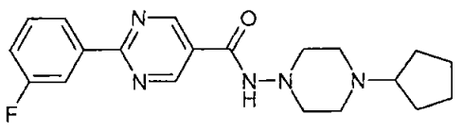
2-Phenyl-pyrimidine-5-carboxylic acid (2,6-dimethyl-piperadin-1-yl)-amide



Following procedures similar to those of Example 64 but substituting 2,6-dimethyl-piperadin-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (2,6-dimethyl-piperadin-1-yl)-amide (69%) as a solid. MS: 311 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95-1.24 (m, 6H), 1.24-1.87 (m, 6H), 1.88-3.60 (m, 2H), 6.35 (br, N-H), 7.53 (s, 3H), 8.52 (s, 2H), 9.10-9.73 (m, 2H).

Example 98

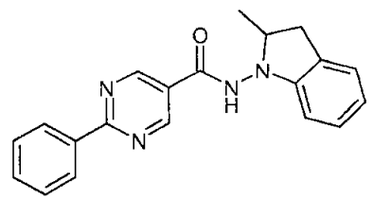
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (4-cyclopentyl-piperazin-1-yl)-amide



Following procedures similar to those of Example 64 but using substituting 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid for 2-phenyl-4-yl-pyrimidine-5-carboxylic acid, and substituting 4-cyclopentyl-piperazin-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (4-cyclopentyl-piperazin-1-yl-amide (64%) as a solid. MS: 370 (M+H).

Example 99

2-Phenyl-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide

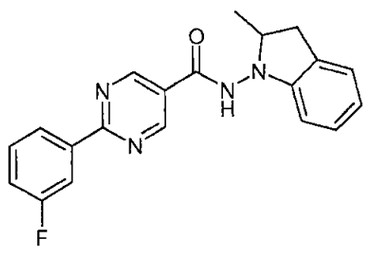


Following procedures similar to those of Example 64 but substituting 2-methyl-2,3-dihydro-indol-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide (32%) as a solid. MS: 331 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (m,

3H), 2.50-2.79 (m, H), 3.03-3.24 (m, H), 3.40-3.58 (m, 0.5H), 3.92 (br, 0.5H), 6.67 (d, 0.5N-H), 6.77-7.33 (m, 4H), 7.51 (m, 3H), 7.98 (s, 0.5N-H), 8.52 (m, 2H), 9.23 (d, 2H). $IC_{50} = 4$ nM.

Example 100

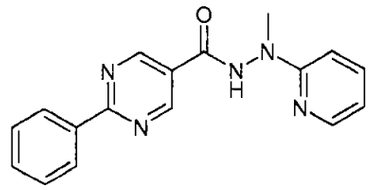
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide



Following procedures similar to those of Example 64 but substituting 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid for 2-phenyl-4-yl-pyrimidine-5-carboxylic acid, and substituting 2-methyl-2,3-dihydro-indol-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide (31%) as a solid. MS: 349 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00-1.48 (m, 3H), 2.43-2.78 (m, 2H), 3.32-4.06 (m, H), 6.50-6.93 (m, 1.5H), 6.93-7.34 (m, 4H), 7.34-7.54 (d, H), 8.05-8.32 (m, 2H), 8.56 (s, 0.5N-H), 9.17 (d, 2H). $IC_{50} = 4$ nM.

Example 101

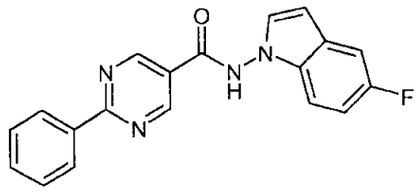
2-Phenyl-pyrimidine-5-carboxylic acid N'-methyl-N'-pyridin-2-yl-hydrazide



Following procedures similar to those of Example 64 but substituting N'-methyl-N'-pyridin-2-yl-hydrazine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid N'-methyl-N'-pyridin-2-yl-hydrazide (31%) as a solid. MS: 306 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.48 (s, 3H), 6.88 (m, 2H), 7.40-7.70 (m, 4H), 8.23 (s, H), 8.52 (m, 2H), 9.13 (br, N-H), 9.28 (s, 2H).

Example 102

2-Phenyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide

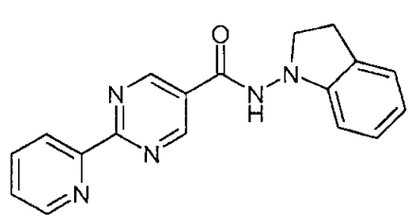


Step 1: A solution of 5-fluoro-1H-indole (16.9 mmol) and potassium tert-butoxide (33.8 mmol) in DMF (76 mL) is stirred at rt under N_2 for 2 h. 0.15 M NH_2Cl.in ether (169.2 mL) is added drop-wise for 15 minutes at rt. The reaction mixture is stirred at rt for 2 h, then quenched with 10 % $Na_2S_2O_3$ aqueous solution and extracted with ether. The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 60-80% EtOAc in heptane to afford 5-fluoro-indole-1-ylamine (751 mg, 30%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80 (br, 2N-H), 6.38 (d, H), 7.00 (m, H), 7.19-7.43 (m, 3H).

Step 2: Diethyl-iso-propylamine (2.30 mmol) is added to a stirred solution of 2-phenyl-pyrimidine-5-carboxylic acid chloride (1.15 mmol) and 5-fluor-indol-1-ylamine (1.15 mmol) in DCM (20 mL) at rt. The reaction mixture is stirred at rt overnight and concentrated *in vacuo*. The residue is dissolved in EtOAc (30 mL), then washed with 5% HCl (10 mL), water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10-40% EtOAc in heptane to afford 2-phenyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide (185 mg, 49%) as a solid. MS: 333 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (s, H) 7.02 (m, H), 7.10-7.38 (m, 4H), 7.55 (s, 3H), 8.53 (s, 2H), 8.70-9.40 (br, 2H). IC_{50} = 3 nM.

Example 103

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide

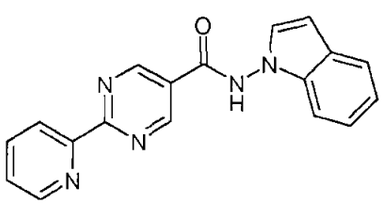


Following procedures similar to those of Example 64 but substituting 2-pyridin-2-yl-pyrimidine-5-carboxylic acid for 2-phenyl-4-yl-pyrimidine-5-carboxylic acid, and substituting

2,3-dihydro-indol-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide (98%) as a solid. MS: 318 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.85-3.20 (m, 2H), 3.77 (t, 2H), 6.76 (d, 0.5N-H), 6.82-7.49 (m, 4H), 7.46 (d, H), 7.89 (d, H), 8.07 (br, 0.5N-H), 8.57 (m, H), 8.84 (d, H), 9.30 (s, 2H). IC_{50} = 3 nM.

Example 104

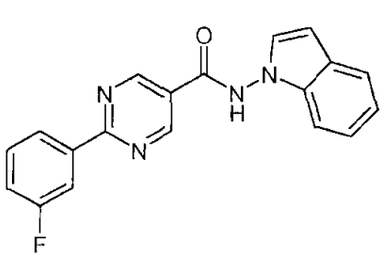
2-Pyridin-2-yl-pyrimidine-5-carboxylic acid indol-1-yl-amide



A suspended solution of 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide (0.28 mmol) and MnO2 (1.42 mmol) in DCM (8 mL) is stirred at rt for 2 h. The reaction mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-5% methanol in DCM to afford 2-pyridin-2-yl-pyrimidine-5-carboxylic acid indol-1-yl-amide (45 mg, 50%) as a solid. MS: 316 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48 (s, H), 6.72-7.48 (m, 5H), 7.56 (s, H), 7.88 (s, H), 8.52 (br, 2H), 9.08 (br, 2H), 11.56 (br, N-H). IC_{50} = 4.5 nM.

Example 105

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid indol-1-yl-amide

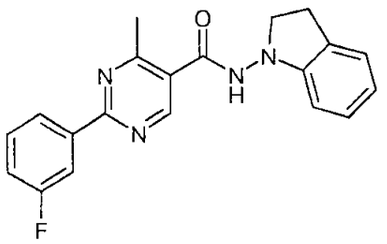


A suspended solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide (0.39 mmol) and MnO2 (1.95 mmol) in DCM (10 mL) is stirred at rt for 40 min. The reaction mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-40% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic indol-1-yl-amide (70 mg, 54%) as a solid. MS: 333

(M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60 (s, H), 7.10 (d, H), 7.14-7.46 (m, 4H), 7.50 (br, H), 7.64 (d, H), 8.37 (d, 2H), 8.60-9.40 (br, 3H). IC_{50} = 5 nM.

Example 106

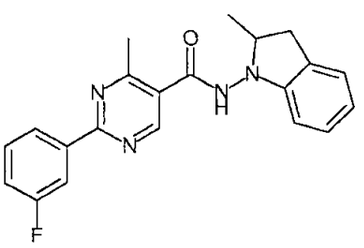
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide



Following procedures similar to those of Example 64 but substituting 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid for 2-phenyl-4-yl-pyrimidine-5-carboxylic acid, and substituting 2,3-dihydro-indol-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide (91%) as a solid. MS: 349 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.77-3.08 (m, 2H), 3.09-3.80 (m, 2H), 6.75-7.00 (m, 2H), 7.04-7.32 (m, 3H), 7.44 (q, H), 8.06-8.31 (m, 2H), 8.51 (d, 2H). IC_{50} = 23 nM.

Example 107

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide

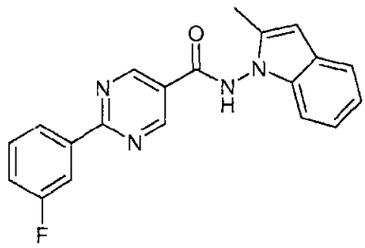


Following procedures similar to those of Example 64 but substituting 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid for 2-phenyl-4-yl-pyrimidine-5-carboxylic acid, and substituting 2-methyl-2,3-dihydro-indol-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide (94%) as a solid. MS: 363 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00-1.50 (d, 3H), 2.30-2.80 (m, 4H),

3.01 (m, H), 3.26-3.96 (m, H), 6.45-7.00 (m, 2H), 7.00-7.30 (m, 3H), 7.41 (q, H), 7.97-8.28 (m, 2H), 8.68 (d, H).

Example 108

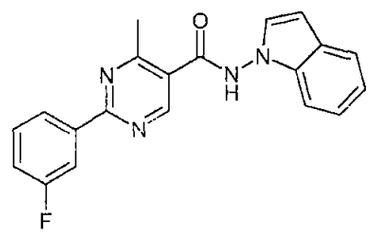
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (2-methyl-indol-1-yl)-amide



A suspended solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide (0.98 mmol) and MnO2 (4.88 mmol) in DCM (15 mL) is stirred at rt for 2 h. The reaction mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-40% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (2-methyl- indol-1-yl)-amide (230 mg, 97%) as a solid. MS: 347 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08-2.40 (m, 3H), 6.27 (s, H), 6.95-7.35 (m, 4H), 7.36-7.65 (m, 2H), 8.20-8.44 (m, 2H), 8.49-9.20 (d, 2H). IC_{50} = 6 nM.

Example 109

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid indol-1-ylamide

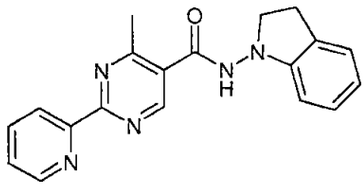


A suspended solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide (0.72 mmol) and MnO2 (3.60 mmol) in DCM (10 mL) is stirred at rt for 40 min. The reaction mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-40% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid indol-1-ylamide (185 mg, 75%) as a solid. MS: 347 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.73 (s, 3H), 6.53 (s, H),

7.03 (d, H), 7.08-7.36 (m, 4H), 7.37-7.75 (m, 2H), 8.04-8.40 (m, 2H), 8.56 (br, H), 8.81 (br, H). IC_{50} = 10 nM.

Example 110

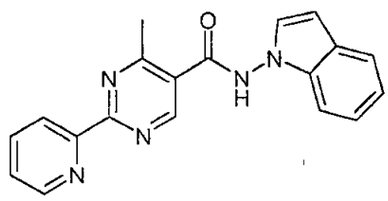
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide



Following procedures similar to those of Example 64 but substituting 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid for 2-phenyl-4-yl-pyrimidine-5-carboxylic acid, and substituting 2,3-dihydro-indol-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide (96%) as a solid. MS: 332 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.78 (s, 3H), 3.09 (t, 2H), 3.77 (t, 2H), 6.70-7.01 (m, 2H), 7.09-7.23 (m, 2H), 7.36-7.46 (m, H), 7.85 (t, H), 8.43-8.64 (m, 2H), 8.80 (d, H). IC_{50} = 3 nM.

Example 111

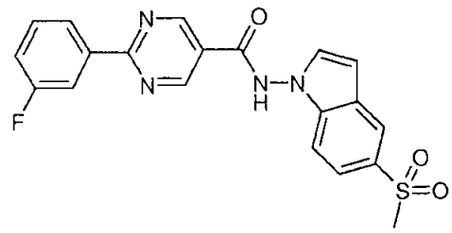
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid indol-1-ylamide



A suspended solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide (1.00 mmol) and MnO2 (5.00 mmol) in DCM (10 mL) is stirred at rt for 60 min. The reaction mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-5% methanol in DCM to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid indol-1-ylamide (196 mg, 60%) as a solid. MS: 330 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.77 (s, 3H), 6.58 (s, H), 7.15 (s, 2H), 7.26 (m, 3H), 7.84 (d, H), 8.44 (s, 2H), 8.73 (s, H), 10.94 (br, N-H). IC_{50} = 5 nM.

Example 112

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide



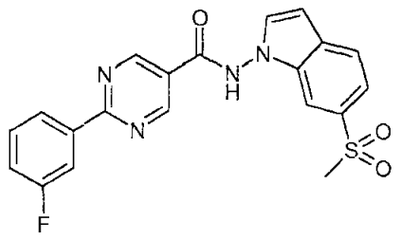
Step 1: A solution of 5-methanesulfonyl-indoline (4.11 mmol) and MnO2 (20.55 mmol) in DCM (20 mL) is stirred at rt overnight. The reaction mixture is filtered and the filtrate is concentrated *in vacuo* to afford 5-methanesulfonyl-1H-indole (782 mg, 100%) as a solid. MS: 196 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (s, 3H), 6.71 (s, H), 7.39 (s, H), 7.53 (d, H), 7.74 (m, H), 8.30 (s, H), 8.66 (br, N-H).

Step 2: A solution of 5-methanesulfonyl-1H-indole (4.1 mmol) and potassium tert-butoxide (8.2 mmol) in DMF (20 mL) is stirred at rt under N_2 for 2 h. 0.15 M NH_2Cl in ether (41 mL) is added drop-wise for 15 min at rt and the reaction mixture is stirred at rt for 2 h. The reaction mixture is quenched with 10 % $Na_2S_2O_3$ aqueous solution, and extracted with ether (3x40 mL). The combined orgaic layer is washed with water (2x30 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with EtOAc and heptane to afford 5-methanesulfonyl-indole-1-ylamine (230 mg, 32%) as a solid. MS: 211 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.08 (s, 3H), 4.94 (br, 2N-H), 6.55 (d, H), 7.34 (m, H), 7.57 (d, H), 7.73 (m, H), 8.21 (m, H).

Step 3: A solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid chloride (0.62 mmol) in EtOAc (10 mL) is added to a stirred solution of 5-methanesulfonyl-indole-1-ylamine (0.62 mmol) and K_2CO_3 (3.08 mmol) in EtOAc (10 mL) and H_2O (10 mL) at 0°C, and the reaction mixture is warmed to rt and stirred overnight. EtOAc is evaporated *in vacuo*, and the resulting solid is collected by filtration. The solid is triturated with DCM to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide (85 mg, 34%) as a solid. MS: 411 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 3.13 (s, 3H), 6.81 (m, H) 7.25-7.39 (m, H), 7.49-7.67 (m, 3H), 7.72-7.84 (m, H), 8.21-8.32 (m, 2H), 8.39 (d, H), 9.41 (s, 2H).

Example 113

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-methanesulfonyl-indol-1-yl)-amide

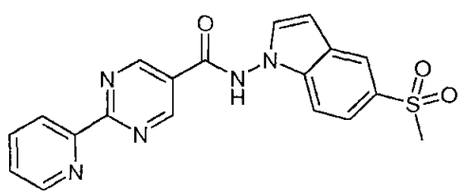


Step 1: A solution of 6-methanesulfonyl-1H-indole (2.66 mmol) and potassium tert-butoxide (5.32 mmol) in DMF (15 mL) is stirred at rt under N_2 for 2 h. 0.15 M NH_2Cl in ether (26.6 mL) is added drop-wise for 15 minutes at rt and the reaction mixture is stirred at rt for 2 h. The reaction mixture is quenched with 10 % $Na_2S_2O_3$ aqueous solution, and extracted with ether (3x20 mL). The combined orgaic layer is washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is triturated with EtOAc to give 6-methanesulfonyl-indole-1-ylamine (270 mg, 51%) as a solid. MS: 211 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (s, 3H), 6.49 (d, H), 7.41 (m, H), 7.61 (d, H), 7.71 (d, H), 8.12 (s, H).

Step 2: A solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid chloride (0.65 mmol) in EtOAc (15 mL) is added to a stirred solution of 5-methanesulfonyl-indole-1-ylamine (0.65 mmol) and potassium carbonate (2.60 mmol) in EtOAc (10 mL) and H_2O (10 mL) at 0°C, and the reaction mixture is warmed to rt and stirred overnight. EtOAc is evaporated *in vacuo*, and the resulting solid is collected by filtration, and purified by silica gel chromatography eluting with 20-60% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-methanesulfonyl-indol-1-yl)-amide (85 mg, 33%) as a solid. MS: 411 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.08 (s, 3H), 6.62 (d, H) 7.33-7.44 (m, 2H), 7.46-7.59 (m, 2H), 7.75 (s, H), 8.29 (d, 2H), 8.39 (d, H), 9.42 (s, 2H), 10.80 (br, H). IC_{50} = 8 nM.

Example 114

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide

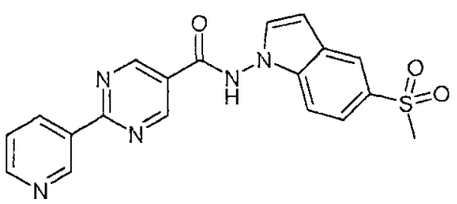


Diethyl-iso-propylamine (3.54 mmol) is added a solution of 2-pyridin-2-yl-pyrimidine-5-carboxylic acid HCl (1.18 mmol), 5-methanesulfonyl-indol-1-ylamine (1.18 mmol) and TBTU (1.77 mmol) in anhydrous DMF (16 mL) at rt. The reaction mixture is stirred at 90°C

overnight and then concentrated *in vacuo*. The residue is dissolved in EtOAc (50 mL) and water (50 mL). The organic layer is separated, washed with water (2x20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is triturated with EtOAc and DCM to affrod 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide (125 mg, 27%) as a solid. MS: 394 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 3.14 (s, 3H), 6.82 (m, H) 7.50-7.72 (m, 3H), 7.80 (m, H), 8.07 (m, H), 8.30 (m, 2H), 8.70(d, H), 8.80 (s, H), 9.51 (s, 2H).

Example 115

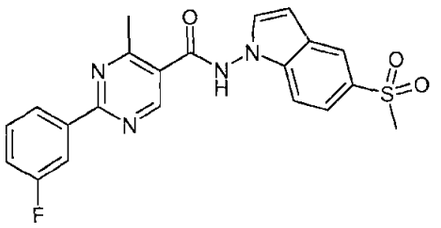
2-Pyridin-3-yl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide



Diethyl-iso-propylamine (3.84 mmol) is added a solution of 2-pyridin-2-yl-pyrimidine-5-carboxylic acid hydrochloride(1.28 mmol), 5-methanesulfonyl-indol-1-ylamine (1.28 mmol) and TBTU (1.92 mmol) in anhydrous DMF (16 mL) at rt. The reaction mixture is stirred at 90°C overnight and then concentrated *in vacuo*. The residue is dissolved in EtOAc (60 mL), and washed with water (2x30 mL) and brine (20 mL), The organic layer is separated, washed with water (2x20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-5% MeOH in DCM to afford 2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide (125 mg, 25%) as a solid. MS: 394 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.10 (s, 3H), 6.61 (m, H) 6.98 (m, H), 7.34 (s, H), 7.51 (m, H), 7.91 (s, H), 8.83 (m, 2H), 9.49 (s, H), 9.77 (s, H), 10.10 (s, N-H).

Example 116

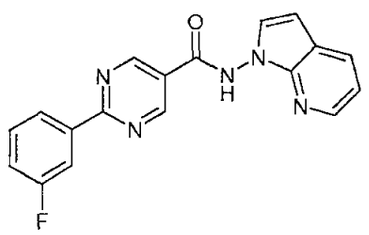
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide



2.0 M of NaHMDS (sodium bis(trimethylsilyl)amide) in THF is added to a stirred solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid chloride (0.72 mmol) and 5-methanesulfonyl-indol-1-ylamine (0.72 mmol) and in anhydrous pyridine (10 mL) at rt. The reaction mixture is stirred at 90°C overnight and then concentrated *in vacuo*. The residue is purified ny silica gel chromatography eluting with 1.5% MeOH in DCM to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide (50 mg, 8%) as a solid. MS: 425 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.86 (s, 3H), 3.02 (s, 3H), 6.55 (s, H) 6.92 (d, H), 7.17-7.38 (m, 3H), 7.53 (m, H), 7.78 (s, H), 8.27 (d, H), 8.38 (d, H), 9.16 (s, H).

Example 117

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide

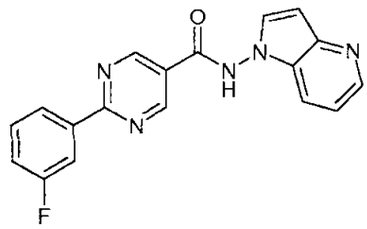


Step 1: A solution of pyrrolo[2,3-b]pyridine (16.9 mmol) and potassium tert-butoxide (33.8 mmol) in DMF (76 mL) is stirred at rt under N_2 for 2 h. 0.15 M NH_2Cl in ether (169.2 mL) is added drop-wise at rt and the reaction mixture is stirred at rt for 2 h. The reaction mixture is quenched with 5 % $Na_2S_2O_3$ aqueous solution (100 mL), and extracted with ether for three times. The combined organic layer is washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 60-80% EtOAc in heptane to afford pyrrolo[2,3-b]pyridin-1-ylamine (703 mg, 31%) as a solid. MS: 134 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.04 (br, 2N-H), 6.35 (d, H), 7.09 (m, H), 7.35 (m, H), 7.91 (m, H), 8.34 (d, H).

Step 2: A solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid chloride (1.13 mmol) in EtOAc (20 mL) is added to a stirred solution of pyrrolo[2,3-b]pyridin-1-ylamine (1.13 mmol) and K_2CO_3 (1.13 mmol) in EtOAc (10 mL) and H_2O (20 mL) at rt and the reaction mixture is stirred at rt overnight. EtOAc is evaporated *in vacuo*, and the resulting solid is collected by filtration to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide (305 mg, 81%) as a solid. MS: 334 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57 (d, H) 7.13-7.55 (m, 4H), 7.99 (m, H), 8.10-8.40 (m, 3H), 9.27 (s, 2H), 12.57 (br, N-H).

Example 118

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide



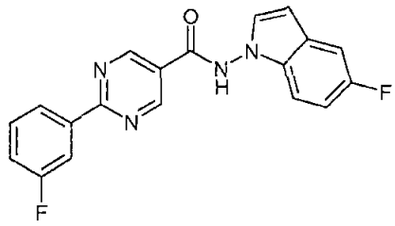
Step 1: A solution of pyrrolo[3,2-b]pyridine (1.64 mmol) and potassium tert-butoxide (3.29 mmol) in DMF (7.3 mL) is stirred at rt under N_2 for 2 h. 0.15 M NH_2Cl in ether (16.3 mL) is added drop-wise at rt and the reaction mixture is stirred at rt for 3 h. The reaction mixture is quenched with 5 % $Na_2S_2O_3$ aqueous solution (10 mL), and extracted with ether. The combined organic layer is washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with EtOAc to afford pyrrolo[3,2-b]pyridin-1-ylamine (136 mg, 62%) as a solid. MS: 134 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.89 (br, 2N-H), 6.61 (d, H), 7.16 (m, H), 7.38 (d, H), 7.76 (d, H), 8.47 (d, H).

Step 2: A solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid chloride (0.45 mmol) in EtOAc (8 mL) is added to a stirred solution of pyrrolo[3,2-b]pyridin-1-ylamine (0.45 mmol) and K_2CO_3 (0.45 mmol) in EtOAc (4 mL) and H_2O (8 mL) at rt, and the reaction mixture is stirred at rt for 30 min. EtOAc is evaporated *in vacuo*, and the resulting solid is collected by filtration to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide (116 mg, 77%) as a solid. MS: 334 (M+H); ^{1}H NMR (300 MHz,

$CDCl_3$): δ 6.60 (d, H) 7.15-7.60 (m, 4H), 8.01 (m, H), 8.10-8.41 (m, 3H), 9.27 (s, 2H), 12.45 (br, N-H). IC_{50} = 18 nM.

Example 119

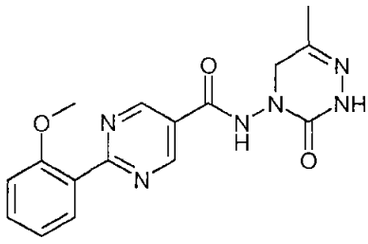
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide



A solution of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid chloride (1 mmol) in EtOAc (20 mL) is added to a stirred solution of 5-fluoro-indol-1-ylamine (1 mmol) and potassium carbonate (1 mmol) in EtOAc (10 mL) and H_2O (20 mL) at rt and the reaction mixture is stirred at rt overnight. EtOAc is evaporated *in vacuo*, and the resulting solid is collected by filtration to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide (148 mg, 42%) as a solid. MS: 351 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (m, H) 7.02 (m, H), 7.12-7.34 (m, 3H), 7.51 (m, H), 8.24 (d, H), 8.34 (s, H), 8.92 (br, H), 9.24 (br, 2H).

Example 120

2-(2-Methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide



Step 1: Following the procedures similar to those of Example 59, step 1, but substituting 2-methoxyphenylboronic acid for 3-methoxyphenylboronic acid, there is prepared 2-(2-methoxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester.

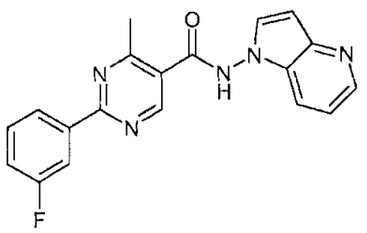
Step 2: Following the procedures similar to those of Example 59, step 2, but substituting 2-(2-methoxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester for 2-(3-methoxy-phenyl)-

pyrimidine-5-carboxylic acid methyl ester, there is prepared 2-(2-methoxy-phenyl)-pyrimidine-5-carboxylic acid.

Step 3: Following the procedures similar to those of Example 59, step 3, but substituting 2-(2-methoxy-phenyl)-pyrimidine-5-carboxylic acid for 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid, there is prepared 2-(2-methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide. MS: 341 (M+H); ^{1}H NMR (DMSO-d_6): δ 1.91 (s, 3H), 3.79 (s, 2H), 4.22 (s, 2H), 7.09 (m, 1H), 7.19 (d, J = 8.2 Hz, 1H), 7.52 (m, 1H), 7.65 (m, 1H), 9.24 (s, 2H), 9.96 (s, 1H), 11.06 (s, 1H). IC_{50} = 199 nM.

Example 121

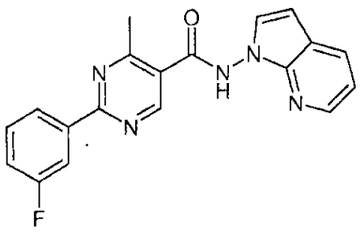
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide



A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid chloride (0.45 mmol) in EtOAc (8 mL) is added to a stirred solution of pyrrolo[3,2-b]pyridin-1-ylamine (0.45 mmol) and potassium carbonate (0.45 mmol) in EtOAc (4 mL) and H_2O(8 mL) at rt and the reaction mixture is stirred at rt overnight. EtOAc is evaporated *in vacuo*, and the resulting solid is collected by filtration. The solid is purified by silica gel chromatography eluting with 20-80% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide (38 mg, 24%) as a solid. MS: 348 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.76 (s, 3H), 6.59 (m, H) 7.07-7.64 (m, 4H), 7.96 (m, H), 8.23 (m, H), 8.32 (m, 2H), 9.12 (s, H), 10.01 (br, N-H).

Example 122

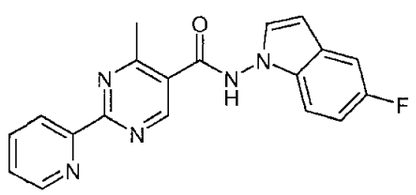
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide



A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid chloride (1 mmol) in EtOAc (10 mL) is added to a stirred solution of pyrrolo[2,3-b]pyridin-1-ylamine (1 mmol) and K_2CO_3 (1 mmol) in EtOAc (20 mL) and H_2O (20 mL) at rt, then stirred at rt overnight. EtOAc is evaporated *in vacuo*, and the resulting solid is collected by filtration. The solid is purified by silica gel chromatography eluting with 20-80% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide (162 mg, 47%) as a solid. MS: 348 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.78 (s, 3H), 6.59 (m, H) 7.09-7.58 (m, 4H), 7.96 (m, H), 8.22 (m, H), 8.31 (d, 2H), 9.14 (s, 2H). IC_{50} = 12 nM.

Example 123

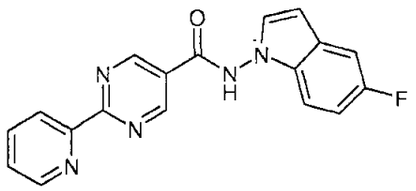
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide



A solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid chloride (1 mmol) in EtOAc (20 mL) is added to a stirred solution of 5-fluoro-indol-1-ylamine (1.20 mmol) and K_2CO_3 (2 mmol) in EtOAc (10 mL) and H_2O (20 mL) at rt, and the reaction mixture is stirred at rt overnight. The reaction mixture is extracted with EtOAc. The organic layer is washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-10% MeOH in DCM to give a solid. The solid is triturated with EtOAc/heptane to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide (122 mg, 35%) as a solid. MS: 348 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.77 (s, 3H), 6.55 (m, H) 7.06 (m, H), 7.32-7.66 (m, 4H), 8.02 (m, H), 8.45 (d, H), 8.79 (s, H), 9.26 (s, H), 12.00 (s, N-H). IC_{50} = 17 nM.

Example 124

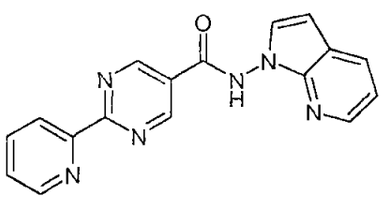
2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide



A solution of 2-pyridin-2-yl-pyrimidine-5-carboxylic acid chloride (1 mmol) in EtOAc (20 mL) is added to a stirred solution of 5-fluoro-indol-1-ylamine (1 mmol) and K_2CO_3 (2 mmol) in EtOAc (10 mL) and H_2O (20 mL) at rt, and the reaction mixture is stirred at rt overnight. EtOAc is evaporated *in vacuo*, and the resulting solid is collected by filtration. The solid is purified by silica gel chromatography eluting with0-10% MeOH in DCM to afford 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide (65 mg, 20%) as a solid. MS: 334 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 6.56 (m, H) 7.04 (m, H), 7.28-7.79 (m, 3H), 8.04 (m, H), 8.49 (m, H), 8.81 (m, H), 9.48 (s, 2H), 12.22 (s, N-H). IC_{50} = 18 nM.

Example 125

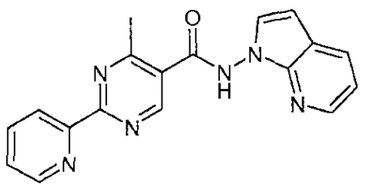
2-Pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridine-1-ylamide



Diethyl-iso-propylamine (1.13 mmol) is added a solution of 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (0.75 mmol), pyrrolo[2,3-b]pyridine-1-ylamine (0.75 mmol) and TBTU in anhydrous DMF (7 mL) at rt, and the reaction mixture is stirred at 80°C overnight. The reaction mixture is concentrated *in vacuo*. The residue is dissolved in EtOAc, washed with water twice, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% MeOH in DCM to give a crude product. The product is crystallized from EtOAc to afford 2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridine-1-ylamide (78 mg, 25%) as a solid. MS: 317 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 6.56 (m, H) 7.24 (m, H), 7.53 (m, H), 7.61 (m, H), 8.01-8.17 (m, 2H), 8.27 (d, H), 8.69 (m, H), 8.78(m, H), 9.51 (s, 2H).

Example 126

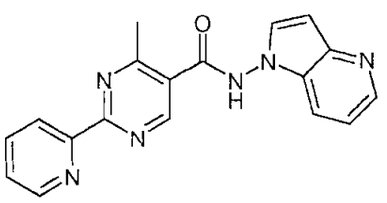
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide



Diethyl-iso-propylamine (1.13 mmol) is added a solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (0.75 mmol), pyrrolo[2,3-b]pyridine-1-ylamine (0.75 mmol) and TBTU (0.9 mmol) in anhydrous DMF (7 mL) at rt, and the reaction mixture is stirred at 80°C overnight. The reaction mixture is concentrated in vacuo. The residue is dissolved in EtOAc, washed with saturated aqueous Na_2CO_3 and water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% CH_3CN in DCM to give a crude product. The crude product is crystallized from EtOAc to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrol[2,3-b]pyridine-1-ylamide (95 mg, 38%) as a solid. MS: 331 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.89 (s, 3H), 6.65 (d, H), 7.23 (m, H), 7.48-7.66 (m, 2H), 8.01-8.15 (m, 2H), 8.29 (m, H), 8.64 (d, H), 8.77 (d, H), 9.33 (s, 2H).

Example 127

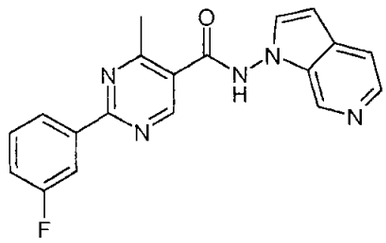
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide



Diethyl-iso-propylamine (1.88 mmol) is added a solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (0.75 mmol), pyrrolo[3,2-b]pyridine-1-ylamine (0.75 mmol) and TBTU (0.9 mmol) in anhydrous DMF (7 mL) at rt, and the reaction mixture is stirred at 80°C for 8 h. The reaction mixture is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-10% MeOH in DCM to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrol[3,2-b]pyridine-1-ylamide (155 mg, 63%) as a solid. MS: 331 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.89 (s, 3H), 7.01 (d, H), 7.64-7.77 (m, 2H), 8.15 (m, H), 8.25 (m, H), 8.59-8.76 (m, 3H), 8.82 (d, H), 9.31 (s, 2H). IC_{50} = 13 nM.

Example 128

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide

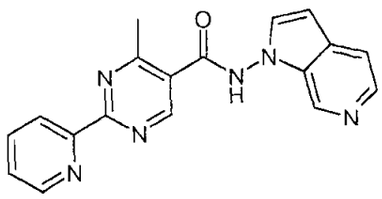


Step 1: A solution of pyrrolo[2,3-c]pyridine (8.47 mmol) and potassium tert-butoxide (16.9 mmol) in DMF (38 mL) is stirred at rt under N_2 for 2 h. 0.15 M NH_2Cl in ether (84.6 mL) is added drop-wise at rt, and the reaction mixture is stirring at rt for 2 h., quenched with 5 % $Na_2S_2O_3$ aqueous solution (10 mL), and extracted with ether. The organic layer is separated, washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-10% MeOH in DCM to afford pyrrolo[2,3-c]pyridin-1-ylamine (226 mg, 11%) as a solid. MS: 134 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.96 (br, 2N-H), 6.43 (d, H), 7.29 (m, H), 7.50 (d, H), 8.29 (d, H), 8.89 (s, H).

Step 2: Diethyl-iso-propylamine (1.13 mmol) is added a solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (0.75 mmol), pyrrolo[2,3-c]pyridine-1-ylamine (0.75 mmol) and TBTU (0.9 mmol) in anhydrous DMF (7 mL) at rt, and the reaction mixture is stirred at 80°C overnight. Water is added and the mixture is extracted with EtOAc. The organic layer is separated, washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 40-100% MeOH in DCM to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide (117 mg, 45%) as a solid. MS: 348 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.84 (s, 3H), 6.72 (d, H), 7.29 (m, H), 7.55 (m, H), 7.71 (m, H), 8.14-8.29 (m, 2H), 8.36 (d, 3), 8.75 (s, H), 9.17 (s, H). IC_{50} = 28.5 nM.

Example 129

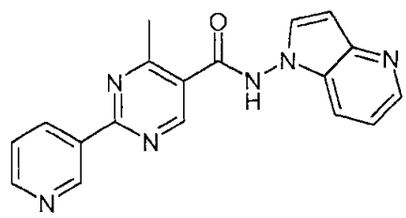
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide



Following procedures similar to those of Example 127 but substituting pyrrolo[2,3-c]pyridine-1-ylamine for pyrrolo[3,2-b]pyridine-1-ylamine, there is prepared 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrol[2,3-c]pyridine-1-ylamide (46%) as a solid. MS: 331 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.79 (s, 3H), 6.64 (d, H), 7.53-7.65 (m, 2H), 7.78 (d, H), 8.02 (m, H), 8.22 (m, H), 8.46 (m, H), 8.80 (d, H), 8.87 (s, H), 9.30 (s, H).

Example 130

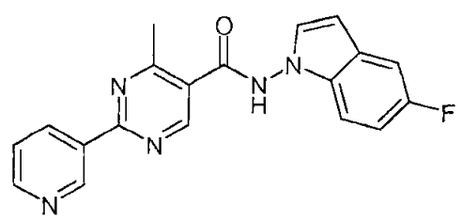
4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide



Following procedures similar to those of Example 127 but substituting 4-methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid for 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid, there is prepared 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridine-1-ylamide (40%) as a solid. MS: 331 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.86 (s, 3H), 6.74 (m, H), 7.31 (m, H), 7.61 (m, H), 7.71 (d, H), 7.92 (d, H), 8.41 (d, H), 8.71 (d, H), 8.91 (d, H), 9.20 (s, H), 9.64 (s, H). IC_{50} = 14 nM.

Example 131

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide

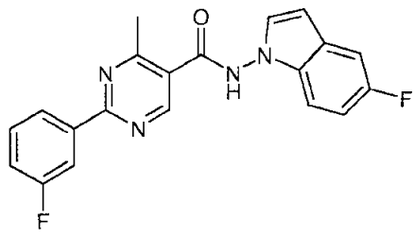


Following procedures similar to those of Example 127 but substituting 4-methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid for 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid,

and substituting 5-fluoro-indol-1-ylamine for pyrrolo[3,2-b]pyridine-1-ylamine, there is prepared 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide (34%) as a solid. MS: 348 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.85 (s, 3H), 6.57 (m, H), 7.02 (m, H), 7.23-7.46 (m, 2H), 7.62 (m, H), 8.70 (d, H), 8.91 (d, H), 9.17 (s, H), 9.63 (s, H).

Example 132

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide

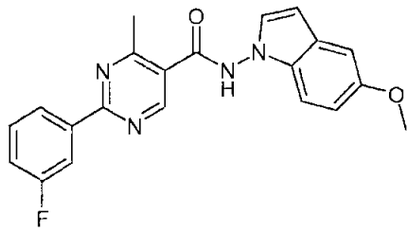


Method A: Following procedures similar to those of Example 127 but substituting 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid for 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid, and substituting 5-fluoro-indol-1-ylamine for pyrrolo[3,2-b]pyridine-1-ylamine, there is prepared 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide (17%) as a solid. MS: 365 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 6.56 (d, H), 7.02 (m, H), 7.22-7.44 (m, 4H), 7.55 (m, H), 8.22 (d, H), 8.36 (d, H), 9.13 (s, H).

Method B: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid chloride (1 mmol) in EtOAc (20 mL) is added to a stirred solution of 5-fluoro-indol-1-ylamine (1 mmol) and K_2CO_3 (1 mmol) in EtOAc (10 mL) and H_2O (20 mL) at rt, then stirred at rt overnight. EtOAc is evaporated *in vacuo*, and the resulting solid is collected by filtration. The solid is crystallized from EtOAc/heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide (62 mg, 17%) as a solid. MS: 365 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.82 (s, H), 6.55 (s, H) 6.90-7.41 (m, 4H), 7.49 (m, H), 8.26 (d, 2H), 8.57 (br, H), 8.96 (br, H). IC_{50} = 19 nM.

Example 133

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-indol-1-yl)-amide

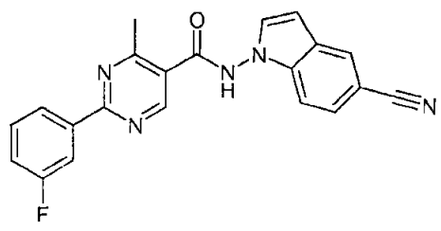


Step 1: A solution of 5-methoxy-1H-indole (16.9 mmol) and potassium tert-butoxide (33.8 mmol) in DMF (76 mL) is stirred at rt under N_2 for 2 h. 0.15 M NH_2Cl in ether (169.2 mL) is added drop-wise for 15 minutes at rt. The reaction mixture is stirred at rt for 2 h, quenched with 5 % $Na_2S_2O_3$ aqueous solution (100 mL), and stirred at rt overnight. The mixture is extracted with ether. The organic layer is separated, washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-20% EtOAc in heptane to afford 5-methoxy-indole-1-ylamine (388 mg, 14%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.78 (br, 2N-H), 6.35 (d, H), 6.94 (d, H), 7.08 (d, H), 7.17 (d, H), 7.30-7.39 (d, H).

Step 2: Following procedures similar to those of Example 127 but substituting2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid for 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid, and substituting 5-methoxy-indol-1-ylamine for pyrrolo[3,2-b]pyridine-1-ylamine, there is prepared 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-indol-1-yl)-amide (43%) as a solid. MS: 377 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.83 (s, 3H), 3.84 (s, 3H), 6.50 (d, H), 6.90 (m, H), 7.12 (d, H), 7.22-7.36 (m, 3H), 7.55 (m, H), 8.22 (d, H), 8.36 (d, H), 9.11 (s, H). IC_{50} = 6 nM.

Example 134

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-cyano-indol-1-yl)-amide



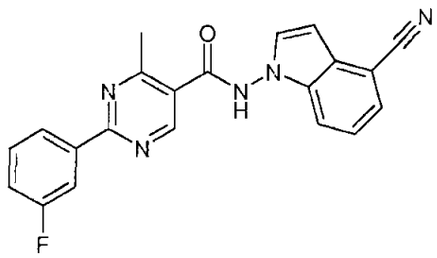
Step 1: NaH (60%, 60 mmol) is potion-wise added to a solution of 5-cyano-1H-indole (20 mmol) in NMP (35 mL), and the reaction mixture is 0°C for 1 h. A solution of HOSA (60 mmol) in NMP (14 mL) is added drop-wise at 0°C. The reaction mixture is warmed to rt and

stirred overnight, then quenched with water and extracted with EtOAc. The organic layer is separated, washed with water three times and with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 20-40% EtOAc in heptane to afford 5-cyano-indole-1-ylamine (531 mg, 16%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.88 (br, 2N-H), 6.53 (d, H), 7.32 (d, H), 7.54 (q, 2H), 7.98 (d, H).

Step 2: Following procedures similar to those of Example 127 but substituting 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid for 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid, and substituting 5-cyano-indol-1-ylamine for pyrrolo[3,2-b]pyridine-1-ylamine, there is prepared 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-cyano-indol-1-yl)-amide (39%) as a solid. MS: 372 (M+H); ^{1}H NMR (300 MHz, DMSO-d^6): δ 2.77 (s, 3H), 6.73 (d, H), 7.45 (m, H), 7.53-7.82 (m, 4H), 8.08-8.23 (m, 2H), 8.32 (d, H), 9.27 (s, H), 12.15 (br, N-H).

Example 135

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (4-cyano-indol-1-yl)-amide



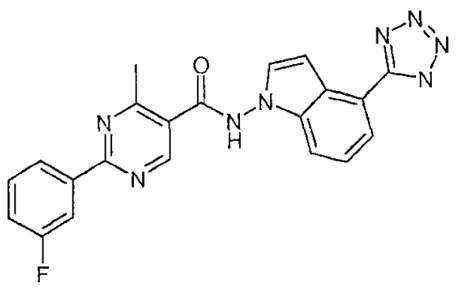
Step 1: Following procedures similar to those of Example 134, step 1, but substituting 4-cyano-1H-indole for 5-cyano-1H-indole, there is prepared 4-cyano-indole-1-ylamine (33%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.1 (br, 2N-H), 6.88 (d, H), 7.22-7.40 (m, 2H), 7.51 (d, H), 7.72 (d, H).

Step 2: Following procedures similar to those of Example 127, but substituting 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid for 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid, and substituting 4-cyano-indol-1-ylamine for pyrrolo[3,2-b]pyridine-1-ylamine, there is prepared 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (4-cyano-indol-1-yl)-amide (29%) as a solid. MS: 372 (M+H); ^{1}H NMR (300 MHz, DMSO-d^6):

δ 2.77 (s, 3H), 6.71 (s, H), 7.32-7.51 (m, 2H), 7.57-7.69 (m, 2H), 7.88 (m, 2H), 8.16 (d, H), 8.31 (d, H), 9.25 (s, H).

Example 136

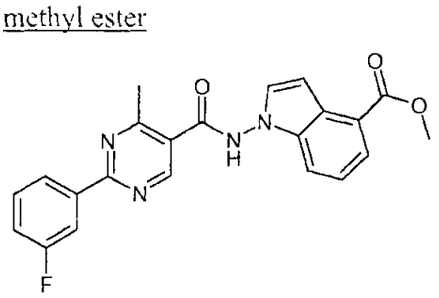
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [4-(1H-tetrazol-5-yl)-indol-1-yl]-amide



A solution of (0.5 mmol), ammonia chloride (6 mmol) and sodium azide(6 mmol) in anhydrous DMF (6 mL) is heated in the microwave at 200°C for 1 h. The reaction mixture is quenched with saturated aqueous Na_2CO_3 solution, and washed with EtOAc. The aqueous layer is separated, acidified with concentrated aqueous HCl to adjust pH to ~ 1, and extracted with EtOAc. The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 3% MeOH in DCM to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [4-(1H-tetrazol-5-yl)-indol-1-yl]-amide (18 mg, 9%) as a solid. MS: 415 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.85 (s, 3H), 7.20-7.35 (m, 2H), 7.44 (m, H), 7.52-7.59 (m, 2H), 7.65 (m, H), 7.77 (d, H), 8.23 (d, H), 8.37 (d, H), 9.18 (s, H).

Example 137

1-{[2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-4-carboxylic acid methyl ester



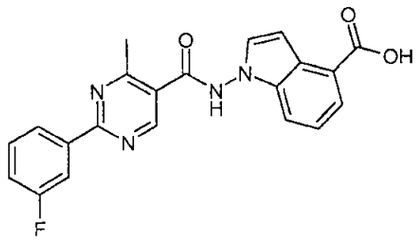
Step 1: Following procedures similar to those of Example 133, step 1, but substituting 1H-indole-4-carboxylic acid methyl ester for 5-methoxy-1H-indole, there is prepared 1-amino-

1H-indole-4-carboxylic acid methyl ester (10%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.88 (br, 2N-H), 7.03 (d, H), 7.33 (m, 2H), 7.49 (d, H), 7.94 (d, H).

Step 2: Following procedures similar to those of Example 127, but substituting 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid for 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid, substituting 1-amino-1H-indole-4-carboxylic acid methyl ester for pyrrolo[3,2-b]pyridine-1-ylamine, and the reaction is stirred at 150°C for 45 minutes, there is prepared 1-{[2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-4-carboxylic acid methyl ester (33%) as a solid. MS: 405 (M+H); ^{1}H NMR (300 MHz, DMSO-d^6): δ 2.77 (s, 3H), 3.92 (s, 3H), 7.44 (m, H), 7.63 (m, H), 7.72 (m, H), 7.76-7.88 (m, 2H), 8.17 (d, H), 8.31 (d, H), 9.26(s, H), 12.06 (br, N-H).

Example 138

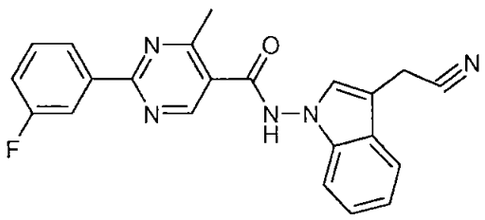
1-{[2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-4-carboxylic acid



A solution of 1-{[2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-4-carboxylic acid methyl ester (0.48 mmol) and LiOH (1.91 mmol) in Methanol/THF/H2O (1:1:1, 6 mL) is stirred at rt overnight. The reaction mixture is diluted with water and washed with DCM. The aqueous layer is separated and acidified with 10% aqueous HCl to adjust pH to ~1. The mixture is extracted with ether twice. The organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 1-{[2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-4-carboxylic acid (186 mg, 99%) as a solid. MS: 391 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.85 (s, 3H), 7.20 (m, H), 7.24-7.40 (m, 2H), 7.46-7.61 (m, 2H), 7.66 (d, H), 7.92 (d, H), 8.23 (d, H), 8.37 (d, H), 9.16 (s, H).

Example 139

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-cyanomethyl-indol-1-yl)-amide

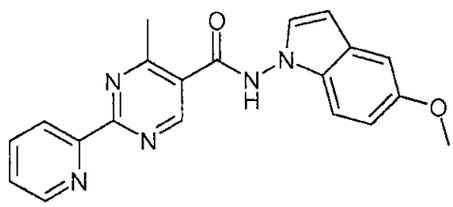


Step 1: Following procedures similar to those of Example 133, step 1, but substituting 1H-indol-3-yl-acetonitrile for 5-methoxy-1H-indole, there is prepared (1-amino-1H-indol-3-yl)-acetonitrile (17%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 2H), 4.80 (br, 2N-H), 7.17-7.25 (m, 2H), 7.33 (t, H), 7.46 (d, H), 7.59 (d, H).

Step 2: Following procedures similar to those of Example 127, but substituting 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid for 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid, substituting 3-cyanomethyl-indol-1-ylamine for pyrrolo[3,2-b]pyridine-1-ylamine, and the reaction is stirred at 150°C for 1 h, there is prepared 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-cyanomethyl-indol-1-yl)-amide (42%) as a solid. MS: 386 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.84 (s, 3H), 4.03 (s, 2H), 7.15-7.48 (m, 5H), 7.55 (m, H), 7.70 (d, H), 8.23 (d, H), 8.37 (d, H), 9.14 (s, H).

Example 140

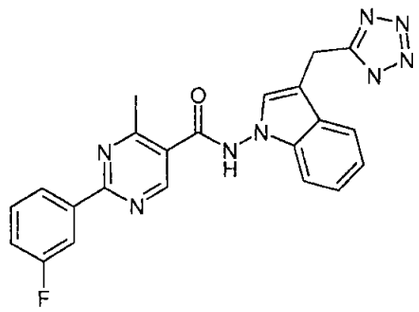
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methoxy-indol-1-yl)-amide



Following procedures similar to those of Example 127, but substituting 5-methoxy-indol-1-ylamine for pyrrolo[3,2-b]pyridine-1-ylamine, and the reaction is stirred at 150°C for 1 h, there is prepared 2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methoxy-indol-1-yl)-amide (22%) as a solid. MS: 360 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.88 (s, 3H), 3.84 (s, 3H), 6.50 (d, H) 6.90 (m, H), 7.13 (d, H), 7.25-7.34 (m, 2H), 7.60 (m, H), 8.05 (m, H), 8.65 (d, H), 8.79 (d, H), 9.20 (s, 2H).

Example 141

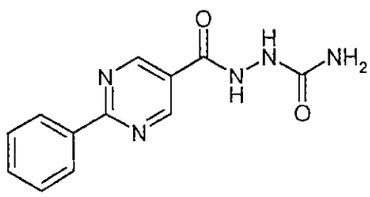
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(1H-tetrazol-5-ylmethyl)-indol-1-yl]-amide



Following procedures similar to those of Example 136, but substituting 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-cyanomethyl-indol-1-yl)-amide for 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (4-cyano-indol-1-yl)-amide, there is prepared 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(1H-tetrazol-5-ylmethyl)-indol-1-yl]-amide (12%) as a solid. MS: 429 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.85 (s, 3H), 4.52 (s, 2H), 7.15 (m, H), 7.24-7.35 (m, 2H), 7.36-7.50 (m, 2H), 7.55 (m, H), 8.23 (d, H), 8.37 (d, H), 9.15 (s, H).

Example 142

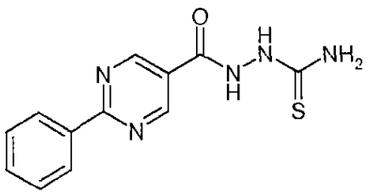
2-(2-Phenyl-pyrimidine-5-carbonyl)-1-hydrazinecarboxamide



Following procedures similar to those of Example 64 but substituting semicarbazide hydrochloride for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-(2-phenyl-pyrimidine-5-carbonyl)-1-hydrozinecarboximide (62%) as a solid. MS: 258 (M+H).

Example 143

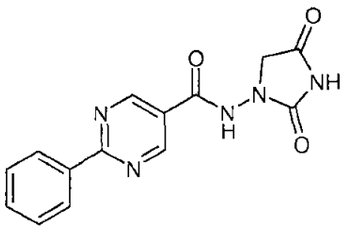
2-(2-Phenyl-pyrimidine-5-carbonyl)-1-hydrazine-1-carbothioamide



Following procedures similar to those of Example 64, but substituting thiosemicarbazide for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-(2-phenyl-pyrimidine-5-carbonyl)-1-hydrozine-1-carbothioamide (27%) as a solid. MS: 274 (M+H).

Example 144

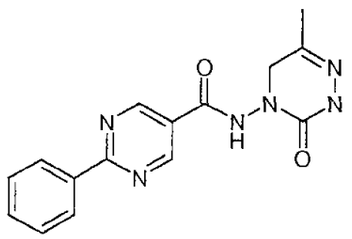
2-Phenyl-pyrimidine-5-carboxylic acid (2,4-dioxo-imidazolidin-1-yl)-amide



Following procedures similar to those of Example 64 but substituting 2,4-dioxo-imidazolidin-1-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (2,4-dioxo-imidazolidin-1-yl)-amide (8%) as a solid. MS: 298 (M+H).

Example 145

2-Phenyl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide

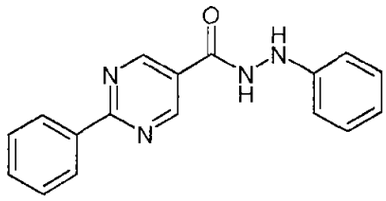


Following procedures similar to those of Example 64 but substituting 6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-ylamine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide (39%) as a solid. MS: 311 (M+H);

^{1}H NMR (300 MHz, CD_3OD): δ 1.98 (s, 3H), 4.32 (s, 2H), 7.45-7.63 (m, 3H), 8.50 (d, 2H), 9.24 (s, 2H).

Example 146

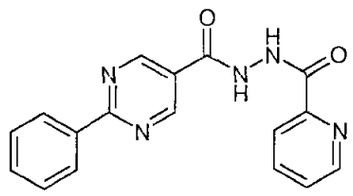
2-Phenyl-pyrimidine-5-carboxylic acid N'-phenyl-hydrazide



Following procedures similar to those of Example 64 but substituting N'-phenyl-hydrazine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid N'-phenyl-hydrazide (18%) as a solid. MS: 291 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.34 (s, N-H), 6.82-7.04 (m, 2H), 7.15-7.39 (m, 3H), 7.40-7.63 (m, 3H), 7.94 (s, N-H), 8.51 (d, 2H), 9.20 (s, 2H).

Example 147

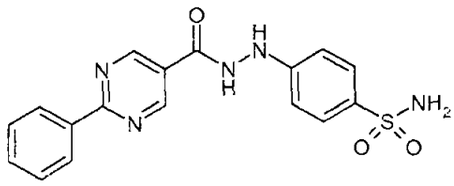
Pyridine-2-carboxylic acid N'-(2-phenyl-pyrimidine-5-carbonyl)-hydrazide



Following procedures similar to those of Example 64, but substituting 2-pyridine-2-carboxylic acid hydrazide for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared pyridine-2-carboxylic acid N'-(2-phenyl-pyrimidine-5-carbonyl)-hydrazide (52%) as a solid. MS: 320 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.75(m, 4H), 7.98-8.14 (m, 2H), 8.46 (d, 2H), 8.73 (d, H), 9.32 (s, 2H), 10.81 (s, N-H), 10.96 (br, N-H).

Example 148

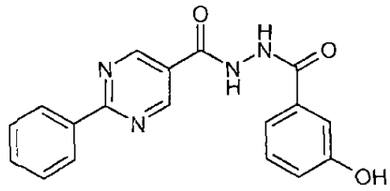
4-[N'-(2-Phenyl-pyrimidine-5-carbonyl)-hydrazino]-benzenesulfonamide



Following procedures similar to those of Example 64, but using substituting 4-hydrazino-benzebesulfonamide for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 4-[N'-(2-phenyl-pyrimidine-5-carbonyl)-hydrazino]-benzenesulfonamide (36%) as a solid. MS: 370 (M+H).

Example 149

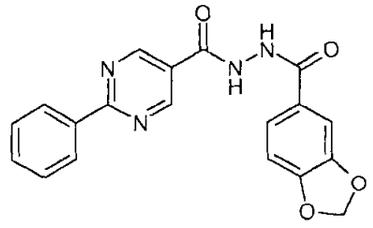
3-Hydroxy-benzoic acid N'-(2-phenyl-pyrimidine-5-carbonyl)-hydrazide



Following procedures similar to those of Example 64, but substituting 3-hydroxy-benzoic acid hydrazide for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 3-hydroxy-benzoic acid N'-(2-phenyl-pyrimidine-5-carbonyl)-hydrazide (56%) as a solid. MS: 335 (M+H).

Example 150

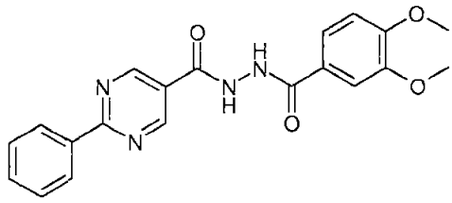
Benzo[1,3]dioxo-5-carboxylic acid N'-(phenyl-pyrimidine-5-carbonyl)-hydrazide



Following procedures similar to those of Example 64, but substituting benzo[1,3]dioxo-5-carboxylic acid hydrazide for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared benzo[1,3]dioxo-5-carboxylic acid N'-(phenyl-pyrimidine-5-carbonyl)-hydrazide (83%) as a solid. MS: 363 (M+H).

Example 151

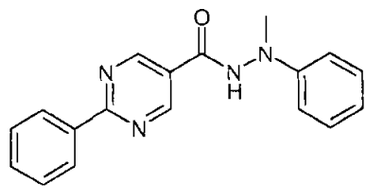
3,4-Dimethoxy-benzoic acid N'-(phenyl-pyrimidine-5-carbonyl)-hydrazide



Following procedures similar to those of Example 64 but substituting 3,4-dimethoxy-benzoic acid hydrazide for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 3,4-dimethoxy-benzoic acid N'-(phenyl-pyrimidine-5-carbonyl)-hydrazide (76%) as a solid. MS: 379 (M+H).

Example 152

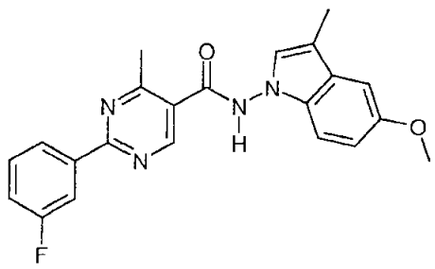
2-Phenyl-pyrimidine-5-carboxylic acid N'-methyl-N'-phenyl-hydrazide



Following procedures similar to those of Example 64, but substituting N'-methyl-N'-phenyl-hydrazine for 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-propionic acid methyl ester, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid N'-methyl-N'-phenyl-hydrazide (80 mg, 88%) as a solid. MS: 305 (M+H).

Example 153

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-indol-1-yl)-amide



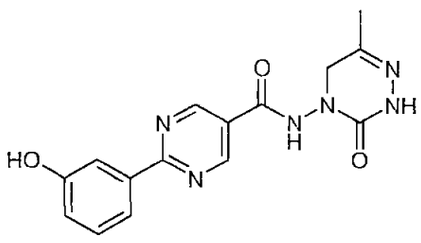
Step 1: A solution of potassium *tert*-butoxide (5.23 g, 46.62 mmol) and 5-methoxy-3-methylindole (3.41 g, 21.15 mmol) in DMF (20 mL) is stirred at rt for 45 min. A solution of monochloroamine in ether (400 mL, 60 mmol) is added *via* an addition funnel over 15 min.

The resulting mixture is stirred for 2 h. The solvent is removed and the residue is partitioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by column chromatography eluting with 10% EtOAc in heptane to afford 5-methoxy-3-methyl-indol-1-ylamine (1.42 g, 38%) as a solid. MS: 176 (M+H); ^{1}H NMR (300MHz, $CDCl_3$): δ 7.26-7.23 (m, 1H), 6.98-6.97 (m, 1H), 6.91-6.87 (m, 2H), 4.64 (br s, 2 H), 3.86 (s, 3H), 2.26-2.25 (m, 3H).

Step 2: A microwave vial (20 mL) is charged with 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (657 mg, 2.83 mmol), HOTT (1.16 g, 3.11 mmol), DIPEA (1.35 mL, 7.73 mmol) and DMF (6 mL). The mixture is stirred at 23°C under N_2 for 15 min. 5-Methoxy-3-methyl-indol-1-ylamine (456 mg, 2.59 mmol) is added and the vial is capped. The resulting mixture is heated in a microwave (Biotage-Initiator) at 150°C for 6 min. The mixture is portioned between EtOAc and water. The organic phase is separated, washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by column chromatography eluting with 45% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-indol-1-yl)-amide (327 mg, 32%) as a solid. MS: 391 (M+H); ^{1}H NMR (300MHz, d_6-DMSO): δ 11.75 (s, 1H), 9.19 (s, 1H), 8.32 (d, 1H), 8.18-8.16 (m, 1H), 7.66-7.62 (m, 1H), 7.45 (td, 1H), 7.30 (d, 1H), 7.22 (s, 1H), 7.05 (d, 1H), 6.85 (dd, 1H), 3.81 (s, 3H), 2.76 (s, 3H), 2.27 (s, 3H).

Example 154

2-(3-Hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide



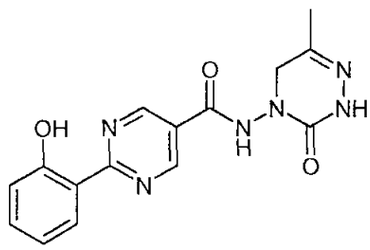
Step 1: Following the procedures similar to those of Example 59, step 1, but substituting 3-hydroxyphenylboronic acid for 3-methoxyphenylboronic acid, there is prepared 2-(3-hydroxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester.

Step 2: Following the procedures similar to those of Example 59, step 2, but substituting 2-(3-hydroxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester for 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester, there is prepared 2-(3-hydroxy-phenyl)-pyrimidine-5-carboxylic acid.

Step 3: Following the procedures similar to those of Example 59, step 3, but substituting 2-(3-hydroxy-phenyl)-pyrimidine-5-carboxylic acid for 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid, there is prepared 2-(3-hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide. MS: 327 (M+H); ^{1}H NMR (DMSO-d_6): δ 1.91 (s, 3H), 4.22(s, 2H), 5.75 (s, 1H), 6.98 (m, 1H), 7.36 (m, 1H), 7.90 (m, 1H), 9.25 (s, 2H), 9.71 (s, 1H), 9.95 (s, 1H), 11.05 (s, 1H). IC_{50} = 21 nM.

Example 155

2-(2-Hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide



Step 1: Following the procedures similar to those of Example 59, step 1, but substituting 2-hydroxyphenylboronic acid for 3-methoxyphenylboronic acid, there is prepared 2-(2-hydroxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester.

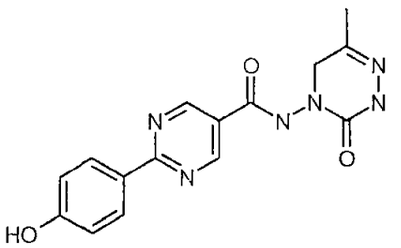
Step 2: Following the procedures similar to those of Example 59, step 2, but substituting 2-(2-hydroxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester for 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid methyl ester, there is prepared 2-(2-hydroxy-phenyl)-pyrimidine-5-carboxylic acid.

Step 3: Following the procedures similar to those of Example 59, step 3, but substituting 2-(2-hydroxy-phenyl)-pyrimidine-5-carboxylic acid for 2-(3-methoxy-phenyl)-pyrimidine-5-carboxylic acid, there is prepared 2-(2-hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide. MS: 327 (M+H); H1 NMR

(DMSO-d_6): δ = 1.91 (s, 3H), 4.22(s, 2H), 7.02 (m, 2H), 7.50 (m, 1H), 8.46 (m, 1H), 9.32 (s, 2H), 9.97 (s, 1H), 11.12 (s, 1H), 12.95 (s, 1H).

Example 156

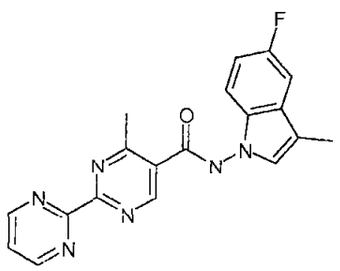
2-(4-Hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide



A mixture of 2-(4-methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide (100 mg, 0.29 mmol), sodium methanethiolate (206 mg, 2.9 mmol) and DMF (2 mL) is stirred at 110°C for 6 h., and then cooled to rt. The reaction mixture is concentrated *in vacuo*, and the residue is purified on a reverse phase HPLC chromatography to afford 2-(4-hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide (32 mg). MS: 327 (M+H); ^{1}H NMR (DMSO-d_6): δ 1.87 (s, 3H), 4.17 (s, 2H), 6.74 (m, 2H), 8.21 (d, *J* = 6.9 Hz, 2H), 9.08 (s, 2H), 9.53 (s, 1H).

Example 157

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide



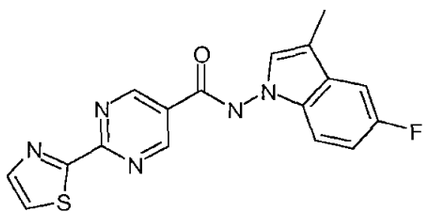
Step 1: A flask containing 2-cyanopyrimidine (16.6 g, 158 mmol), ammonium acetate (14.6 g, 189.6 mmol) and N-acetylcysteine (2.58 g, 15.8 mmol) and ethanol (160 mL) is heated to reflux. After 1.25 h, the reaction is allowed to cool slightly (to approximately 50°C), and sodium *tert*-butoxide (15.18 g, 158 mmol) and ethanol (160 mL) are added. After stirring for 10 minutes, 2-dimethylaminomethylene-3-oxo-butyric acid ethyl ester (33.6 g, 181.7 mmol) is

added. The reaction is then heated to reflux for an additional 2 h. The reaction is then allowed to cool to rt, and sodium hydroxide (12.6 g, 316 mmol) in water (50 mL) is added. After 2 h, the reaction is chilled in an ice water bath and the reaction pH is adjusted to ~ 3 using a solution of ~ 12M aqueous HCl. The reaction mixture is then reduced *in vacuo* to ~ 100 mL. Additional water (100 mL) is added and the suspension is chilled in an ice water bath, filtered and the solids are washed with minimal chilled water. The solids are then dried *in vacuo* to afford 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (85%).
MS: 217 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.80 (s, 3H), 7.66 (t, 1H), 9.01 (d, 2H), 9.14 (s, 1H).

Step 2. 4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (0.5 g, 2.31 mmol) is combined with 5-fluoro-3-methyl-indol-1-yl-ammonium chloride (464 mg, 2.31 mmol), N-methylmorpholine (233 mg, 2.31 mmol) and DMF (10 mL). The suspension is stirred for 5 minutes at rt, then 4-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-4-methyl-morpholin-4-ium chloride is added (640 mg, 2.31 mmol). The reaction is heated to 50°C for 4 h. The reaction is then poured into water (50 mL), the suspension is chilled for 2 h in the refrigerator, and then filtered. The solids are then suspended in acetonitrile at 50°C for 4 h, cooled, then filtered to afford 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide (60%). MS: 363 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H), 2.77 (s, 3H), 7.07 (dt, 1H), 7.36 (dd, 1H), 7.38 (s, 1H), 7.44-7.48 (m, 1H), 7.70 (t, 1H), 9.05 (d, 2H), 9.29 (s, 1H), 11.9 (s, 1H). IC_{50} = 4.5 nM.

Example 158

2-Thiazol-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide



Step 1: A flask is charged with 2-cyanothiazole (6.7 g, 60.9 mmol), ammonium acetate (5.63 g, 73 mmol), N-acetylcysteine (993 mg, 6.09 mmol), and methanol (60mL). The reaction is then heated to reflux overnight. The reaction is reduced *in vacuo* to yield a residue that is used in the next step without further modifications.

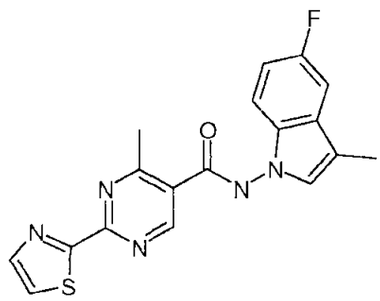
Step 2: The crude residue from Step 1 is suspended in DMF (100 mL). To this is added sodium 2-ethoxycarbonyl-3-oxo-but-1-en-1-olate (13.86 g, 70 mmol). The reaction is then heated to 100°C for 1.5 h then allowed to cool to rt. The reaction is then poured into ice water (1 L). The suspension is filtered and the filtrate is successively extracted with DCM (100 mL) and EtOAc (200 mL). The organic layers are dried (Na_2SO_4), filtered and concentrated to yield a residue (10.31 g).

Step 3: The residue from Step 2 (6.26 g, 28.32 mmol) is combined with a solution of sodium hydroxide (2.26 g, 56.65 mmol) in water (90 mL) and methanol (90 mL) and stirred at rt overnight. The volume of solution is reduced by half under *vacuo* and the pH is adjusted to 3 with aqueous HCl (approximately 12 M). The solid is collected by filtration and dried *in vacuo* to afford 2-thiazol-2-yl-pyrimidine-5-carboxylic acid (56% over 3 steps). MS: 208 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, 1H), 8.16 (d, 1H), 9.32 (s, 2H).

Step 4 : A mixture of 2-thiazol-2-yl-pyrimidine-5-carboxylic acid (50 mg, 0.244 mmol), 5-fluoro-3-methyl-indol-1-yl-ammonium chloride (49 mg, 0.244 mmol), diisopropylethylamine (31.5 mg, 0.244 mmol) in DMF (1 mL) is stirred at rt for 5 min. 4-(4,6-Dimethoxy-[1,3,5]triazin-2-yl)-4-methyl-morpholin-4-ium chloride (37 mg, 0.244 mmol) is added. The reaction is heated to 50°C for 1.5 h and then concentrated *in vacuo*. The residue is taken up in DMSO- d^6 then purified via reverse phase C18 HPLC chromatography eluting with water and acetonitrile containing 0.1% TFA buffer to afford 2-thiazol-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide (58%). MS: 354 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H), 7.05 (dt, 1H), 7.32 (s, 1H), 7.32-7.44 (m, 2H), 8.11 (d, 1H), 8.19 (d, 1H), 9.42 (s, 2H), 12.12 (s, 1H).

Example 159

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide

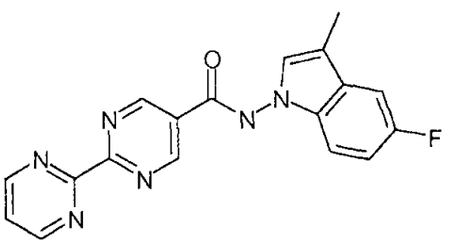


Step 1: A solution of 2-cyanothiazole (1.55 g, 14.2 mmol) in MeOH (12 mL) is treated with *N*-acetylcysteine (234 mg, 1.42 mmol), ammonium acetate (1.5 g, 18.5 mmol) and heated in a microwave at 120°C for 15 min. The mixture is then treated with 2-dimethylaminomethylene-3-oxo-butyric acid ethyl ester (3.2 g, 17.0 mmol) and KO*t*-Bu (2.2 g, 20 mmol), and heated in a microwave at 120°C for an additional 15 min. The mixture is then treated with a solution of KOH (1.2 g, 20 mmol) in H_2O (5 mL) and heated at reflux for 1 h. The mixture is neutralized with concentrated aqueous HCl. The precipitate is collected by filtration and dried to afford 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (1.95 g, 62%). MS: 222 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.77 (s, OH, 1H), 9.18 (s, 1H), 8.13 (d, 1H), 8.07 (d, 1H), 2.81 (s, 3H).

Step 2: A mixture of 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (221 mg, 1 mmol), 5-fluoro-3-methyl-indol-1-yl-ammonium chloride (200 mg, 1 mmol) and N-methylmorpholine (101 mg, 1 mmol) in DMF (5 mL) is stirred at rt for 5 min. 4-(4,6-Dimethoxy-[1,3,5]triazin-2-yl)-4-methyl-morpholin-4-ium chloride (277 mg, 1 mmol) is added and the reaction is heated to 50°C for 4 h. The reaction mixture is then poured into water (50 mL). The precipitate is collected via filtration and dried *in vacuo* to provide 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide (68%). MS: 368 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H), 2.76 (s, 3H), 7.06 (dt, 1H), 7.35-7.38 (m, 2H), 7.42-7.47 (m, 1H), 8.07 (d, 1H), 8.14 (d, 1H), 9.22 (s, 1H), 11.9 (s, 1H).

Example 160

[2,2']Bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide

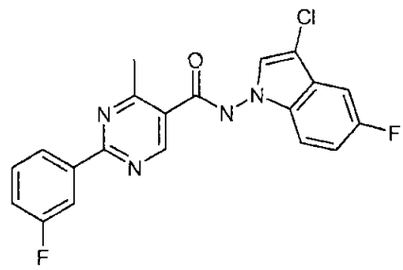


Step 1: A pressure vessel is charged with 2-cyanopyrimidine (7.88 g, 75 mmol), N-acetyl cysteine (1.22g, 7.5 mmol), ammonium acetate (6.93 g, 90 mmol), and MeOH (75 mL). The vessel is sealed and heated at 110°C for 1.5 h, and then cooled to rt. To the reaction mixture is added sodium 2-ethoxycarbonyl-3-oxo-but-1-en-1-olate (17 g, 86.25 mmol) and MeOH (75 mL). The mixture is heated to reflux for 1.5 h and then cooled to rt. NaOH (6 g, 150 mmol) and water (80 mL) are added. The mixture is stirred for 30 min or until LC-MS indicates complete hydrolysis of the intermediate ester. The pH of the reaction mixture is adjusted to ~ 3 with concentrated (~12 M) aqueous HCl. MeOH is evaporated *in vacuo*, and the resulting precipitate is collected via filtration and washed with minimal chilled water to yield [2,2']bipyrimidinyl-5-carboxylic acid (59%). MS: 203 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (t, 1H), 9.06 (d, 2H), 9.40 (s, 2H).

Step 2: A mixture of [2,2']bipyrimidinyl-5-carboxylic acid (166 mg, 0.82 mmol), 5-fluoro-3-methyl-indol-1-yl-ammonium chloride (164 mg, 0.82 mmol) and DIPEA (106 mg, 0.82 mmol) in DMF (5 mL) is stirred at rt for 5 min. 4-(4,6-Dimethoxy-[1,3,5]triazin-2-yl)-4-methyl-morpholin-4-ium chloride (226 mg, 0.82 mmol) is added. The reaction mixture is heated to 50°C for 1.5 h and then concentrated *in vacuo*. The residue is taken up in DMSO- d^6 and then purified via reverse phase C18 HPLC chromatography eluting with water and acetonitrile containing 0.1% TFA buffer to afford [2,2']bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide (56%). MS: 349 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H), 7.05 (dt, 1H), 7.33 (s, 1H), 7.36 (dd, 1H), 7.42-7.46 (m, 1H), 7.72 (t, 1H), 9.07 (d, 2H), 9.51 (s, 2H), 12.17 (s, 1H).

Example 161

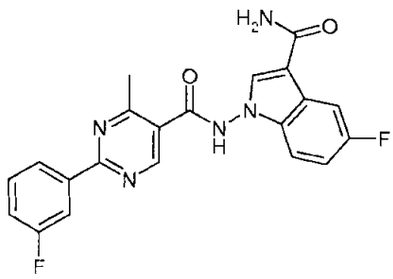
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylicacid(3chloro-5-fluoro-indol-1-yl)-amide



A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide (300 mg, 0.824 mmol) in MeCN (20 mL) is treated with NCS (185 mg, 1.42 mmol) and the mixture is stirred at 60°C in a sealed flask for 2 h. The mixture is then concentrated, diluted with 10% aqueous $Na_2S_2O_8$ (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% - 20% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylicacid(3chloro-5-fluoro-indol-1-yl)-amide (160 mg, 49%). MS: 399 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.04 (d, 1H), 7.92 (d, 1H), 7.18 (m, 1H), 7.04 (s, 1H), 7.00 (m, 3), 6.76 (m, 1), 2.52 (s, 3H).

Example 162

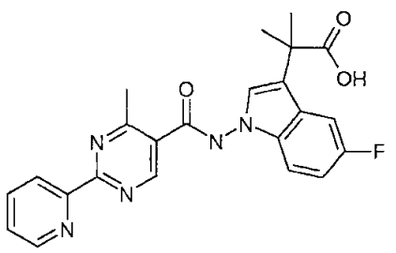
5-Fluoro-1-{[2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indole-3-carboxylic acid amide



A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide (300 mg, 0.82 mmol) in 2-Me-THF (7 mL) is treated with chlorosulfonyl isocyanate (CSI) (85 uL, 2.0 mmol) at 0°C, and the mixture is warmed to rt for 2 h. The mixture is then cooled to 0°C, treated with 1 M NaOH (1 mL), diluted with brine (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 5-fluoro-1-{[2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indole-3-carboxylic acid amide (275 mg, 83%). MS: 408 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.27 (s, 1H), 8.35 (d, 1H), 8.26 (s, 1H), 8.20 (d, 1H), 7.95 (d, 1H), 7.59 (m, 3H), 7.15 (m, 1H), 2.78 (s, 3H). IC_{50} = 8 nM.

Example 163

2-{5-Fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indol-3-yl}-2-methyl-propionic acid



Step 1: A solution of (5-fluoro-1H-indol-3-yl)-acetic acid methyl ester (3 g, 14.8 mmol) in MeCN (25 mL) is treated with Boc_2O (4.3 g, 16.3 mmol) and DMAP (200 mg, 1.63 mmol), and the mixture is stirred at rt for 1 h. The mixture is diluted with saturated aqueous NH_4Cl (50 mL), and extracted with DCM (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 8% EtOAc in heptane to afford 5-fluoro-3-methoxycarbonylmethyl-indole-1-carboxylic acid *tert*-butyl ester (1.6 g, 35%). MS: 371 (M+Na+ACN); ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (m, 1H), 7.59 (s, 1H), 7.17 (m, 1H), 7.04 (m, 1H), 3.72 (s, 3H), 3.67 (s, 2H), 1.55 (s, 9H).

Step 2: A solution of 5-fluoro-3-methoxycarbonylmethyl-indole-1-carboxylic acid *tert*-butyl ester (1.6 g, 5.2 mmol) in 2-Me-THF (50 mL) at –78°C is treated with LDA (5.7 mL 1.8 M in THF, 10.4 mmol) and stirred for 0.5 h. MeI (1.02 mL, 15.6 mmol) is added and the mixture is warmed to 0°C over 2 h. The mixture is diluted with saturated aqueous NH_4Cl (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 5-fluoro-3-(1-methoxycarbonyl-1-methyl-ethyl)-indole-1-carboxylic acid *tert*-butyl ester, which is used in the next step without further purification.

Step 3: A solution of 5-fluoro-3-(1-methoxycarbonyl-1-methyl-ethyl)-indole-1-carboxylic acid *tert*-butyl ester (5.2 mmol) in MeOH (25 mL) is treated with K_2CO_3 (720 mg, 5.2 mmol) and heated at reflux for 2 h. The mixture is diluted with brine (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 2-(5-fluoro-1H-indol-3-yl)-2-methyl-propionic acid methyl ester (650 mg,

53%, 2 steps), which is used in the next step without further purification. MS: 236 (M+H); ^{1}H NMR (300 MHz, DMSO- d_6): δ 7.35 (m, 1H), 7.30 (m, 1H), 7.14 (m, 1H), 6.91 (m, 1H), 3.54 (s, 3H), 1.57 (s, 6H).

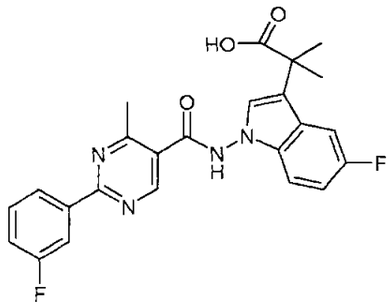
Step 4: A suspension of NaH (1.02 g, 25.5 mmol, 60% in mineral oil) in DMF (25 mL) at 0°C is treated with 2-(5-fluoro-1H-indol-3-yl)-2-methyl-propionic acid methyl ester (400 mg, 1.7 mmol) and stirred at 0°C for 0.5 h. The mixture is treated with HOSA (960 mg, 8.5 mmol) portion wise and warmed to rt over 2h. The mixture is then poured over ice, filtered through a pad of Celite, and extracted with EtOAc (3 x 100 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 2-(1-amino-5-fluoro-1H-indol-3-yl)- 2-methyl-propionic acid methyl ester, which is used in the next step without further purification.

Step 5: A solution of 2-(1-amino-5-fluoro-1H-indol-3-yl)- 2-methyl-propionic acid methyl ester (0.85 mmol) and 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (201 mg, 0.935 mmol) in DMF (8.5 mL) is stirred at 40°C for 0.5 h. The mixture is treated with DMTMM (246 mg, 0.89 mmol) and stirred at 60°C for 1 h. The mixture is concentrated *in vacuo*, diluted with saturated aqueous Na_2CO_3 (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 2-{5-fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indol-3-yl}-2-methyl-propionic acid methyl ester, which is used in the next step without further purification.

Step 6: A solution of 2-{5-fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indol-3-yl}-2-methyl-propionic acid methyl ester (0.85 mmol) in MeOH (5 mL) is treated with 10% aqueous NaOH (2 mL) and stirred at rt overnight. The mixture is then concentrated, diluted with EtOAc (50 mL), and extracted with 10% aqueous NaOH (3 x 50 mL). The aqueous layer is acidified with 12 M aqueous HCl, extracted with DCM (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is triturated with Et_2O to afford 2-{5-fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indol-3-yl}-2-methyl-propionic acid (100 mg, 27%, 3 steps). MS: 434 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.26 (s, 1H), 8.79 (m, 1H), 8.44 (d, 1H), 8.03 (t, 1H), 7.59 (m, 1H), 7.53 (s, 1H), 7.49 (m, 1H), 7.35 (d, 1H), 7.08 (t, 1H), 2.79 (s, 3H), 1.59 (s, 6H).

Example 164

2-(5-Fluoro-1-{[2-(3-fluoro-phenyl) -4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-3-yl)-2-methyl-propionic acid

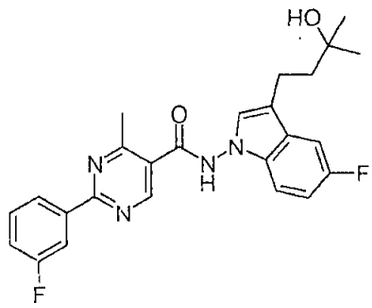


Step 1: A solution of 2-(1-amino-5-fluoro-1H-indol-3-yl)- 2-methyl-propionic acid methyl ester (0.85 mmol) and 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (217 mg, 0.935 mmol) in DMF (8.5 mL) is stirred at 40°C for 0.5 h. The mixture is treated with DMTMM (246 mg, 0.89 mmol) and stirred at 60°C for 1 h. The mixture is concentrated *in vacuo*, diluted with saturated aqueous Na_2CO_3 (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 2-(5-fluoro-1-{[2-(3-fluoro-phenyl) -4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-3-yl)-2-methyl-propionic acid methyl ester, which is used in the next step without further purification.

Step 2: A solution of 2-(5-fluoro-1-{[2-(3-fluoro-phenyl) -4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-3-yl)-2-methyl-propionic acid methyl ester (0.85 mmol) in MeOH (5 mL) is treated with 10% aqueous NaOH (2 mL) and stirred at rt overnight. The mixture is then concentrated, diluted with EtOAc (50 mL), and extracted with 10% aqueous NaOH (3 x 50 mL). The aqueous layer is acidified with 12 M HCl, and extracted with DCM (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is triturated with Et_2O to afford 2-(5-fluoro-1-{[2-(3-fluoro-phenyl) -4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-3-yl)-2-methyl-propionic acid (139 mg). MS: 451 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.22 (s, 1H), 8.33 (d, 1H), 8.18 (d, 1H), 7.63 (m, 1H), 7.50 (m, 3H), 7.33 (m, 1H), 7.07 (m, 1H), 2.78 (s, 3H), 1.59 (s, 6H). IC_{50} = 7 nM.

Example 165

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3- (3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide



Step 1: A solution of 5-fluoroindole (10.5 g, 78 mmol) in MeCN (150 mL) at 0°C is treated with methyl vinyl ketone (9.5 mL, 117 mmol) and $Sc(OTf)_3$ (383 mg, 0.78 mmol) and stirred for 1 h. The mixture is then stirred an additional 6 h at rt. The mixture is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% - 50% EtOAc in heptane to afford 4-(5-fluoro-1H-indol-3-yl)-butan-2-one (11.1 g, 70%).

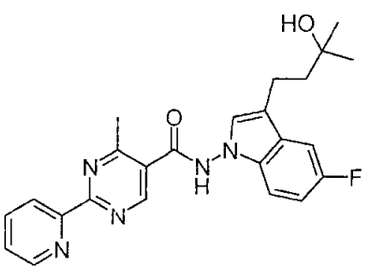
Step 2: A solution of 4-(5-fluoro-1H-indol-3-yl)-butan-2-one (11.1 g, 54.1 mmol) in THF (200 mL) at 0°C is treated with MeMgBr (54.1 mL, 3 M in THF, 162.3 mmol) and stirred at 0°C for 2 h, and warmed to rt overnight. The mixture is then poured over ice, treated with solid NH_4Cl (3 g), and extracted with EtOAc (3 x 120 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% - 60% EtOAc in heptane to afford 4-(5-fluoro-1H-indol-3-yl)-2-methyl-butan-2-ol (3.07 g, 26%). MS: 222 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (s, NH, 1H), 7.22 (m, 2H), 7.03 (s, 1H), 6.93 (m, 1H), 2.81 (m, 2H), 1.90 (m, 2H), 1.33 (s, 6H).

Step 3: A suspension of NaH (8.1 g, 204 mmol, 60% in mineral oil) in DMF (100 mL) at 0°C is treated with 4-(5-fluoro-1H-indol-3-yl)-2-methyl-butan-2-ol (3 g, 13.6 mmol) and stirred at 0°C for 0.5 h. The mixture is treated with HOSA (7.7 g, 68 mmol) portion wise and warmed to rt over 2h. The mixture is then poured over ice, filtered through a pad of Celite, and extracted with EtOAc (3 x 100 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by filtration through a short plug of silica gel to afford 4-(1-amino-5-fluoro-1H-indol-3-yl)- 2-methyl-butan-2-ol, which is used in the next step without further purification. MS: 237 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 1H), 7.22 (m, 1H), 6.98 (m, 2H), 4.71 (s, NH_2, 2H), 2.75 (m, 2H), 1.86 (m, 2H), 1.31 (s, 6H).

Step 4: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (278 mg, 1.2 mmol) and 4-(1-amino-5-fluoro-1H-indol-3-yl)- 2-methyl-butan-2-ol (1.2 mmol) in DMF (10 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (331 mg, 1.2 mmol) and stirred at 50°C for 1 h. The mixture is concentrated *in vacuo*, diluted with saturated aqueous Na_2CO_3 (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 50% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3- (3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide (330 mg, 61%). MS: 451 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 9.10 (s, 1H), 8.36 (d, 1H), 8.23 (d, 1H), 7.55 (m, 1H), 7.32 (m, 3H), 7.18 (s, 1H), 7.03 (m, 1H), 3.91 (s, OH, 1H), 2.84 (s, 3H), 2.82 (m, 2H), 1.91 (m, 2H), 1.31 (s, 6H).

Example 166

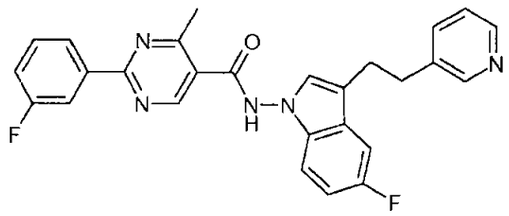
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide



A solution of 2-(2-pyridyl)-4-methyl-pyrimidine-5-carboxylic acid (516 mg, 4 mmol) and 4-(1-amino-5-fluoro-1H-indol-3-yl)- 2-methyl-butan-2-ol (566 mg, 4 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (662 mg, 4 mmol) and stirred at 50°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 4% - 10% MeOH in DCM to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide (450 mg, 44%). MS: 434 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.25 (s, 1H), 8.81 (d, 1H), 8.47 (d, 1H), 8.02 (m, 1H), 7.58 (m, 1H), 7.43 (m, 3H), 7.06 (m, 1H), 4.29 (s, OH, 1H), 2.78 (s, 3H), 2.72 (m, 2H), 1.77 (m, 2H), 120 (s, 6H).

Example 167

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3- (2-pyridin-3-yl-ethyl)-indol-1-yl]- amide



Step 1: A solution of 5-fluorogramine (576 mg, 3 mmol) and pyridine-3-carboxaldehyde (531 mg, 3 mmol) in MeCN (6 mL) is treated with Bu_3P (1.12 mL, 4.5 mmol) and stirred at 90°C for 24 h. The mixture is concentrated, filtered through a pad of silica gel eluting with 30% EtOAc in heptane to afford 5-fluoro-3-(2-pyridin-3-yl-vinyl)-1H-indole as a mixture of olefin isomers, which is used in the next step without further purification.

Step 2: A solution of 5-fluoro-3-(2-pyridin-3-yl-vinyl)-1H-indole (3 mmol) in MeOH (10 mL) is treated with Pd/C (200 mg) and shaken in a Parr apparatus under 40 atm of H_2 for 18 h. The mixture is filtered through Celite and the filtrate is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0% - 10% MeOH in DCM to afford 5-fluoro-3-(2-pyridin-3-yl-ethyl)-1H-indole (360 mg, 50%, 2 steps).

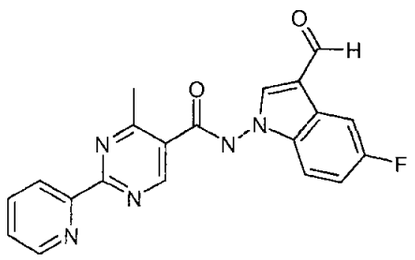
Step 3: A suspension of NaH (600 mg, 15 mmol, 60% in mineral oil) in DMF (10 mL) at 0°C is treated with 5-fluoro-3-(2-pyridin-3-yl-ethyl)-1H-indole (240 mg, 1 mmol) and stirred at 0°C for 0.5 h. The mixture is treated with HOSA (565 mg, 5 mmol) portion wise and warmed to rt over 2h. The mixture is then poured over ice, filtered through a pad of Celite, and extracted with EtOAc (3 x 1050 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 5-fluoro-3-(2-pyridin-3-yl-ethyl)-indol-1-ylamine, which is used in the next step without further purification.

Step 4: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (232 mg, 1 mmol) and 5-fluoro-3-(2-pyridin-3-yl-ethyl)-indol-1-ylamine (255 mmol) in DMF (10 mL) is stirred at 50°C for 10 min. The mixture is treated with DMTMM (276 mg, 1 mmol) and stirred at 50°C for 0.5 h. The mixture is diluted with saturated aqueous Na_2CO_3 (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by triturating in MeOH:H_2O (2:1) to

afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(2-pyridin-3-yl-ethyl)-indol-1-yl]- amide (6 mg, 1%). MS: 470 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.21 (s, 1H), 8.51 (m, 1H), 8.40 (m, 1H), 8.33 (d, 1H), 8.19 (d, 1H), 7.74 (d, 1H), 7.63 (m, 1H), 7.45 (m, 4H), 7.33 (m, 1H), 7.06 (m, 1H), 3.29 (s, 2H), 3.01 (s, 2H), 2.77 (s, 3H).

Example 168

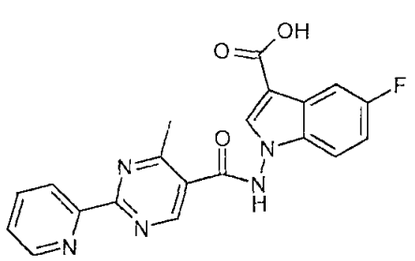
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-formyl-indol-1-yl)-amide



A solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide (250 mg, 0.55 mmol) in H_2O (5.5 mL) is treated with DDQ (369 mg, 1.6 mmol) in EtOAc (0.5 mL), and stirred at rt for 2 h. The mixture is diluted with EtOAc (50 mL), washed with brine (50 mL), and extracted with saturated aqueous $NaHCO_3$ (3 x 50 mL). The aqueous layer is acidified to pH 2 with HCl (conc.) and washed with Et_2O (50 mL). The aqueous layer is neutralized with 10% aqueous NaOH and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by triturating in Et_2O to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-formyl-indol-1-yl)-amide (87 mg, 43%). MS: 376 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.53 (s, NH, 1H), 10.00 (s, 1H), 9.34 (m, 1H), 8.81 (m, 1H), 8.66 (s, 1H), 8.48 (m, 1H), 8.04 (m, 1H), 7.86 (m, 1H), 7.72 (m, 1H), 7.61 (m, 1H), 7.27 (m, 1H), 2.80 (s, 3H).

Example 169

5-Fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indole-3-carboxylic acid



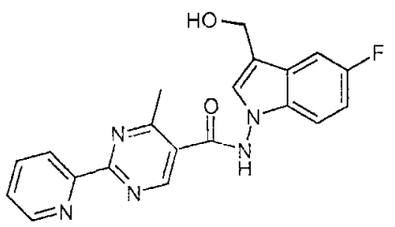
Step 1: A solution of 5-fluoro-1H-indole-3-carboxylic acid methyl ester (510 mg, 2.6 mmol) in NMP (6.5 mL) at rt is treated with KO*t*-Bu (342 mg, 2.9 mmol) and stirred at rt for 0.5 h. A solution of *O*-amino-4-nitrobenzoic acid (558 mg, 3.0 mmol) in NMP (2.5 mL) is added and the mixture is stirred for 3 h. The mixture is diluted with EtOAc (50 mL) and washed with 10% aqueous $NaHCO_3$ (50 mL). The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 1-amino-5-fluoro-1H-indole-3-carboxylic acid methyl ester, which is used in the next step without further purification.

Step 2: A solution of 2-(2-pyridyl)-4-methyl-pyrimidine-5-carboxylic acid (559 mg, 2.6 mmol) and 1-amino-5-fluoro-1H-indole-3-carboxylic acid methyl ester (540 mg, 2.6 mmol) in DMF (25 mL) is stirred at 50°C for 0.5 h. The mixture is treated with DMTMM (718 mg, 2.6 mmol) and stirred at 50°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 1% - 10% MeOH in DCM to afford 5-fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indole-3-carboxylic acid methyl ester.

Step 3: A solution of 5-fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indole-3-carboxylic acid methyl ester (2.6 mmol) in MeOH (10 mL) is treated with an aqueous solution of KOH (500 mg, 8.9 mmol) in H_2O (200 mL) and heated at reflux for 2 h. The mixture is diluted with EtOAc (50 mL) and extracted with 1% aqueous KOH (3 x 50 mL). The combined aqueous layer is neutralized with HCl (conc.), and the precipitate is collected by filtration and dried *in vacuo* to afford 5-fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indole-3-carboxylic acid (195 mg, 19%, 3 steps). MS: 392 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.44 (s, OH, 1H), 12.31 (s, NH, 1H), 9.31 (s, 1H), 8.81 (d, 1H), 8.48 (d, 1H), 8.35 (s, 1H), 8.03 (m, 1H), 7.77 (m, 1H), 7.62 (m, 2H), 7.19 (m, 1H), 2.79 (s, 3H).

Example 170

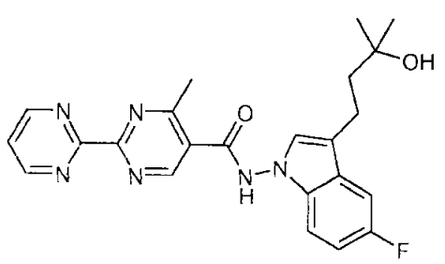
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-hydroxymethyl-indol-1-yl)-amide



A solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-formyl-indol-1-yl)-amide (230 mg, 0.614 mmol) in MeOH (10 mL) is treated with $NaBH_4$ (233 mg, 6.14 mmol) and stirred at rt for 1 h. The mixture is diluted with EtOAc (50 mL) and H_2O, neutralized with HCl (conc.), and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by preparative reverse-phase HPLC eluting with 20% - 100% MeCN in H_2O to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-hydroxymethyl-indol-1-yl)-amide (90 mg, 8%). MS: 378 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.92 (s, NH, 1H), 9.27 (s, 1H), 8.81 (d, 1H), 8.47 (d, 1H), 8.05 (m, 1H), 7.61 (m, 1H), 7.44 (m, 3H), 7.10 (m, 1H), 5.00 (t, OH, 1H), 4.66 (d, 2H), 2.78 (s, 3H).

Example 171

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide

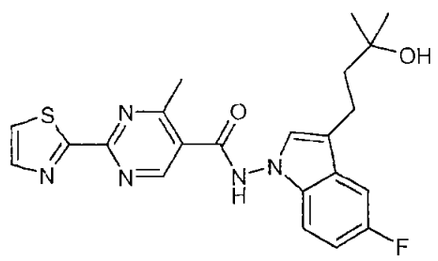


A solution of 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (300 mg, 1.38 mmol) and 4-(1-amino-5-fluoro-1H-indol-3-yl)- 2-methyl-butan-2-ol (325 mg, 1.38 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (380 mg, 1.38 mmol) and stirred at 50°C for 2 h. The mixture is diluted with saturated aqueous Na_2CO_3 (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0% - 7% MeOH in DCM to afford 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide (200 mg, 33%). MS: 435 (M+H); ^{1}H NMR (300

MHz, CD_3OD): δ 9.26 (s, 1H), 9.09 (d, 2H), 7.70 (t, 1H), 7.29 (m, 2H), 7.22 (s, 1H), 7.01 (m, 1H), 2.90 (s, 3H), 2.82 (m, 2H), 1.91 (m, 2H), 1.31 (s, 6H).

Example 172

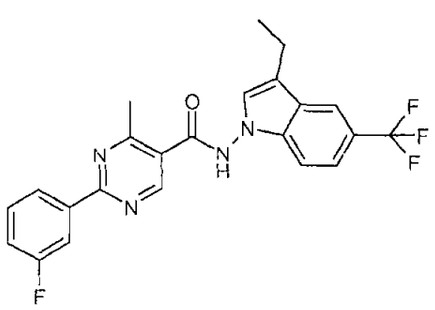
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide



A solution of 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (300 mg, 1.36 mmol) and 4-(1-amino-5-fluoro-1H-indol-3-yl)- 2-methyl-butan-2-ol (325 mg, 1.38 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (380 mg, 1.38 mmol) and stirred at 50°C for 2 h. The mixture is diluted with saturated aqueous Na_2CO_3 (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0% - 7% MeOH in DCM to afford 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide (155 mg, 26%). MS: 440 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.22 (s, 1H), 8.14 (d, 1H), 8.08 (d, 1H), 7.40 (m, 3H), 7.06 (m, 1H), 4.31 (s, OH, 1H), 2.76 (s, 3H), 2.71 (m, 2H), 1.77 (m, 2H), 1.20 (s, 6H). IC_{50} = 5 nM.

Example 173

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide



Step 1: A solution of 2-iodo-4-trifluoromethyl-phenylamine (10 g, 34.8 mmol) in DCM (100 mL) is treated with TFAA (5.55 mL, 41.8 mmol) and pyridine (3.4 mL, 41.8 mmol), and stirred at rt for 1 h. The mixture is diluted with H_2O (150 mL), and extracted with DCM (3 x 150 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is diluted with MeCN (100 mL), treated with *trans*-crotyl bromide (5.4 mL, 52.2 mmol) and K_2CO_3 (9.6 g, 69.6 mmol), and heated at reflux for 2 h. The mixture is cooled, filtered through a pad of Celite and concentrated. The residue is purified by silica gel chromatography eluting with 0% - 10% EtOAc in heptane to afford N-but-2-enyl-2,2,2-trifluoro-N-(2-iodo-4-trifluoromethyl-phenyl)-acetamide (12.7 g, 84%). MS: 438 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.67 (s, 1H), 7.26 (m, 1H), 5.52 (m, 2H), 4.88 (m, 1H), 3.51 (m, 1H), 1.68 (d, 3H).

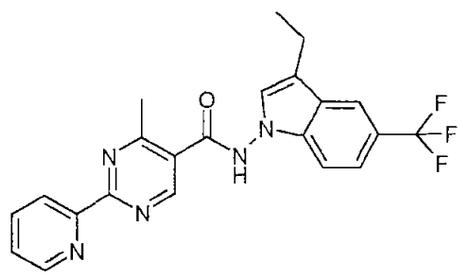
Step 2: A solution of *N*-but-2-enyl-2,2,2-trifluoro-*N*-(2-iodo-4-trifluoromethyl-phenyl)-acetamide (12.7 g, 29 mmol) in DMF (60 mL) is treated with *n*-Bu_4NCl (8.8 g, 32 mmol), $Pd(OAc)_2$ (131 mg, 0.58 mmol), and stirred at 100°C for 2 h. The mixture is cooled to rt, diluted with EtOAc (150 mL), filtered through a pad of silica gel, and washed with 1 M HCl (150 mL). The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% - 30% EtOAc in heptane to afford 3-ethyl-5-trifluoromethyl-1H-indole (2.6 g, 42%). MS: 214 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, NH, 1H), 7.89 (s, 1H), 7.41 (m, 2H), 7.07 (m, 1H), 2.81 (q, 2H), 1.34 (t, 3H).

Step 3: A suspension of NaH (7 g, 176 mmol, 60% in mineral oil) in DMF (50 mL) at 0°C is treated with 3-ethyl-5-trifluoromethyl-1H-indole (2.4 g, 11.3 mmol) and stirred at 0°C for 1 h. The mixture is treated with HOSA (6.6 g, 59 mmol) portion wise and warmed to rt over 2 h. The mixture is then poured over ice, filtered through a pad of Celite, and extracted with EtOAc (3 x 150 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% - 50% EtOAc in heptane to afford 3-ethyl-5-trifluoromethyl-indol-1-ylamine (1.3 g, 50%). MS: 229 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.45 (s, 2H), 7.02 (s, 1H), 4.74 (s, NH_2, 2H), 2.77 (q, 2H), 1.31 (t, 3H).

Step 4: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (232 mg, 1.0 mmol) and 3-ethyl-5-trifluoromethyl-indol-1-ylamine (228 mg, 1 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (276 mg, 1 mmol) and stirred at 50°C for 2 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 5 min. The precipitate is collected by filtration and dried *in vacuo* to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide (240 mg, 54%). MS: 443 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.24 (s, 1H), 8.34 (d, 1H), 8.26 (d, 1H), 8.19 (s, 1H), 7.58 (m, 2H), 7.42 (m, 3H), 2.84 (q, 2H), 2.78 (s, 3H), 1.31 (t, 3H).

Example 174

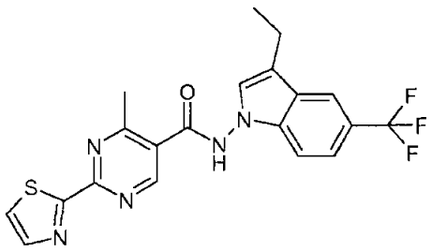
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide



A solution of 2-(2-pyridyl)-4-methyl-pyrimidine-5-carboxylic acid (215 mg, 1 mmol) and 3-ethyl-5-trifluoromethyl-indol-1-ylamine (228 mg, 1 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (276 mg, 1 mmol) and stirred at 50°C for 2 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 5 min. The precipitate is collected by filtration and dried *in vacuo* to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide (235 mg, 55%). MS: 426 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.28 (s, 1H), 8.81 (d, 1H), 8.48 (d, 1H), 8.03 (m, 1H), 7.99 (s, 1H), 7.60 (m, 4H), 2.82 (q, 2H), 2.79 (s, 3H), 1.31 (t, 3H).

Example 175

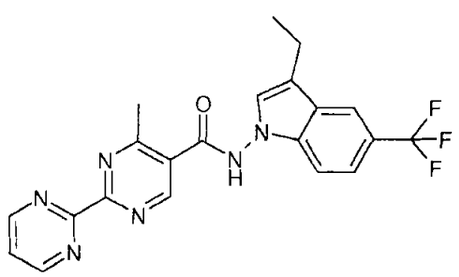
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide



A solution of 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (221 mg, 1 mmol) and 3-ethyl-5-trifluoromethyl-indol-1-ylamine (228 mg, 1 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (276 mg, 1 mmol) and stirred at 50°C for 2 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 5 min. The precipitate is collected by filtration and dried *in vacuo* to afford 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide (250 mg, 58%). MS: 432 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.07 (s, NH, 1H), 9.25 (s, 1H), 8.15 (d, 1H), 8.09 (d, 1H), 7.99 (s, 1H), 7.68 (d, 1H), 7.51 (m, 2H), 2.77 (s, 3H), 2.74 (q, 2H), 1.29 (t, 3H).

Example 176

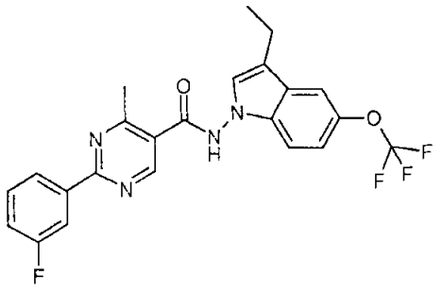
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide



A solution of 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (216 mg, 1 mmol) and and 3-ethyl-5-trifluoromethyl-indol-1-ylamine (228 mg, 1 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (276 mg, 1 mmol) and stirred at 50°C for 2 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 5 min. The precipitate is collected by filtration and dried *in vacuo*. The solid is triturated in Et_2O to afford 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide (100 mg, 23%). MS: 427 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.11 (s, NH, 1H), 9.32 (s, 1H), 9.07 (d, 2H), 8.00 (s, 1H), 7.69 (m, 2H), 7.53 (m, 2H), 2.80 (q, 2H), 2.79 (s, 3H), 1.31 (t, 3H). IC_{50} = 8 nM.

Example 177

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide



Step 1: A solution of 2-bromo-4-trifluoromethoxy-phenylamine (7.6 g, 29.7 mmol) in DCM (60 mL) is treated with TFAA (5 mL, 35.6 mmol) and pyridine (2.87 mL, 35.6 mmol), and stirred at rt overnight. The mixture is diluted with H_2O (150 mL), and extracted with DCM (3 x 150 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is diluted with MeCN (60 mL), treated with *trans*-crotyl bromide (4.6 mL, 44.5 mmol) and K_2CO_3 (8.1 g, 59 mmol), heated at reflux for 1 h, and then stirred at rt for 2 h. The mixture is filtered through a pad of Celite and the filtrate is concentrated. The residue is purified by silica gel chromatography eluting with 0% - 15% EtOAc in heptane to afford *N*-(2-bromo-4-trifluoromethoxy-phenyl)-*N*-but-2-enyl-2,2,2-trifluoro-acetamide (10.5 g, 87%). MS: 406 (M+); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.22 (m, 2H), 5.52 (m, 2H), 4.86 (m, 1H), 3.57 (m, 1H), 1.65 (d, 3H).

Step 2: A solution of *N*-(2-bromo-4-trifluoromethoxy-phenyl)-*N*-but-2-enyl-2,2,2-trifluoro-acetamide (10 g, 24.7 mmol) in DMF (50 mL) is treated with *n*-Bu_4NCl (7.5 g, 27.2 mmol), $Pd(OAc)_2$ (221 mg, 0.98 mmol), and stirred at 100°C for 1 h. H_2O (10 mL) is added, and the mixture is cooled to rt, filtered through a pad of silica gel. The filtrate is extracted with heptane (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0% - 25% EtOAc in heptane to afford 3-ethyl-5-trifluoromethoxy-1H-indole (3.1 g, 55%). MS: 230 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (s, NH, 1H), 7.44 (s, 1H), 7.29 (m, 1H), 7.07 (m, 2H), 2.77 (q, 2H), 1.32 (t, 3H).

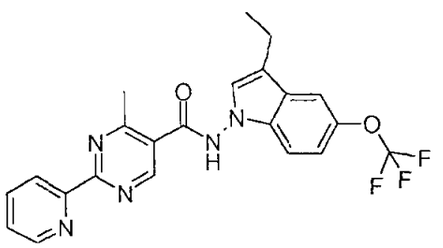
Step 3: A suspension of NaH (7.9 g, 197 mmol, 60% in mineral oil) in DMF (60 mL) at 0°C is treated with 3-ethyl-5-trifluoromethoxy-1H-indole (3 g, 13.1 mmol) and stirred at 0°C for 1

h. The mixture is treated with HOSA (7.4 g, 65.5 mmol) portion wise and warmed to rt over 2h. The mixture is then poured over ice and filtered through a pad of Celite. The filtrate is extracted with heptane (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% - 30% EtOAc in heptane to afford 3-ethyl-5-trifluoromethoxy-indol-1-ylamine (2.05 g, 64%). MS: 245 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (m, 2H), 7.11 (m, 1H), 7.00 (s, 1H), 4.72 (s, NH_2, 2H), 2.73 (q, 2H), 1.29 (t, 3H).

Step 4: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (250 mg, 1.1 mmol) and 3-ethyl-5-trifluoromethoxy-indol-1-ylamine (244 mg, 1 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (276 mg, 1 mmol) and stirred at 50°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 10 min. The precipitate is collected by filtration, washed with H_2O (50 mL) and heptane (50 mL), and dried *in vacuo* to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide (270 mg, 59%). MS: 459 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.51 (s, NH, 1H), 9.08 (s, 1H), 8.35 (d, 1H), 8.24 (d, 1H), 7.48 (m, 2H), 7.22 (m, 2H), 7.11 (m, 2H), 2.85 (s, 3H), 2.80 (q, 2H), 1.35 (t, 3H).

Example 178

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide

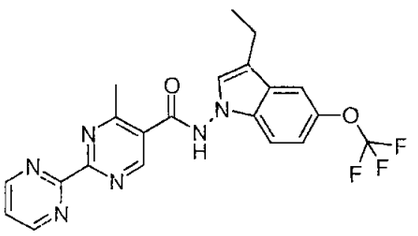


A solution of 2-(2-pyridyl)-4-methyl-pyrimidine-5-carboxylic acid (250 mg, 1.1 mmol) and 3-ethyl-5-trifluoromethoxy-indol-1-ylamine (244 mg, 1.0 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (276 mg, 1.0 mmol) and stirred at 50°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 10 min. The precipitate is collected by filtration, washed with H_2O (50 mL) and heptane (50 mL), and dried *in vacuo* to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide (300 mg, 68%). MS: 442 (M+H); ^{1}H NMR (300 MHz,

DMSO-d_6): δ 9.27 (s, 1H), 8.81 (d, 1H), 8.47 (d, 1H), 8.03 (m, 1H), 7.57 (m, 3H), 7.47 (s, 1H), 7.21 (d, 1H), 2.78 (s, 3H), 2.74 (q, 2H), 1.29 (t, 3H).

Example 179

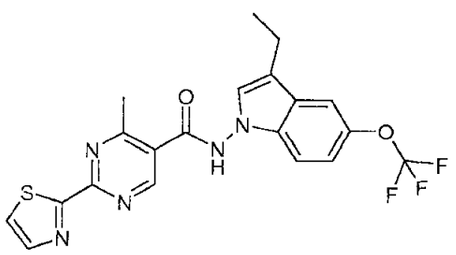
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide



A solution of 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (250 mg, 1.1 mmol) and 3-ethyl-5-trifluoromethoxy-indol-1-ylamine (244 mg, 1 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (276 mg, 1.0 mmol) and stirred at 50°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 10 min. The precipitate is collected by filtration, washed with H_2O (50 mL) and heptane (50 mL), and dried *in vacuo* to afford 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide (130 mg, 29%). MS: 443 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.25 (s, 1H), 9.05 (d, 2H), 7.69 (t, 1H), 7.64 (s, 1H), 7.54 (m, 2H), 7.14 (d, 1H), 2.80 (s, 3H), 2.76 (q, 2H), 1.29 (t, 3H).

Example 180

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide

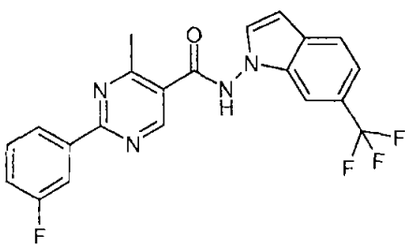


A solution of 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (250 mg, 1.1 mmol) and 3-ethyl-5-trifluoromethoxy-indol-1-ylamine (244 mg, 1.0 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (276 mg, 1.0 mmol) and stirred at 50°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 10 min.

The precipitate is collected by filtration, washed with H_2O (50 mL) and heptane (50 mL), and dried *in vacuo* to afford 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide (250 mg, 56%). MS: 448 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.23 (s, 1H), 8.15 (m, 1H), 8.09 (m, 1H), 7.55 (m, 2H), 7.48 (s, 1H), 7.19 (d, 1H), 2.78 (s, 3H), 2.71 (m, 2H), 1.29 (t, 3H).

Example 181

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide



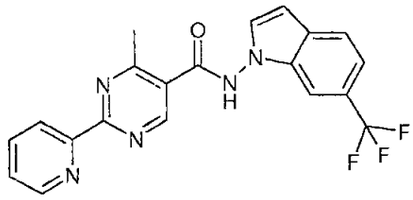
Step 1: A suspension of NaH (6.5 g, 162 mmol, 60% in mineral oil) in DMF (54 mL) at 0°C is treated with 6-trifluoromethylindole (2.0 g, 10.8 mmol) and stirred at 0°C for 0.5 h. The mixture is treated with HOSA (6.1 g, 54 mmol) portion wise and warmed to rt over 2h. The mixture is then poured over ice and filtered through a pad of Celite. The filtrate is extracted with Et_2O (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% - 30% EtOAc in heptane to afford 6-trifluoromethyl-indol-1-ylamine (1.79 g, 83%). MS: 201 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.67 (d, 1H), 7.35 (d, 1H), 7.30 (m, 1H), 6.45 (d, 1H), 4.83 (s, NH_2, 2H).

Step 2: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (278 mg, 1.2 mmol) and 6-trifluoromethyl-indol-1-ylamine (200 mg, 1 mmol) in DMF (5 mL) is stirred at 50°C for 0.5 h. The mixture is treated with DMTMM (290 mg, 1.05 mmol) and stirred at 50°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is triturated with Et_2O/heptane overnight. The precipitate is collected by filtration, washed with H_2O (50 mL) and heptane (50 mL), and dried *in vacuo* to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide (180 mg, 44%). MS: 415 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.09 (s,

NH, 1H), 9.33 (s, 1H), 8.35 (d, 1H), 8.20 (d, 1H), 7.90 (s, 1H), 7.79 (m, 2H), 7.65 (m, 1H), 7.46 (m, 2H), 6.74 (d, 1H), 2.79 (s, 3H).

Example 182

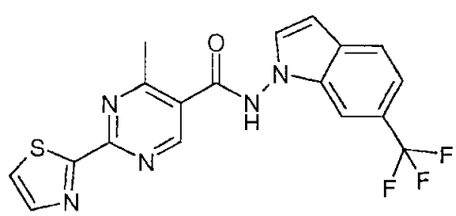
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide



A solution of 2-(2-pyridyl)-4-methyl-pyrimidine-5-carboxylic acid (258 mg, 1.2 mmol) and 6-trifluoromethyl-indol-1-ylamine (200 mg, 1 mmol) in DMF (5 mL) is stirred at 50°C for 0.5 h. The mixture is treated with DMTMM (290 mg, 1.05 mmol) and stirred at 50°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is triturated with Et_2O/heptane overnight. The precipitate is collected by filtration, washed with H_2O (50 mL) and heptane (50 mL), and dried *in vacuo* to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide (160 mg, 40%). MS: 398 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.13 (s, NH, 1H), 9.36 (s, 1H), 8.82 (d, 1H), 8.48 (d, 1H), 8.04 (m, 1H), 7.83 (m, 3H), 7.60 (m, 1H), 7.44 (d, 1H), 6.74 (d, 1H), 2.80 (s, 3H).

Example 183

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide

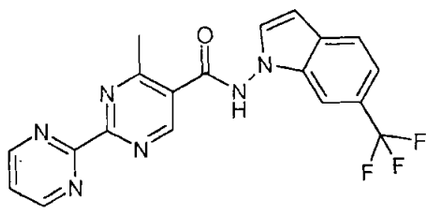


A solution of 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (265 mg, 1.2 mmol) and 6-trifluoromethyl-indol-1-ylamine (200 mg, 1 mmol) in DMF (5 mL) is stirred at 50°C for 0.5 h. The mixture is treated with DMTMM (290 mg, 1.05 mmol) and stirred at 50°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*.

The residue is triturated with Et_2O/heptane overnight. The precipitate is collected by filtration, washed with H_2O (50 mL) and heptane (50 mL), and dried *in vacuo* to afford 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide (160 mg, 40%). MS: 404 (M+H): ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.12 (s, NH, 1H), 9.33 (s, 1H), 8.15 (d, 1H), 8.05 (d, 1H), 7.91 (s, 1H), 7.79 (m, 2H), 7.44 (m, 1H), 6.73 (d, 1H), 2.77 (s, 3H).

Example 184

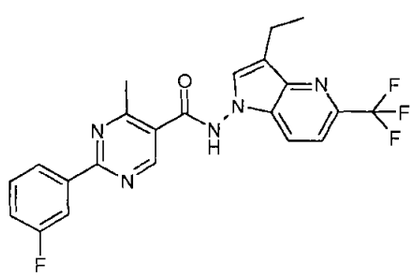
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide



A solution of 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (259 mg, 1.2 mmol) and 6-trifluoromethyl-indol-1-ylamine (200 mg, 1 mmol) in DMF (5 mL) is stirred at 50°C for 0.5 h. The mixture is treated with DMTMM (290 mg, 1.05 mmol) and stirred at 50°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is triturated with Et_2O/heptane overnight. The precipitate is collected by filtration, washed with H_2O (50 mL) and heptane (50 mL), and dried *in vacuo* to afford 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide (100 mg, 25%). MS: 399 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.16 (s, NH, 1H), 9.39 (s, 1H), 9.06 (d, 2H), 7.92 (s, 1H), 7.81 (m, 2H), 7.70 (t, 1H), 7.44 (d, 1H), 6.74 (d, 1H), 2.79 (s, 3H).

Example 185

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide



Step 1: A solution of 2-iodo-6-trifluoromethyl-pyridin-3-ylamine (5.09 g, 17.7 mmol) in DCM (50 mL) is treated with TFAA (3 mL, 21.2 mmol) and pyridine (1.7 mL, 21.2 mmol), and stirred at rt for 1 h. The mixture is diluted with H_2O (150 mL), and extracted with DCM (3 x 150 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is diluted with MeCN (50 mL), treated with *trans*-crotyl bromide (2.8 mL, 26.6 mmol) and K_2CO_3 (4.7 g, 34.4 mmol), and heated at reflux for 2 h. The mixture is filtered through a pad of Celite. The filtrate is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0% - 25% EtOAc in heptane to afford N-but-2-enyl-2,2,2-trifluoro-N-(2-iodo-6-trifluoromethyl-pyridin-3-yl) -acetamide (5.5 g, 71%). MS: 439 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, 1H), 7.53 (d, 1H), 5.52 (m, 2H), 4.98 (m, 1H), 3.58 (m, 1H), 1.68 (d, 3H).

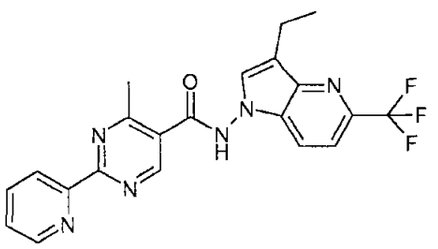
Step 2: A solution of N-but-2-enyl-2,2,2-trifluoro-N-(2-iodo-6-trifluoromethyl-pyridin-3-yl) -acetamide (5.2 g, 11.9 mmol) in DMF (24 mL) is treated with *n*-Bu_4NCl (3.6 g, 13.1 mmol), $Pd(OAc)_2$ (107 mg, 0.48 mmol), and stirred at 100°C for 1 h. H_2O (10 mL) is added, and the mixture is cooled to rt and filtered through a pad of silica gel. The filtrate is extracted with EtOAc/heptane (3 x 50 mL) (1:1). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 5% - 50% EtOAc in heptane to afford 3-ethyl-5-trifluoromethyl-1H-pyrrolo[3,2-b]pyridine (2.2 g, 86%). MS: 215 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (s, NH, 1H), 7.73 (d, 1H), 7.50 (d, 1H), 7.34 (d, 1H), 2.93 (q, 2H), 1.36 (t, 3H).

Step 3: A suspension of NaH (4.65 g, 116 mmol, 60% in mineral oil) in DMF (40 mL) at 0°C is treated with 3-ethyl-5-trifluoromethyl-1H-pyrrolo[3,2-b]pyridine (2 g, 7.75 mmol) and stirred at 0°C for 1 h. The mixture is treated with HOSA (4.4 g, 38.8 mmol) portion wise and warmed to rt over 2h. The mixture is then poured over ice, treated with solid NH_4Cl (3 g), and filtered through a pad of Celite. The filtrate is extracted with Et_2O (3 x 150 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 30% - 50% EtOAc in heptane to afford 3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-ylamine (1.5 g, 84%). MS: 230 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.97 (d, 1H), 7.59 (d, 1H), 7.54 (s, 1H), 6.12 (s, NH_2, 2H), 2.78 (q, 2H), 1.28 (t, 3H).

Step 4: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (278 mg, 1.1 mmol) and 3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-ylamine (230 mg, 1 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (290 mg, 1.05 mmol) and stirred at 50°C overnight. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 10 min. The precipitate is collected by filtration, washed with H_2O (50 mL) and heptane (50 mL), and dried *in vacuo* to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide (195 mg, 44%). MS: 444 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.16 (s, NH, 1H), 9.28 (s, 1H), 8.34 (d, 1H), 8.18 (m, 2H), 7.86 (s, 1H), 7.65 (m, 2H), 7.45 (m, 1H), 2.83 (q, 2H), 2.78 (s, 3H), 1.35 (t, 3H).

Example 186

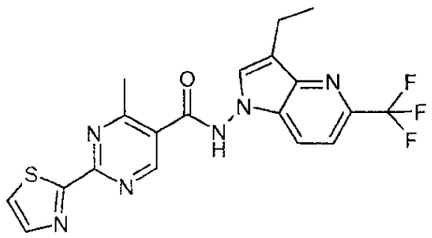
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide



A solution of 2-(2-pyridyl)-4-methyl-pyrimidine-5-carboxylic acid (258 mg, 1.1 mmol) and 3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-ylamine (230 mg, 1.0 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (290 mg, 1.05 mmol) and stirred at 50°C overnight. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 10 min. The precipitate is collected by filtration, washed with H_2O (50 mL) and heptane (50 mL), and dried *in vacuo* to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide (175 mg, 41%). MS: 427 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.18 (s, NH, 1H), 9.31 (s, 1H), 8.80 (d, 1H), 8.45 (d, 1H), 8.16 (d, 1H), 8.01 (m, 1H), 7.88 (s, 1H), 7.72 (d, 1H), 7.59 (m, 1H), 2.81 (q, 2H), 2.79 (s, 3H), 1.35 (t, 3H).

Example 187

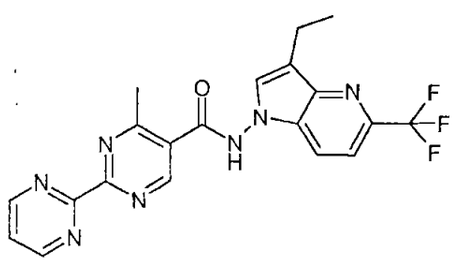
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide



A solution of 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (88 mg, 0.40 mmol) and 3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-ylamine (89 mg, 0.40 mmol) in DMF (5 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (113 mg, 0.41 mmol) and stirred at 50°C overnight. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 10 min. The precipitate is collected by filtration, washed with H_2O (50 mL) and heptane (50 mL), and dried *in vacuo* to afford 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide (75 mg, 40%). MS: 433 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.19 (s, NH, 1H), 9.28 (s, 1H), 8.15 (m, 2H), 8.08 (d, 1H), 7.87 (s, 1H), 7.72 (d, 1H), 2.83 (q, 2H), 2.77 (s, 3H), 1.35 (t, 3H).

Example 188

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide

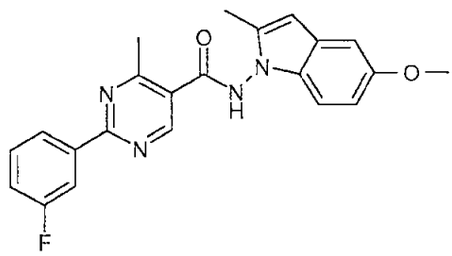


A solution of 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (259 mg, 1.2 mmol) and 3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-ylamine (230 mg, 1.0 mmol) in DMF (5 mL) is stirred at 50°C for 0.5 h. The mixture is treated with DMTMM (290 mg, 1.05 mmol) and stirred at 50°C overnight. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by preparative reverse-phase HPLC eluting with 20% - 100% MeCN in H_2O to afford 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide (230 mg, 54%). MS: 428 (M+H);

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.28 (s, 1H), 9.05 (d, 2H), 8.11 (d, 1H), 7.98 (s, 1H), 7.69 (t, 1H), 7.64 (d, 1H), 2.83 (q, 2H), 2.80 (s, 3H), 1.34 (t, 3H).

Example 189

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-2-methyl-indol-1-yl)-amide

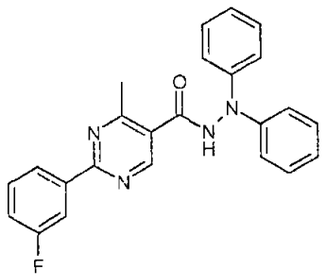


Step 1: A suspension of NaH (1.25 g, 51 mmol, 60% in mineral oil) in DMF (47 mL) at 0°C is treated with 5-methoxy-2-methylindole (500 mg, 3.1 mmol) and stirred at 0°C for 0.5 h. The mixture is treated with HOSA (1.92 g, 17.0 mmol) portion wise and warmed to rt over 2h. The mixture is then poured over ice, and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 5-methoxy-2-methyl-indol-1-ylamine, which is used in the next step without further purification.

Step 2: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (719 mg, 3.1 mmol) and 5-methoxy-2-methyl-indol-1-ylamine (550 mg, 3.1 mmol) in DMF (4 mL) is stirred at 50°C for 15 min. The mixture is treated with DMTMM (856 mg, 3.1 mmol) and stirred at 50°C for 1 h. The mixture is concentrated *in vacuo*, diluted with EtOAc (50 mL), and washed with saturated aqueous Na_2CO_3 (50 mL). The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 30% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-2-methyl-indol-1-yl)-amide (180 mg, 15%, 2 steps). MS: 391 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.23 (s, 1H), 8.34 (d, 1H), 8.18 (d, 1H), 7.63 (m, 1H), 7.46 (m, 1H), 7.31 (d, 1H), 7.02 (d, 1H), 6.77 (m, 1H), 6.25 (s, 1H), 3.76 (s, 3H), 2.77 (s, 3H), 2.34 (s, 3H).

Example 190

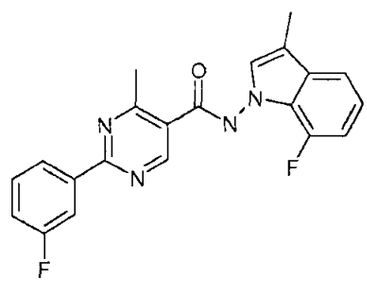
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid *N',N'*-diphenyl-hydrazide



A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (500 mg, 2.2 mmol) and *N,N*-diphenyl-hydrazine (422 mg, 2.2 mmol) in DMF (3 mL) is stirred at 50°C for 15 min. The mixture is treated with DMTMM (633 mg, 2.2 mmol) and stirred at 50°C for 3 h. The mixture is diluted with EtOAc (50 mL), and washed with saturated aqueous Na_2CO_3 (50 mL). The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 75% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid *N',N'*-diphenyl-hydrazide (60 mg, 7%). MS: 399 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.04 (s, 1H), 8.30 (d, 1H), 8.15 (m, 1H), 7.61 (m, 1H), 7.44 (m, 1H), 7.35 (m, 4H), 7.22 (m, 4H), 7.04 (m, 2H), 2.64 (s, 3H). IC_{50} = 16 nM.

Example 191

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (7-fluoro-3-methyl-indol-1-yl)-amide

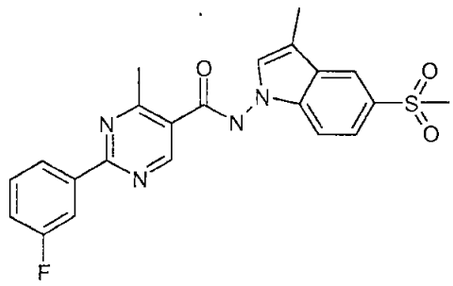


Step 1: A suspension of NaH (805 mg, 20.1 mmol, 60% in mineral oil) in DMF (5 mL) at 0°C is treated with 7-fluoro-3-methylindole (200 mg, 1.34 mmol) and stirred at 0°C for 1 h. The mixture is treated with HOSA (757 mg, 6.7 mmol) portion wise and warmed to rt over 2 h. The mixture is then poured over ice, and extracted with EtOAc (3 x 100 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 7-fluoro-3-methyl-indol-1-ylamine, which is used in the next step without further purification.

Step 2: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (1.34 mmol) and 7-fluoro-3-methyl-indol-1-ylamine (342 mg, 1.47 mmol) in DMF (15 mL) is stirred at 50°C for 1 h. The mixture is treated with DMTMM (407 mg, 1.47 mmol) and stirred at 50°C for 4 h. The mixture is concentrated *in vacuo*, diluted with Et_2O (50 mL), and washed with saturated aqueous Na_2CO_3 (50 mL). The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0% -100% DCM in EtOAc to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (7-fluoro-3-methyl-indol-1-yl)-amide (241 mg, 48%). MS: 379 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.05 (s, 1H), 8.32 (d, 1H), 8.18 (d, 1H), 7.64 (m, 1H), 7.45 (m, 1H), 7.40 (m, 1H), 7.31 (s, 1H), 7.05 (m, 2H), 2.74 (s, 3H), 2.29 (s, 3H).

Example 192

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-3-methyl-indol-1-yl)-amide



Step 1: A solution of allyl-(2-iodo-4-methanesulfonyl-phenyl)-amine (1.43 g, 4.1 mmol) in DMF (20 mL) is treated with *n*-Bu_4NCl (1.47 g, 5.32 mmol), $Pd(OAc)_2$ (56.6 mg, 0.2 mmol), and stirred at 100°C for 1 h. HCl (5.3 mL, 3 M) is added, and the mixture is cooled to rt, filtered through a pad of Celite, and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 60% EtOAc in heptane to afford 5-methanesulfonyl-3-methyl-1H-indole (370 mg, 43%).

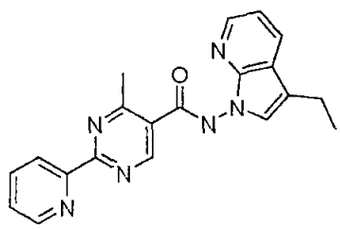
Step 2: A suspension of NaH (1.06 g, 26.6 mmol, 60% in mineral oil) in DMF (15 mL) at 0°C is treated with 5-methanesulfonyl-3-methyl-1H-indole (370 mg, 1.77 mmol) and stirred at 0°C for 1 h. The mixture is treated with HOSA (1 g, 8.85 mmol) portion wise and warmed to rt overnight. The mixture is then poured over ice, and extracted with EtOAc (3 x 100 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 5-

methanesulfonyl-3-methyl-indol-1-ylamine, which is used in the next step without further purification.

Step 3: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (1.77 mmol) and 5-methanesulfonyl-3-methyl-indol-1-ylamine (452 mg, 1.95 mmol) in DMF (15 mL) is stirred at rt for 1 h. The mixture is treated with DMTMM (538 mg, 1.95 mmol) and stirred at 60°C for 1.5 h. The mixture is diluted with EtOAc (50 mL), and washed with saturated aqueous Na_2CO_3 (50 mL). The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0% - 100% EtOAc in heptane, and then by triturating in Et_2O to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-3-methyl-indol-1-yl)-amide (106 mg, 14%). MS: 439 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.15 (s, 1H), 8.37 (d, 1H), 8.24 (m, 2H), 7.82 (m, 1H), 7.59 (d, 1H), 7.54 (m, 1H), 7.34 (s, 1H), 7.29 (m, 1H), 3.13 (s, 3H), 2.83 (s, 3H), 2.42 (s, 3H).

Example 193

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide trifluoroacetic acid salt



Step 1: (Ref.: J. Org. Chem. 2002, 67, 6226-6227) 7-Azaindole (5 g, 42.3 mmol) is added to a stirred suspension of $AlCl_3$ (22.6 g, 169 mmol) in DCM (300 mL). After stirring at rt for 1 h, acetyl chloride (13.3g, 169 mmol) is added drop wise and the resulting mixture is stirred for 18 h. The mixture is cooled to 0°C, quenched with MeOH (150 mL) and stirred for 1 h. Silica gel is added to the mixture, the solvents are removed under vacuum, and the residue is purified by silica gel chromatography eluting with 10% MeOH in DCM to afford 1-(1H-pyrrolo [2,3-b]pyridin-3-yl)-ethanone (1.6g). ^{1}H NMR (300 MHz, CH_3OD): δ 8.93(d, 1H), 8.45(s, 2H), 7.50(t, 1H), 3.30(s, 3H).

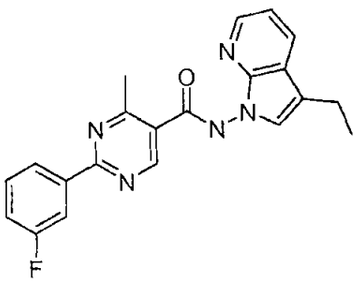
Step 2: To a solution of 1-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-ethanone (1.34 g, 8.38 mmol) in TFA (25 mL) is added triethylsilane (6.09 g, 52.4 mmol) and stirred at rt for 18 h. The mixture is concentrated, diluted with 2 N aqueous KOH solution and extracted three times with DCM. The combined organic layer is dried (Na_2SO_4), filtered and evaporated. The resulting residue is chromatographed through silica gel eluting with 10% MeOH in DCM to afford 3-ethyl-1H-pyrrolo[2,3-b]pyridine (0.91 g). MS: 147 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.23 (broad s, 1H), 8.32 (d, 1H), 7.94 (s,1H), 7.05-7.14 (m, 2H), 2.80 (q, 2H), 1.35 (t,3H).

Step 3: 3-Ethyl-1H-pyrrolo[2,3-b]pyridine (0.91 g, 6.2 mmol) and KO*t*Bu (1.39 g, 12.4 mmol) are dissolved in DMF (28 mL) and stirred for 2 h at rt. While vigorously sparging with nitrogen, NH_2Cl (92 ml 0.15 M in ether) is added in portions. The reaction mixture is stirred at rt for 2 h. The mixture is cooled 0^0C and then quenched with $Na_2S_2O_3$ (2.7 g) in water (50 mL). After standing at rt for 18 h, the mixture is concentrated, triturated in DCM and filtered. The filtrate is concentrated and chromatographed through silica gel eluting with 10% MeOH in DCM to afford 3-ethyl-pyrrolo[2,3-b]pyridin-1-yl- amine (380 mg). MS: 162 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, 1H), 7.90 (d, 1H), 7.04-7.13(m, 2H), 4.96 (broad s, 2H), 2.76 (q, 2H), 1.33 (t, 3H).

Step 4. A mixture of 3-ethyl-pyrrolo[2,3-b]pyridin-1-ylamine (126 mg, 0.78 mmol), 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (168 mg, 0.78 mmol), HATU (356 mg, 0.936 mmol) and DIPEA (302 mg, 2.34 mmol) in DMF (4 mL) is heated at 150^0C for 1 h. The reaction is quenched with water and extracted with EtOAC. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is first chromatographed through silica gel eluting wiht 10% MeOH in DCM. The resulting product is chromatographed again using reverse phase HPLC eluting with 0.1% TFA in water and acetonitrale to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide trifluoroacetic acid salt (29 mg). MS: 359 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 9.45 (s, 1H), 9.04 (d, 1H), 8.93 (d, 1H), 8.67 (t, 1H), 8.31 (d, 1H), 8.19-8.08 (m, 2H), 7.34 (s, 1H), 7.27 (dd, 1H), 2.96 (s, 3H), 2.85 (q, 2H), 1.39 (t, 3H).

Example 194

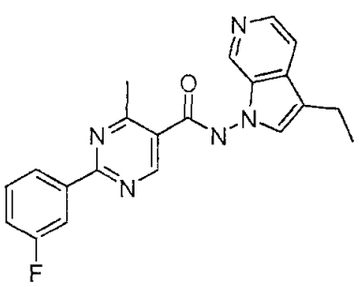
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide



A mixture of 3-ethyl-pyrrolo[2,3-b]pyridin-1-ylamine (126 mg, 0.78 mmol), 2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (180 mg, 0.78 mmol), HATU (356 mg, 0.036 mmol) and DIPEA (302 mg, 2.34 mmol) in DMF (4 mL) is heated at 150°C for 1 h. The reaction is quenched with water and extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 0-100% ethyl acetate in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide (128 mg). MS: 376 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.10 (s, 1H), 8.25-8.33 (m, 2H), 8.16 (d, 1H), 8.05 (d, 1H), 7.62 (q, 1H), 7.39-7.48 (m, 2H), 7.16 (dd, 1H), 2.78 (s, 3H), 2.75 (q, 2H), 1.29(t, 3H).

Example 195

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3c] pyridin-1-yl)-amide

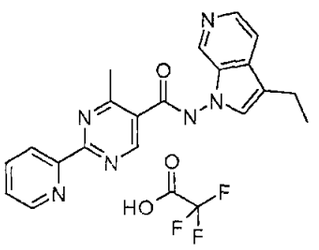


A mixture of 3-ethyl-pyrrolo[2,3-c]pyridin-1-ylamine (93 mg, 0.577 mmol), 2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (134 mg, 0.757 mmol), HATU (263 mg, 0.692 mmol) and DIPEA (223 mg, 1.73 mmol) in DMF (3 mL) is heated at 150° C for 1 h. The reaction is quenched with water and extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is purified by silica gel column chromatography eluting with 0-100% ethyl acetate in heptane to afford 2-(3-Fluoro-phenyl)-4-

methyl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide (86 mg). MS: 376 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 9.15 (s, 1H), 8.69 (s, 1H), 8.37 (d, 1H), 8.15-8.26 (m, 2H), 7.70 (d, 1H), 7.55 (q, 1H), 7.49 (s, 1H), 7.29 (t, 1H), 2.80-2.90 (m, 5 H), 1.38 (t, 3H). IC_{50} = 7 nM.

Example 196

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide trifluoroacetic acid salt



Step 1: (Ref.: J. Org. Chem. 2002, 67, 6226-6227) 6-Azaindole (2.5 g, 21.25 mmol) is added to a stirred suspension of $AlCl_3$ (11.3 g, 84.5 mmol) in CH_2Cl_2 (150 mL). After stirring at rt for 1 h, acetyl chloride (6.65g, 84.5 mmol) is added drop wise and the resulting mixture is stirred for 18 h. The mixture is cooled to 0°C, quenched with MeOH (75 mL) and stirred for 1 h. Silica gel (40 mL), MeOH and DCM are added to the mixture, the solvents are removed under vacuum and the residue is purified by silica gel chromatography eluting with 10% MeOHl in DCM to afford 1-(1H-pyrrolo[2,3-c]pyridin-3-yl)-ethanone (1.52g, 45%). MS: 161 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 9.20 (s, 1H), 8.95 (s, H), 7.82(d, 1H), 8.72 (d, 1H), 8.43 (d, 1-H), 2.64(s, 3H).

Step 2: To a solution of 1-(1H-pyrrolo[2,3-c]pyridin-3-yl)-ethanone (1.53 g, 9.55 mmol) in TFA (29 mL) triethylsilane (6.88g, 59.21 mmol) is added and stirred at rt for 18 h. The mixture is concentrated and extracted with EtOAc. The organic layer is washed with 2 N aqueous KOH, dried (Na_2SO_4), filtered and evaporated. The residue is chromatographed through silica gel eluting with 10% MeOH in DCM to afford 3-ethyl-1H-pyrrolo[2,3-c]pyridine (1.35 g, 97%). MS: 147 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.3 (broad, N-H) 9.46 (s, 1H), 8.04 (s, 1H), 7.71-7.88 (m, 2H), 2.88 (q, 2H), 1.39 (t, 3H).

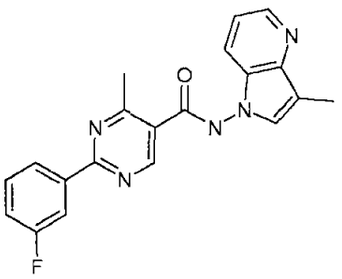
Step 3: 3-Ethyl-1H-pyrrolo[2,3-c]pyridine (1.21 g, 8.29 mmol) and KO*t*Bu (1.86 g, 16.57 mmol) are dissolved in DMF (47 mL) and stirred for 2 h at rt. While vigorously purging with

nitrogen, NH_2Cl (101 mL 0.15 M in ether) is added in portions. The reaction mixture is stirred at rt for 1 h. The mixture is then cooled to 0^0C and quenched with $Na_2S_2O_3$ (4.3 g) in water (80 mL). After standing at rt for 2 days, the layers are separated. Brine is added to the aqueous layer and then extracted with EtOAc. The organic layers are combined and dried (Na_2SO_4) to give a mixture of 3-ethyl-pyrrolo[2,3-c]pyridin-1-ylamine and starting material. This mixture is purified by chromatography through silica gel eluting with10% MeOH in DCM to afford 3-ethyl-pyrrolo[2,3-c]pyridin-1-ylamine (93 mg). The remaining mixture of starting material and product is collected and dissolved in DCM. This solution is cooled to 0^0C and charged with BOC_2O (164 mg, 0.75 mmol). The resulting mixture is purified by silica gel chromatography eluting with 10% MeOH in DCM to afford aaditional 3-ethyl-pyrrolo[2,3-c]pyridin-1-ylamine (145 mg). ^1H NMR (300 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.25 (d, 1H), 7.48 (d, 1H), 7.10 (s, 1H), 4.88 (s, 2H), 2.75 (q, 2H), 1.35(t, 3H).

Step 4. A mixture of 3-ethyl-pyrrolo[2,3-c]pyridin-1-ylamine (122 mg, 0.757 mmol), 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (163 mg, 0.757 mmol), HATU (356 mg, 0.936 mmol) and DIPEA (294 mg, 2.27 mmol) in DMF (4 mL) is heated at 150^0 C for 1 h. The reaction is quenched with water and the extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 10% MeOH in DCM. The resulting product is chromatographed again using reverse phase HPLC eluting with 0.1% TFA in water and acetonitrale to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide trifluoroacetic acid salt (42 mg, 9.5%). MS: 359 (M+H); ^1H NMR (300 MHz, DMSO- d^6): δ 9.43 (s, 1H), 9.37 (s, 1H), 8.80 (d, 1H), 8.45 (t, 2H), 8.26 (s, 1H), 8.22 (d, 1H), 8.03 (t, 1H), 7.59 (t, 1H), 2.86 (q, 2H), 2.80 (s, 3H), 1.32 (t, 3H).

Example 197

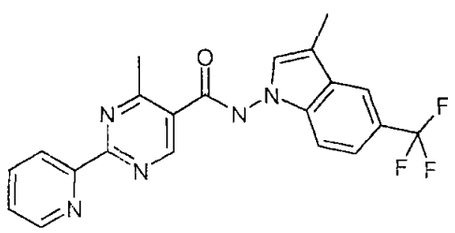
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide



A mixture of 3-methyl-pyrrolo[3,2-b]pyridin-1-yl amine (75% pure) (240 mg, <1.63 mmol), 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (379 mg, 1.63 mmol), HATU (744 mg, 1.96 mmol) and DIPEA (388 mg, 4.89 mmol) in DMF (5 mL) is heated at 150°C for 1 h. The reaction is quenched with water, extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 10% MeOH in DCM. The resulting product is recrystallized with ether to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide (197 mg, 44%). MS: 362 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 9.14 (s, 1H), 8.40 (d, 1H), 8.36 (d, 1H), 8.22 (d, 1H), 7.85(d, 1H), 7.55 (q 1H), 7.47 (s, 1H), 7.25-7.34 (m, 2H), 2.83 (s, 3H), 2.42(s, 3H). IC_{50} = 2 nM.

Example 198

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-5-trifluoromethyl-indol-1-yl)-amide



Step1: To a mixture of 2-iodo-4-trifluoromethyl-aniline (5 g, 17.4 mmol), KO*t*-Bu (2.05 g, 18.3 mmol) and THF (200 mL) at −78°C, is added allyl bromide (2.21 g, 18.3 mmol). The resulting mixture is warmed to rt and stirred for 18 h. Water is added, and the mixture is extracted with EtOAc. The organic layer is separated, dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 0-50% EtOAc in heptane to afford allyl-(2-iodo-4-trifluoromethyl-phenyl)-amine (1.9 g, 33%). MS 328 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.45 (d, 1 H), 5.88-6.02 (m, 1H), 5.33 (d, 1 H), 5.25 (d, 1H), 4.72(broad s, 1H), 3.90 (s, 2H).

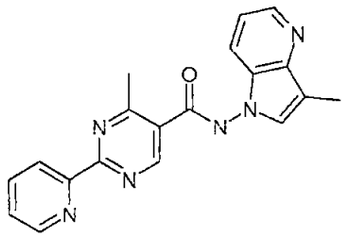
Step 2: A mixture of allyl-(2-iodo-4-trifluoromethyl-phenyl)-amine (1.75 g, 5.35 mmol), tetrabutylammonium chloride (1.68 g, 5.35 mmol), palladium acetate (120 mg, 0.54 mmol) and potassium carbonate (2.22 g, 16.0 mmol) in DMF (50 mL) is heated at 80^0 C for 1.5 h. The reaction is quenched with water and extracted three times with DCM. The combined organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 0-40% EtOAc in heptane to afford 3-methyl-5-trifluoromethyl-1H-indole (401 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (broad s, 1H), 7.90 (s, 1 H), 7.44 (s, 1H), 7.10 (s, 1H), 2.38 (s, 3H).

Step 3: 60% NaH (1.21 g, 30.2 mmol) is added to a stirred solution of 3-methyl-5-trifluoromethyl-1H-indole (400 mg, 2.01 mmol) in DMF (6 mL) at 0^{0}C in portions. The mixture is stirred at 0^{0}C for 1 h. HOSA (1.14g, 10.0 mmol) is added in portions at 0^{0}C and the mixture is allowed to warm to rt over 2 h. The reaction is quenched with aqueous saturated ammonium chloride, extracted with extracted three times with DCM. The combined organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 0-40% EtOAc in heptane to afford 3-methyl-5-trifluoromethyl-indol-1-ylamine (223 mg, 52%). MS: 215 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 7.48 (s, 2H), 7.04 (s, 1H), 4.77 (s, 2H), 2.34 (s, 3H).

Step 4: A mixture of 3-methyl-5-trifluoromethyl-indol-1-ylamine (223 mg, 1.04 mmol), 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (224 g, 1.04 mmol), HATU (475 mg, 1.25 mmol), DIPEA (404 mg 3.13 mmol) is stirred in DMF at 150^0 C for 1h. The reaction is quenched with water, extracted with extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 10% MeOH in DCM to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-5-trifluoromethyl-indol-1-yl)-amide (122 mg, 28%). MS: 412 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 9.22 (s, 1H), 8.79 (d, 1H), 8.66 (d, 1H), 8.06 (t, 1H), 7.91 (s, 1H), 7.60 (dd, 1H), 7.51 (s, 2H), 7.29 (s, 3H), 2.88 (s, 3H), 2.40 (s, 3H).

Example 199

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide



Step 1: To a solution of 3-amino-2-chloropyridine (5 g 38.9 mmol) in THF (35 mL) is added 2 M NaHMDS in THF (38.9 mL, 77.8 mmol). After stirring at rt for 15 min, BOC_2O (7.7g, 35.6 mmol) in THF (20 mL) is added in one portion and then stirred for 5 h at rt. 0.1% aqueous HCl is added. The mixture is extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 0-50% EtOAc in heptane to afford (2-chloro-pyridin-3-yl)-carbamic acid tert-butyl ester (7.18g, 89%). MS: 229 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (d, 1H), 8.05 (dd, 1H), 7.23 (dd, 1H), 7.02 (broad s, 1H), 1.55 (s, 9H)).

Step 2: A mixture of (2-chloro-pyridin-3-yl)-carbamic acid tert-butyl ester (7 g, 30.7 mmol), allyl bromide (5.26g, 40.8 mmol) and cesium carbonate (20.8g, 63.8 mmol) in DMF (280 mL) is heated at 60^0 C for 1 h. The reaction is quenched with water, extracted with EtOAC. The organic layer is dried (Na_2SO_4), filtered and concentrated to afford allyl-(2-chloro-pyridin-3-yl)-carbamic acid tert-butyl ester (8.03g, 98%), which is sued in the next step with no further purification.

Step 3: A mixture of allyl-(2-chloro-pyridin-3-yl)-carbamic acid tert-butyl ester (8.03 g, 30 mmol), tetrabutylammonium chloride (9.4 g, 30 mmol), palladium acetate (673 mg, 3 mmol) and potassium carbonate (12.4 g, 3 mmol) in DMF (300 mL) is heated at 80^0 C for 1.5 h. The reaction is quenched with DCM and washed with water. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 0-40% EtOAc in heptane to afford 3-methyl-pyrrolo[3,2-b]pyridine-1-carboxylic acid tert-butyl ester and 3-methylene-2,3-dihydro-pyrrolo[3,2-b]pyridine-1-carboxylic acid tert-butyl ester (1.58 g).

Step 4: The above mixture is then stirred in DCM (10 mL) and TFA (10 mL) at rt for 3 h. The reaction is concentrated, and 2 M KOH aqueous solution and DCM are added. The precipitate is collected by filtration to afford 3-methyl-1H-pyrrolo[3,2-b]pyridine potassium salt (1 g,

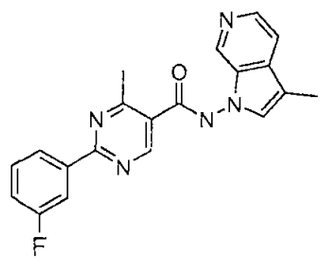
20%). MS: 133 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 8.26(d, 1H), 7.75(d, 1H), 7.33(s, 1H), 7.12(dd, 1H), 2.36 (s, 3H).

Step 5: A mixture of 3-methyl-1H-pyrrolo[3,2-b]pyridine potassium salt (1 g, 5.88 mmol), KOtBu (660mg, 5.88 mmol) in DMF (26 mL) is purged with N_2 and stirred at rt for 2 h. Chloramine in ether (0.15 M, 29 mL) is added and the mixture is stirred for 45 min. The reaction is cooled to 0^0C. $Na_2S_2O_3$ (3.4 g) in water (70 mL) is added and the mixture is stirred for 15 min. The mixture is concentrated *in vacuo*. The residue is triturated with DCM and then filtered. The filtrate is washed with 2 M aqueous KOH, dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 10% MeOH in DCM to afford a mixture of starting material and 3-methyl-pyrrolo[3,2-b]pyridin-1-yl amine (839 mg,~ 64%, ~66 mol% pure), which is used in the next step without further purification.

Step 6: A mixture of 3-methyl-pyrrolo[3,2-b]pyridin-1-yl amine (839 mg, < 5.71 mmol), 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (1.32 g, 6.13 mmol), HATU (2.6 g, 6.85 mmol), DIPEA (2.21 g 17.1 mmol) in DMF (17 mL) is stirred at 150^0C for 1h. The reaction is quenched with water and ether. The water layer is concentrated *in vacuo*. The residue is chromatographed through silica gel eluting with a mixture of DCM, MeOH and triethylamine (9.5: 0.5: 0.05) to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide (134 mg). MS: 345 345 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 9.22 (s, 1H), 8.79 (d, 1H), 8.64 (d, 1H), 8.40(d, 1H), 8.05 (t, 1H), 7.87 (d, 1H), 7.60 (t, 1H), 7.49 (s, 1H) 7.30 (dd, 1H), 2.87 (s, 3H), 2.42 (s, 3H).

Example 200

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3c]pyridin-1-yl)-amide

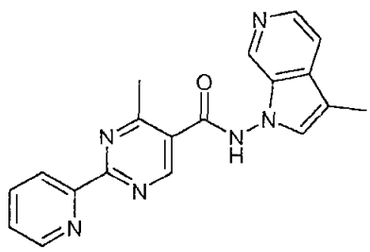


Step 1: 60% Sodium hydride (6.69 g, 167 mmol) is added to a stirred solution of 3-methyl-1H-pyrrolo[2.3-c]pyridine (1.47 g, 11.2 mmol) in DMF (33 mL) portion wise at 0^0 C for 1 h. Hydroxylamine-O-sulfonic acid (6.3 g, 55.8 mmol) is added in potions at 0^0C and stirred for 2 h at 0^0C. The reaction mixture is quenched at 0^0C with water, concentrated *in vacuo* to remove DMF. The residue is triturated in DCM. The solid is filtered off and the filtrate is concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10% MeOH in DCM to afford 3-methyl-pyrrolo[2,3-c]pyridin-1-ylamine (1 g, 61%). MS: 148 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.27 (d, 1H), 7.46 (d, 1H), 7.09 (s, 1H), 2.30 (s, 3H).

Step 2: A mixture of 3-methyl-pyrrolo[2,3-c]pyridin-1-ylamine (224 mg, 1.53 mmol), 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (354 mg, 1.53 mmol), HATU (693 mg, 1.82 mmol) and DIPEA (593 mg, 4.59 mmol) in DMF (8 mL) is stirred at 150^0C for 1 h. The reaction is quenched with water, extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-100% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide (55 mg). MS: 362 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 9.15 (s, 1H), 8.69 (s, 1H), 8.37 (d, 1H), 8.24 (s, 1H), 8.20 (d, 1H), 7.68 (d, 1H), 7.55 (q, 1H), 7.47 (s, 1H), 7.29 (t, 1H), 2.84(s, 3H), 2.39 (s, 3H).

Example 201

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide



Step 1: To a solution of 3-amino-4-chloropyridine (6.56 g, 51 mmol) in THF (46 mL) is added 2 M NaHMDS in THF (50 mL, 100 mmol). After stirring at rt for 15 min BOC_2O (10.1 g, 46.4 mmol) in THF (26 mL) is added in one portion and the mixture is stirred for 3 h at rt. 0.1% aqueous HCl (590 mL) is added. The mixture is extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is purified by silica gel

chromatography eluting with 0-50% EtOAc in heptane to afford (4-chloro-pyridin-3-yl)-carbamic acid tert-butyl ester (6.78g, 76 %). MS: 229 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.38 (ms 1H), 8.23 (d, 1H), 7.30 (dd, 1H), 6.85 (broad s, 1H), 1.57 (s, 9H).

Step 2: A mixture of (4-chloro-pyridin-3-yl)-carbamic acid tert-butyl ester (6.78 g, 29.7 mmol), allyl bromide (5.1 g, 40.8 mmol) and cesium carbonate (20.1 g, 61.8 mmol) in DMF (200 mL) is heated at 60^{0}C for 1 h. The reaction is quenched with water, extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is purified by silica gel column chromatography eluting with 0-40% EtOAc in heptane to afford allyl-(4-chloro-pyridin-3-yl)-carbamic acid tert-butyl ester (5.66 g, 71%). MS: 269 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42(d, 1H), 7.40 (d, 1H), 5.80-5.98 (m, 1H), 4.35-4.51 (m, 1H), 3.90-4.07 (m, 1H).

Step 3: A mixture of allyl-(4-chloro-pyridin-3-yl)-carbamic acid tert-butyl ester (7.68 g, 28.7 mmol), tetrabutylammonium chloride (9.0g, 28.7 mmol), palladium acetate (643 mg, 2.87 mmol) and potassium carbonate (11.9 g, 86.0 mmol) in DMF (200 mL) is heated at 80^{0}C for 1.5 h. The reaction mixture is diluted with DCM and washed three times with water. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is purified by silica gel column chromatography eluting with 0-40% EtOAc in heptane to afford a mixture of 3-methyl-pyrrolo[2,3-c]pyridine-1-carboxylic acid tert-butyl ester and 3-methylene-2,3-dihydro-pyrrolo[2,3-c]pyridine-1-carboxylic acid tert-butyl ester (3.1 g total).

Step 4: The above mixture is stirred in DCM (10 mL) and TFA (10 mL) at rt for 18 h and then concentrated *in vacuo*. 2 M aqueous KOH is added. The mixture is extracted with EtOAC. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is purified by silica gel column chromatography eluting with 10% MeOH in DCM to afford 3-methyl-1H-pyrrolo[2,3-c]pyridine (1.98 g, 69%). MS: 133 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.10 (broad s, 1H), 8.79 (s, 1H), 8.28 (d, 1H), 7.52 (d, 1H), 7.20 (s, 1H) 2.36 (s, 2H).

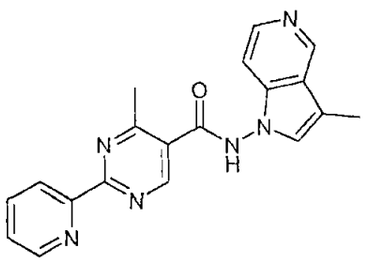
Step 5: A mixture of 3-methyl-1H-pyrrolo[2,3-c]pyridine (1.21 g, 9.16 mmol), KOtBu (2.05 g, 18.3 mmol) in DMF (41 mL) is purged with N_2 and stirred at rt for 2 h. Chloramine in ether (0.15 M, 92 mL) is added and the mixture is stirred for 20 min. The reaction is cooled to 0^{0}C and a solution of $Na_2S_2O_3$ (5 g) in water (80 mL) is added. The mixture is stirred for 10

min, and then concentrated *in vacuo*. The residue is triturated in DCM and filtered. DCM is added, cooled to 0^0C and charged with BOC_2O (541 mg, 2.48 mmol). The resulting mixture is separated by silica gel chromatography eluting with 10% MeOH in DCM to afford 3-methyl-pyrrolo[2,3-c]pyridin-1-yl amine (468 mg, 35 %). MS: 148 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.27 (d, 1H), 7.46 (d, 1H), 7.09 (s, 1H), 2.30 (s, 3H).

Step 6: A mixture of 3-methyl-pyrrolo[2,3-c]pyridin-1-yl amine (467 mg, 3.18 mmol), 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (683 g, 3.18 mmol), HATU (1.45 g, 3.81 mmol), DIPEA (1.23 g 9.54 mmol) in DMF (10 mL) is stirred at 150^0 C for 1h. The reaction is quenched with water, and $NaHCO_3$ (320 mg, 3.81 mmol) and EtOAC are added. The resulting solid is collected by filtration and then triturated with hot water. The mixture is filtered again and the solid is dried under vacuum to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide (484 mg). MS: 345 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 9.24 (s, 1H), 8.79 (d, 2H), 8.65 (d, 1H), 8.21 (d, 1H), 8.05 (t, 1H), 7.72 (d, 1H), 7.60 (s, 1H), 7.57 (s, 1H), 2.88 (s, 3H), 2.40 (s, 3H).

Example 202

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide



Step 1: To a solution of 4-amino-3-chloropyridine (15 g, 116.7 mmol) in THF (60 mL) is added NaHMDS in THF (1 M, 233. mL, 233 mmol). After stirring at rt for 30 min, BOC_2O (23.2 g, 106 mmol) in THF (45 mL) is added in one portion and the mixture is stirred for 3 h at rt. Additional BOC_2O (2 g, 9.0 mmol) in THF (40 mL) is added and the reaction is stirred for 18 h at rt. 0.1% aqueous HCl (1.35 L) is added. The mixture is extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is recrystalized from ether to afford (3-chloro-pyridin-4-yl)-carbamic acid tert-butyl ester (4 g). The mother liquor is purified by silica gel column chromatography eluting with 0-50% EtOAc in heptane. The collected product is crystallized from ether to afford additional 4.5 g of (3-chloro-pyridin-

4-yl)-carbamic acid tert-butyl ester (total yield 8.5 g). MS: 229 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (s, 1H), 8.38 (d, 1H), 8.17 (d, 1H), 7.18 (broad s, 1H) 1.57 (s, 9H).

Step 2: A mixture of (3-chloro-pyridin-3-yl)-carbamic acid tert-butyl ester (8.4 g, 36.8 mmol), allyl bromide (7.46 g, 39.1 mmol) and cesium carbonate (24.9 g, 76.4 mmol) in DMF (100 mL) is heated at 60^{0}C for 1 h. The reaction is quenched with water, extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-40% EtOAc in heptane to afford allyl-(3-chloro-pyridin-3-yl)-carbamic acid tert-butyl ester (8.4 g, 85%). MS: 269 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (s, 1H), 8.49 (d, 1H), 7.18 (d, 1H), 5.80-5.96 (m, 1H) 5.15 (s, 1H), 5.10(d, 1H), 4.2 (broad s, 1H), 1.43 (s, 9H).

Step 3: A mixture of allyl-(3-chloro-pyridin-4-yl)-carbamic acid tert-butyl ester (8.25 g, 30.8 mmol), tetrabutylammonium chloride (9.67g, 30.8 mmol), palladium acetate (691 mg, 3.08 mmol) and potassium carbonate (12.8 g, 92.3 mmol) in DMF (100 mL) is heated at 80^{0}C for 1.5 h. The reaction is diluted with DCM and washed three times with water. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 0-40% EtOAc in heptane to afford a mixture 3-methyl-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester and 3-methylene-2,3-dihydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (4.21 g, total).

Step 4: The mixture from step 3 is stirred in DCM (10 mL) and TFA (10 mL) at rt for 18 h. The reaction is concentrated. 2 M aqueous KOH solution is added, and the mixture is extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is chromatographed through silica gel eluting with 10% MeOH in DCM to afford of 3-methyl-1H-pyrrolo[3,2-c]pyridine (1.91g, 47%). MS: 133 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (s, 1H), 8.24 (d, 1H), 7.37 (d, 1H), 7.11 (s, 1H) 2.40 (s, 3H).

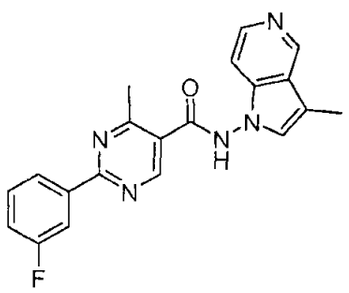
Step 5: A mixture of 3-methyl-1H-pyrrolo[3,2-c]pyridine (1.91 g, 14.47 mmol) and KO*t*Bu (3.25 g, 28.9 mmol) in DMF (65 mL) is purged with N_2 and stirred at rt for 2 h. Chloramine in ether (0.15 M, 145 mL) is added and the mixture is stirred for 20 min. The reaction is cooled to 0^{0}C and a solution of $Na_2S_2O_3$ (800 mg) in water (130 mL) is added. The mixture is stirred for 10 min at 0^{0}C, and then concentrated *in vacuo*. The residue is triturated in DCM

and filtered. DCM is added to the filtrate, cooled to 0^0C and treated with BOC_2O (793 mg, 3.6 mmol). The mixture is concentrated *in vacuo*, and the residue is purified by silica gel chromatography eluting with 10% MeOH in DCM to afford 3-methyl-pyrrolo[3,2-c]pyridin-1-yl amine (842 mg, 35 %). MS: 148 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.36 (d, 1H), 7.32 (d, 1H), 6.95 (s, 1H) 4.77 (s, 2H), 2.37 (s, 3H).

Step 6: A mixture of 3-methyl-pyrrolo[3,2-c]pyridin-1-yl amine (223 mg, 1.52 mmol), 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (329 mg, 1.52 mmol), HATU (693 mg, 1.82 mmol) and DIPEA (593 mg, 4.59 mmol) in DMF (8 mL)is stirred at 150°C for 1 h. The reaction is quenched with water and $NaHCO_3$ (168 mg, 2 mmol). The mixture is concentrated in vacuo. The residue is purified by silica gel chromatography eluting with 10% meOH in DCM to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide (91 mg, 17%). MS: 345 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.34 (s, 2H), 8.79 (d, 1H), 8.53 (d, 1H), 8.45 (d, 1H), 8.13 (d, 1H), 8.02 (t, 1H), 7.86 (s, 1H), 7.59 (t, 1H), 2.77 (s, 3H), 2.43 (s, 3H).

Example 203

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide

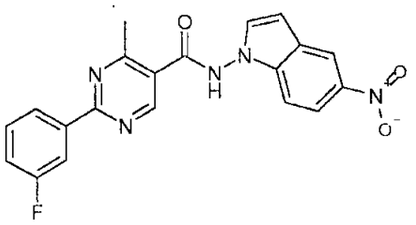


A mixture of 3-methyl-pyrrolo[3,2-c]pyridin-1-ylamine (224 mg, 1.52 mmol), 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (354 mg, 1.52 mmol), HATU (693 mg, 1.82 mmol) and DIPEA (593 mg, 4.59 mmol) in DMF (8 mL) is heated at 150^0C for 1 h. The reaction is quenched with water, $NaHCO_3$ (168 mg, 2 mmol) is added and the mixture is extracted with EtOAc. The oganic layer is separated, dried (Na_2SO_4), filtered and concentrated. The residue is first purified by silica gel column chromatography eluting with 10% MeOH in DCM and then recrystallized from EtOAc to afford 2-(3-fluoro-phenyl)-4-

methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide (198 mg). MS: 362 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 9.12 (s, 1H), 8.86 (s, 1H), 8.35 (d, 1H), 8.15-8.31 (m, 2H), 7.47-7.60 (m, 2H), 7.35 (s, 1H), 7.29 (t, 1H), 2.84 (s, 3H), 2.44 (s, 3H).

Example 204

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-nitro-indol-1-yl)-amide

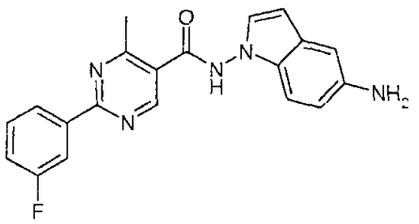


Step 1: NaH (60%, 421.5 mmol) is added portion-wise to a solution of 5-nitro-1H-indole (28.1 mmol) in anhydrous DMF (80 mL) at 0°C and the mixture is stirred at 0°C under N_2 for 10 min. HOSA (140.5 mmol) is added portion-wise for 30 minutes and the mixture is stirred at 0°C for 2 h. The reaction is quenched with water. Additional water (250 mL) is added and the mixture is extracted with EtOAc (3x 100 mL). The combined organic layer is washed with water (2x30 mL), brine (30 mL), dried (Na_2SO_4), filtered and concentrated. The residue is washed with heptane (2x20 mL) and recrystallized from EtOAc to afford 5-nitro-indole-1-ylamine (4.84 g, 97%) as a solid. MS: 178 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.93(br, 2N-H), 6.62(d, H), 7.30(d, H), 7.52(d, H), 8.17(d, H), 8.58 (s, H).

Step 2: DIPEA (12.65 mmol) is added a solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (4.22 mmol), 5-nitro-indole-1-ylamine (4.22 mmol) and HOTT (S-(1-oxido-2-pyridyl)-thio-N,N,N',N'-tetramethyluronium hexafluorophosphate) (7.6 mmol) in anhydrous DMF (15 mL) and the mixture is heated at 80-90°C overnight. After evaporation of solvent, the residue is dissolved in EtOAc (150 mL), washed with water (20 mL), 5% sodium sulfate (20 mL), water (mL) and brine (20 mL). The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is kept at rt overnight to yield 4-methyl-2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-nitro-indol-1-yl)-amide (730 mg, 44%) as a solid. MS: 392 (M+H); ^{1}H NMR (300 MHz, DMSO-d^6): δ 2.78(s, 3H), 6.88(d, H), 7.38-7.53(m, H), 7.57-7.76(m, 2H), 7.81(d, H), 8.06-8.32(m, 2H), 8.34(d, H), 8.65(d, H), 9.27(s, 2H).

Example 205

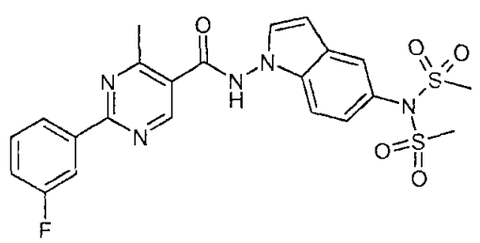
2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-amino-indol-1-yl)-amide



A solution of 4-methyl-2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-nitro-indol-1-yl)-amide (1.64 mmol) in MeOH (45 mL) and 10% Pd/C (0.16 mmol) is hydrogenated in a 500 mL Paar bottle under 50 psi at rt overnight. Pd/C is filtered off. The filtrate is concentrated to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-amino-indol-1-yl)-amide (545 mg, 92%) as a solid. MS: 362 (M+H): ^{1}H NMR (300 MHz, CD_3OD): δ 3.84(s, H), 6.37(d, H), 6.81(dd, H), 7.01(d, H), 7.16-7.36(m, 3H), 7.55(m, H), 8.23(d, H), 8.36(d, H), 9.50 (s, H).

Example 206

2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-(dimethanesulfonyl)-amino-indol-1-yl]-amide

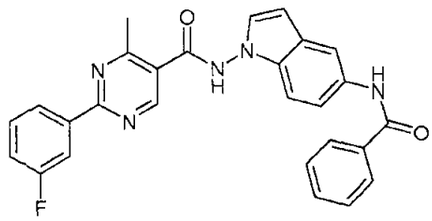


A mixture of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-amino-indol-1-yl)-amide (0.43 mmol) and methanesulfonyl chloride (0.52 mmol) in anhydrous DCM (10 mL) is stirred at 0°C and triethylamine (1.29 mmol) is added. The reaction mixture is stirred at 0°C for 1 h, and then warmed to rt and stirred for 30 minutes. DCM is added (20 mL), and the mixture is washed with 4% HCl (15 mL), water (10 mL) and brine (15 mL). The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is purified by chromatography using silica gel eluting with 0-60% EtOAC in DCM to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-(dimethanesulfonyl)-amino-indol-1-yl]-amide (85 mg, 38%)

as a solid. MS: 518 (M+H): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.75(s, 3H), 2.90(s, 3H), 3.66(s, 3H), 6.51(s, H), 7.04-7.53(m, 6H), 8.03(d, H), 8.12(d, H), 8.60(s, H).

Example 207

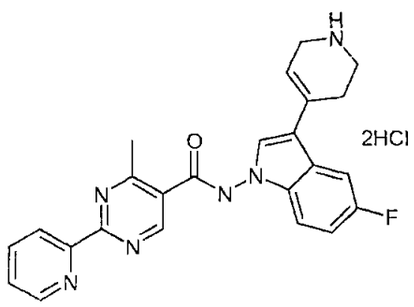
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-benzoylamino-indol-1-yl)-amide



A solution of benzoyl chloride (0.85 mmol) in anhydrous DCM (2 mL) is added drop-wise to a solution of 4-methyl-2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-amino-indol-1-yl)-amide (0.47 mmol) and triethylamine (1.41 mmol) in anhydrous DCM (16 mL) and the mixture is stirred at rt overnight. The reaction mixture is concentrated *in vacuo*. The residue is dissolved in EtOAc (25 mL), and washed with water (2X20 mL) and brine (10 mL). The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is triturated with EtOAc to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-benzoylamino-indol-1-yl)-amide (95 mg, 43%) as a solid. MS: 466 (M+H): ^{1}H NMR (300 MHz, DMSO-d^6): δ 2.99(s, 3H), 6.72(d, H), 7.38-7.48(m, H), 7.48-7.80(m, 6H), 7.83-8.016(m, 3H), 8.07-8.20(m, H), 8.23-8.35(m, 2H), 9.24(s, H), 10.25(br, H).

Example 208

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-indol-1-yl]-amide dichlorochloride



Step 1: A mixture of 5-fluoroindole (6.65 g, 49.2 mmol) and 4-piperidone hydrate hydrochloride (18.9 g, 123 mmol) in methanol solution of 2 N KOH (90 mL) is refluxed for 6

h. After cooling to rt, water (150 mL) is added and stirred at rt for 30 minutes. The resulting precipitate is filtered, washed with water (10 mL) and ether (15 mL), and dried *in vacuo* to afford 5-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-indole (6.34 g, 60%). MS: 217 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (br, H), 7.57 (dd, H), 7.24-7.37 (m, H), 7.23 (s, H), 6.98 (t, H), 6.20 (s, H), 3.62 (m, 2H), 3.16 (m, 2H), 2.50 (s, 2H).

Step 2: A solution of di-tert-butyl dicarbonate (504 mg, 2.31 mmol) in DCM (10 mL) is added to a stirred solution of 5-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-indole (500 mg, 2.31 mmol) in DCM (20 mL) at rt and stirred at rt overnight. The reaction mixture is concentrated *in vacuo* to afford 4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (730 mg). MS: 317 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (br, H), 7.56 (d, H), 7.31 (m, H), 7.26 (s, H), 6.99 (t, H), 6.13 (s, H), 4.17(m, 2H), 3.70 (m, 2H), 2.57 (s, 2H), 1.54 (s, 9H).

Step 3: A solution of 4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (730 mg, 2.31 mmol) in anhydrous DMF is added slowly to a stirred solution of 60 % NaH (1108 mg, 27.72 mmol) in anhydrous DMF (20 mL) at 0°C under N_2 and stirred at rt for an hour. HOSA (1305 mg, 11.55 mmol) is added portion-wise at 0°C, stirred at 0°C for 5 hours, poured into ice/water (350 mL) and extracted with ether (3 x 35 mL). The combined organic extract is washed with water (2 x 20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is washed with heptane (3 x 5 mL) to afford 4-(1-Amino-5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (715 mg, 94%) as a solid. MS: 332 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, H), 7.36 (m, H), 7.20 (s, H), 7.04 (t, H), 6.06 (s, H), 4.78 (s, 2H), 4.15(m, 2H), 3.69 (t, 2H), 2.54 (s, 2H), 1.55 (s, 9H).

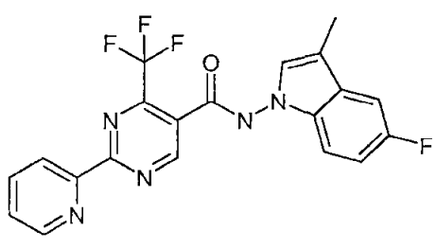
Step 4: Triethylamine (2.6 mmol) is added to a stirred solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (1.30 mmol) and iso-butyl chloroformate (1.95 mmol) in anhydrous DCM (20 mL) at rt under N_2 and stirred at rt for 2 h. The reaction mixture is concentrated *in vacuo*. The residue is dried *in vacuo* and THF (30 mL) is added. The mixture is filtered and the filtrate is concentrated to afford iso-butyl-[1-(4-methyl-2-pyridin-2-yl-pyrimidin-5-yl]]-carbonate (350mg, 85%).

Step 5: Sodium bis(trimethylsilyl)amide (2 N) in THF (0.83 mL) is added to a stirred solution of 4-(1-amino-5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (367 mg,1.11 mmol) in anhydrous DMF (20 mL) at rt under N_2, then stirred at rt for 15 min. A solution of iso-butyl-[1-(4-methyl-2-pyridin-2-yl-pyrimidin-5-yl]]-carbonate (350mg, 1.11 mmol) in anhydrous DMF (5 mL) is added slowly at rt and stirred at 60°C for 18 hours under N_2. DMF is evaporated off. The residue is dissolved in EtOAc (60 mL), washed with water (3x20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0-20% MeOH in DCM to afford 4-{5-fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indol-3-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (158 mg, 28%).

Step 6: A solution of 4-{5-fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indol-3-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (158 mg) in DCM (15 ml) is bubbled with HCl gas for 10 min at rt, then stirred at rt for 18 h. DCM is evaporated off and the residue is triturated with MeOH (2 mL). The solide is collected by filtration and dried to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-indol-1-yl]-amide dichlorochloride (81 mg, 54%). MS: 429 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ =2.89(m, 2H), 2.96(s, 3H), 3.53(t, 2H), 3.94(m, H), 6.27(s, H), 7.12(t, H), 7.46(q, H), 7.59-7.71(m, H), 8.28 (t, H), 8.85 (t, H), 8.99(d, H), 9.15(d, H), 9.41(s, H).

Example 209

2-Pyridin-2-yl-4-trifluoromethyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide

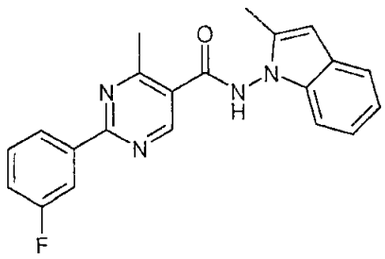


A solution of 2-pyridin-2-yl-4-trifluoromethyl-pyrimidine-5-carboxylic acid (219 mg, 0.81 mmol), 5-fluoro-3-methyl-indol-1-ylamine (0.98 mmol), DIPEA (158 mg, 1.23 mmol) and HATU (1.06 mmol) in anhydrousDMF (8 mL) is stirred at 80°C overnight. The reaction mixture is diluted with EtOAc (40 mL) and washed with water (4x20 mL) and brine (20 mL).

The organic layer is dried (Na_2SO_4), filtered and concentrated in vacuo. The residue is purified by silica gel chromatography eluting with 1%-50% EtOAc in DCM. The collected product is recrystallized from DCM to afford 2-pyridin-2-yl-4-trifluoromethyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide (105 mg, 31%) as a solid. MS: 416 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ =2.32(s, 3H), 7.04(t, H), 7.16(s, H), 7.25(dd, H), 7.34(q, H), 7.67(dd, H), 8.11 (t, H), 8.70 (d, H), 8.82(d, H), 9.57(s, H). IC_{50} = 8 nM.

Example 210

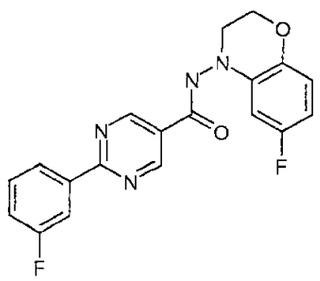
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-indol-1-yl)-amide



A mixture of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide (246 mg, 0.68 mmol) and MnO_2 (296 mg, 3.4 mmol) in DCM (10 mL) is stirred at rt for 1.5 h. The reaction mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is triturated with ether to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-indol-1-yl)-amide (158, 65%). MS: 361 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.83 (s, 3H), 6.36 (s, H), 7.10-7.29 (m, 3H), 7.44-7.62 (m, H), 8.17 (s, H), 8.25 (d, H), 8.35 (d, H), 8.97 (s, H).

Example 211

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-1,4-benzoxazin-4-yl)-amide



Step 1: $LiAlH_4$ (14.7 mmol, 1 M solution in THF) is added to a solution of 6-fluoro-4H-benzo[1,4]oxazin-3-one (1.23 g, 7.35 mmol) in THF at rt and heated to reflux for 2 hrs. The reaction mixture is quenched with a few drops of water followed by slow addition of ethyl acetate (10 mL). The solid is filtered off, and washed with EtOAc. The filtrate is concentrated *in vacuo* to afford 6-fluoro-3,4-dihydro-2H-benzo[1,4]oxazine (1 g). MS: 154 (M+H).

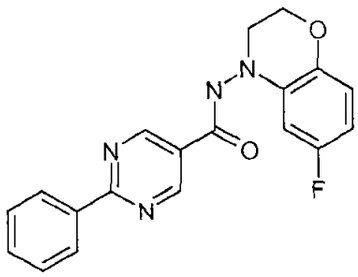
Step 2: Isoamyl nitrite is added to a solution of 6-fluoro-3,4-dihydro-2H-benzo[1,4] oxazine (1g) in DCM (15 mL) and heated to reflux overnight. The reaction mixture is concentrated *in vacuo* and the residue is purified by silica gel chromatography eluting with 10% EtOAc in heptane to give 6-Fluoro-4-nitroso-3,4-dihydro-2H-benzo[1,4]oxazine (0.83 g).

Step 3: $LiAlH_4$ in THF (1 M, 6.58 mL) is added to a solution of 6-fluoro-4-nitroso-3,4-dihydro-2H-benzo[1,4]oxazine (0.8 g) in THF (10 mL) at 0^0 C and then stirred at rt overnight. The reaction mixture is quenched with a few drops of water followed by addition of EtOAc (10 mL). The solid is filtered off, and washed with EtOAc (15 mL). The filtrate is concentrated *in vacuo* and the residue is purified by silica gel column chromatography eluting with 15% EtOAc in heptane to afford 6-fluoro-2,3-dihydro-benzo[1,4]oxazin-4-ylamine (0.44 mg).

Step 4: DIPEA (174 µL) is added to a mixture of 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (218 mg), HATU (380 mg) and 6-fluoro-2,3-dihydro-benzo[1,4]oxazin-4-ylamine (220 mg) in DMF (15 mL) and then heated at 80 ^{0}C overnight. The reaction mixture is concentrated *in vacuo* and the residue is purified by silica gel column chromatography eluting with 30% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-1,4-benzoxazin-4-yl)-amide (81 mg). MS: 369 (M+H); ^{1}H NMR (300 MHz, DMSO-D_6): δ 11.05 (s, 1H), 9.35 (s, 2H), 8.32 (dd, 1H), 8.18 (dd, 1H), 7.65 (m, 1H), 7.5 (m, 1H), 6.8-6.7 (m, 2H), 6.52-6.45 (m, 1H), 4.36 - 4.33 (m, 2H), 3.65 (m, 2H). IC_{50} = 12 nM.

Example 212

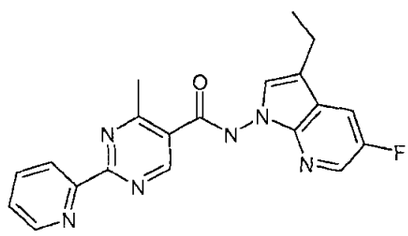
2-Phenyl-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-1,4-benzoxazin-4-yl)-amide



Following procedures similar to those of step 4 in Example 211, but substituting 2-phenyl-pyrimidine-5-carboxylic acid for 2-(3-fluoro-phenyl)-pyrimidine-5-carboxylic acid, there is prepared 2-phenyl-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-1,4-benzoxazin-4-yl)-amide as solid. MS: 351 (M+H); ^{1}H NMR (300 MHz, DMSO-D_6): δ 11.03 (s, 1H), 9.33 (s, 2H), 8.49-8.46 (m, 2H), 7.61-7.55 (m, 3H), 6.8-6.7 (m, 2H), 6.52-6.45 (m, 1H), 4.36 - 4.33 (m, 2H), 3.65-3.25 (m, 2H). IC_{50} = 21 nM.

Example 213

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide



Step 1: A solution of 5-fluoro-3-iodo-pyridin-2-ylamine (3 g, 12.6 mmol) in DCM (40 mL) is treated with TFAA (2.1 mL, 15.1 mmol) and pyridine (1.2 mL, 15.1 mmol), and stirred at rt for 2 h. The mixture is diluted with H_2O (150 mL), and extracted with DCM (3 x 150 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is diluted with MeCN (40 mL), treated with *trans*-crotyl bromide (2 mL, 18.9 mmol) and K_2CO_3 (3.5 g, 25.2 mmol), and heated at reflux for 2 h. The mixture is cooled, filtered through a pad of Celite and concentrated. The residue is purified by silica gel chromatography eluting with 5% - 30% EtOAc in heptane to afford *N*-but-2-enyl-2,2,2-trifluoro-*N*-(5-fluoro-3-iodo-pyridin-2-yl)-acetamide (2.5 g, 51%). MS: 389 (M+H); ^{1}H NMR

(300 MHz, $CDCl_3$): δ 8.36 (m, 1H), 7.98 (s, 1H), 5.55 (m, 2H), 4.62 (m, 1H), 3.96 (m, 1H), 1.61 (m, 3H).

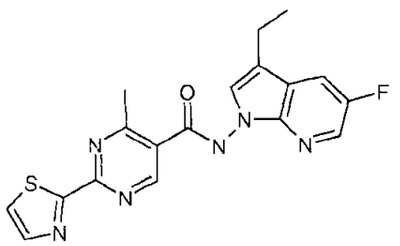
Step 2: A solution of *N*-but-2-enyl-2,2,2-trifluoro-*N*-(5-fluoro-3-iodo-pyridin-2-yl)-acetamide (2.57 g, 6.5 mmol) in DMF (10 mL) is treated with *n*-Bu_4NCl (2 g, 7.15 mmol), $Pd(OAc)_2$ (59 mg, 0.26 mmol), and stirred at 100°C for 2 h. The mixture is cooled to rt, diluted with EtOAc (50 mL), filtered through a pad of silica gel, and washed with 1 M HCl (50 mL). The organic layer is separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 25% - 70% EtOAc in heptane to afford 3-ethyl-5-fluoro-1H-pyrrolo[2,3-b]pyridine (0.75 g, 70%). MS: 165 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.62 (s, NH, 1H), 8.17 (m, 1H), 7.60 (m, 1H), 7.16 (s, 1H), 2.74 (q, 2H), 1.31 (t, 3H).

Step 3: A suspension of NaH (2.7 g, 68 mmol, 60% in mineral oil) in DMF (20 mL) at 0°C is treated with 3-ethyl-5-fluoro-1H-pyrrolo[2,3-b]pyridine (745 mg, 4.5 mmol) and stirred at 0°C for 1 h. The mixture is treated with HOSA (2.5 g, 22.5 mmol) portion wise and warmed to rt over 2 h. The mixture is then poured over ice, filtered through a pad of Celite, and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 30% - 50% EtOAc in heptane to afford 3-ethyl-5-fluoropyrrolo[2,3-b]pyridin-1-ylamine (685 mg, 84%). MS: 180 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.56 (m, 1H), 7.14 (s, 1H), 4.93 (s, NH_2, 2H), 2.697 (q, 2H), 1.28 (t, 3H).

Step 4: A solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (490 mg, 2.28 mmol) and 3-ethyl-5-fluoropyrrolo[2,3-b]pyridin-1-ylamine (340 mg, 1.9 mmol) in DMF (6 mL) is stirred at 40°C for 1 h. The mixture is treated with DMTMM (524 mg, 1.9 mmol) and stirred at 40°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 5 min. The precipitate is collected by filtration and dried *in vacuo* to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide (427 mg, 60%). MS: 377 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.94 (s, NH, 1H), 9.14 (s, 1H), 8.81 (d, 1H), 8.47 (d, 1H), 8.30 (s, 1H), 8.03 (m, 2H), 7.61 (m, 2H), 2.81 (s, 3H), 2.75 (q, 2H), 1.29 (t, 3H).

Example 214

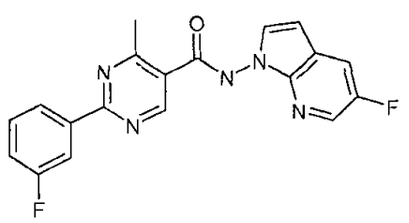
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide



A solution of 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (509 mg, 2.28 mmol) and 3-ethyl-5-fluoropyrrolo[2,3-b]pyridin-1-ylamine (340 mg, 1.9 mmol) in DMF (6 mL) is stirred at 40°C for 1 h. The mixture is treated with DMTMM (524 mg, 1.9 mmol) and stirred at 40°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 5 min. The precipitate is collected by filtration and dried *in vacuo* to afford 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide (481 mg, 66%). MS: 383 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.95 (s, NH, 1H), 9.10 (s, 1H), 8.29 (s, 1H), 8.14 (d, 1H), 8.08 (d, 1H), 8.00 (m, 1H), 7.57 (s, 1H), 2.79 (s, 3H), 2.75 (q, 2H), 1.29 (t, 3H).

Example 215

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide



Step 1: A solution of 5-fluoro-3-iodo-pyridin-2-ylamine (4 g, 16.8 mmol) in THF (50 mL) and trimethylsilylacetylene (4.7 mL, 33.6 mmol) is treated with $PdCl_2(PPh_3)_4$ (353 mg, 0.5 mmol), CuI (96 mg, 0.5 mmol) and triethylamine (7 mL, 50.4 mmol) and stirred at rt for 2 h. The mixture is filtered through Celite and concentrated. The residue is purified by silica gel chromatography eluting with 10% - 35% EtOAc in heptane to afford 5-fluoro-3-trimethylsilanylethynyl-pyridin-2-ylamine (3.3 g, 94%). MS: 209 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, 1H), 7.30 (m, 1H), 4.89 (s, NH_2, 2H), 0.25 (s, 9H).

Step 2: A solution of 5-fluoro-3-trimethylsilanylethynyl-pyridin-2-ylamine (3.2 g, 15.4 mmol) in MeOH (77 mL) and K_2CO_3 (1.1 g, 7.7 mmol) is stirred at rt for 0.5 h. The mixture is filtered through Celite and concentrated. The residue is purified by silica gel chromatography eluting with 15% - 55% EtOAc in heptane to afford 3-ethynyl-5-fluoro-pyridin-2-ylamine (1.55 g, 74%). MS: 137 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, 1H), 7.35 (m, 1H), 4.91 (s, NH_2, 2H), 3.44 (s, 1H).

Step 3: A solution of 3-ethynyl-5-fluoro-pyridin-2-ylamine (1.25 g, 9.2 mmol) in DMF (20 mL) is treated with $(Rh(cod)_2Cl)_2$ (23 mg, 0.023 mmol) and tris-(4-fluoro-phenyl)-phosphane (115 mg, 0.368 mmol) and stirred at 85°C for 0.5 h. The mixture is then poured over brine (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 35% - 75% EtOAc in heptane to afford 5-fluoro-1H-pyrrolo[2,3-b]pyridine (1.05 g, 84%). MS: 137 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.15 (s, NH, 1H), 7.99 (s, 1H), 7.44 (d, 1H), 7.18 (s, 1H), 6.28 (s, 1H).

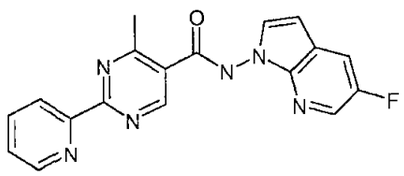
Step 4: A suspension of NaH (4.4 g, 110 mmol, 60% in mineral oil) in DMF (37 mL) at 0°C is treated with 5-fluoro-1H-pyrrolo[2,3-b]pyridine (1.0 g, 7.4 mmol) and stirred at 0°C for 1 h. The mixture is treated with HOSA (4.2 g, 37 mmol) portion wise and warmed to rt over 2 h. The mixture is then poured over ice, filtered through a pad of Celite, and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 30% - 70% EtOAc in heptane to afford 5-fluoro-pyrrolo[2,3-b]pyridin-1-ylamine (980 mg, 88%). MS: 152 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.60 (m, 1H), 7.42 (m, 1H), 6.36 (s, 1H), 5.01 (s, NH_2, 2H).

Step 5: A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (529 mg, 2.28 mmol) and 5-fluoro-pyrrolo[2,3-b]pyridin-1-ylamine (288 mg, 1.9 mmol) in DMF (6 mL) is stirred at 40°C for 1 h. The mixture is treated with DMTMM (524 mg, 1.9 mmol) and stirred at 40°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 5 min. The precipitate is collected by filtration and dried *in vacuo* to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-

amide (475 mg, 68%). MS: 366 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.12 (s, 1H), 8.30 (m, 2H), 8.18 (d, 1H), 7.97 (d, 1H), 7.82 (d, 1H), 7.59 (m, 1H), 7.44 (m, 1H), 6.59 (d, 1H), 2.80 (s, 3H).

Example 216

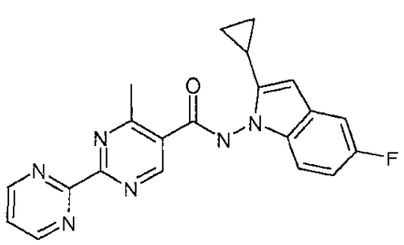
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide



A solution of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (440 mg, 2.28 mmol) and 5-fluoro-pyrrolo[2,3-b]pyridin-1-ylamine (288 mg, 1.9 mmol) in DMF (6 mL) is stirred at 40°C for 1 h. The mixture is treated with DMTMM (524 mg, 1.9 mmol) and stirred at 40°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 5 min. The precipitate is collected by filtration and dried *in vacuo* to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide (343 mg, 52%). MS: 349 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.17 (s, 1H), 8.81 (d, 1H), 8.53 (d, 1H), 8.27 (s, 1H), 8.01 (m, 1H), 7.90 (m, 1H), 7.77 (d, 1H), 7.57 (m, 1H), 6.60 (d, 1H), 2.84 (s, 3H).

Example 217

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (2-cyclopropyl-5-fluoro-indol-1-yl)-amide



Step 1: A solution of 4-fluoro-2-iodoaniline (2 g, 8.4 mmol) in THF (15 mL) and cyclopropylacetylene (1.4 mL, 16.9 mmol) is treated with $PdCl_2(PPh_3)_4$ (177 mg, 0.25 mmol), CuI (48 mg, 0.25 mmol) and triethylamine (3.5 mL, 25.2 mmol) and stirred at rt for 2 h. The mixture is filtered through Celite and concentrated. The residue is purified by silica gel chromatography eluting with 0% - 35% EtOAc in heptane to afford 2-cyclopropylethynyl-4-

fluoro-phenylamine (1.1 g, 74%). MS: 176 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (m, 1H), 6.81 (m, 1H), 6.59 (m, 1H), 4.00 (s, NH_2, 2H), 1.49 (m, 1H), 0.82 (m, 4H).

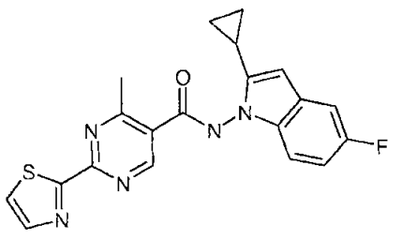
Step 2: A solution of 2-cyclopropylethynyl-4-fluoro-phenylamine (0.80 g, 4.5 mmol) in PhMe (16 mL) is treated with $InBr_3$ (80 mg, 0.23 mmol) and stirred at 110°C for 0.5 h. The mixture is then poured over brine (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 0% - 25% EtOAc in heptane to afford 2-cyclopropyl-5-fluoro-1H-indole (610 mg, 78%). MS: 176 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, NH, 1H), 7.12 (m, 2H), 6.83 (m, 1H), 6.09 (s, 1H), 1.90 (m, 1H), 0.95 (m, 2H), 0.77 (m, 2H).

Step 3: A suspension of NaH (1.9 g, 47 mmol, 60% in mineral oil) in DMF (20 mL) at 0°C is treated with 2-cyclopropyl-5-fluoro-1H-indole (550 mg, 3.14 mmol) and stirred at 0°C for 1 h. The mixture is treated with HOSA (1.8 g, 15.7 mmol) portion wise and warmed to rt over 2 h. The mixture is then poured over ice, filtered through a pad of Celite, and extracted with EtOAc (3 x 50 mL). The combined organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 5% - 35% EtOAc in heptane to afford 2-cyclopropyl-5-fluoro-indol-1-ylamine (420 mg, 70%). MS: 191 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 1H), 7.11 (m, 1H), 6.92 (m, 1H), 5.90 (s, 1H), 4.57 (s, NH_2, 2H), 2.07 (m, 1H), 1.02 (m, 2H), 0.75 (m, 2H).

Step 4: A solution of 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (184 mg, 0.85 mmol) and 2-cyclopropyl-5-fluoro-indol-1-ylamine (135 mg, 0.71 mmol) in DMF (3 mL) is stirred at 40°C for 1 h. The mixture is treated with DMTMM (235 mg, 0.71 mmol) and stirred at 40°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 5 min. The precipitate is collected by filtration and dried *in vacuo* to afford 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (2-cyclopropyl-5-fluoro-indol-1-yl)-amide (35 mg, 13%). MS: 389 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.93 (s, NH, 1H), 9.31 (s, 1H), 9.06 (d, 2H), 7.70 (m, 1H), 7.42 (m, 1H), 7.26 (m, 1H), 6.97 (m, 1H), 6.16 (s, 1H), 2.79 (s, 3H), 1.97 (m, 1H), 1.01 (m, 2H), 0.74 (m, 2H).

Example 218

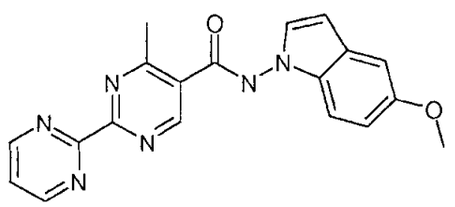
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (2-cyclopropyl-5-fluoro-indol-1-yl)-amide



A solution of 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (188 mg, 0.85 mmol) and 2-cyclopropyl-5-fluoro-indol-1-ylamine (135 mg, 0.71 mmol) in DMF (3 mL) is stirred at 40°C for 1 h. The mixture is treated with DMTMM (235 mg, 0.71 mmol) and stirred at 40°C for 1 h. The mixture is diluted with saturated aqueous Na_2CO_3 (5 mL) and stirred for 5 min. The precipitate is collected by filtration and dried *in vacuo* to afford 4-methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (2-cyclopropyl-5-fluoro-indol-1-yl)-amide (60 mg). MS: 394 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.26 (s, 1H), 8.15 (d, 1H), 8.08 (d, 1H), 7.43 (m, 1H), 7.24 (m, 1H), 6.97 (m, 1H), 6.18 (s, 1H), 2.77 (s, 3H), 1.95 (m, 1H), 1.01 (m, 2H), 0.73 (m, 2H).

Example 219

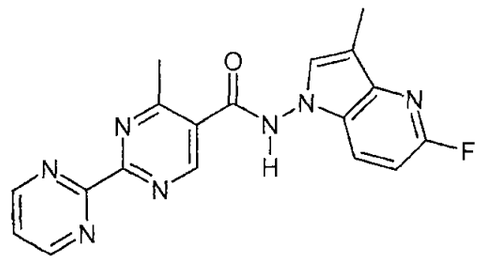
2-Pyrimidin-2-yl-4-methyl-pyrimidine-5-carboxylic acid (5-methoxyl-indol-1-yl)-amide



A solution of 2-pyrimidin-2-yl-4-methyl-pyrimidine-5-carboxylic acid (496 mg, 2.30 mmol) and 5-methoxy-indol-1-ylamine (0.98 mmol) in anhydrous DMF (10 mL) is stirred at 50°C for 30 min. DMTMM (555 mg, 2.01 mmol) is added and stirred at 50°C for an hour. DMF is evaporated off. The residue is mixed with water (40 mL) and stirred at rt for 20 minutes. The solid is collected by filtration, washed with water (3x 5 mL) and dried in vacuum to afford 2-pyrimidin-2-yl-4-methyl-pyrimidine-5-carboxylic acid (5-methoxyl-indol-1-yl)-amide (410 mg) as a solid. MS: 361 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.93(s, 3H), 4.84(s, 3H), 7.04(t, H), 6.50(d, H), 6.92(d, H), 7.14(s, H), 7.26-7.37(m, 2H), 7.72 (t, H), 9.09 (d, 2H), 9.27(s, H).

Example 220

4-Methyl-[2,2`]bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide



Step 1: Bromine (1.96 g, 12.2 mmol) is added to a mixture of 2-fluoro-5-aminopyridine (1.37 g, 12.2 mmol) and sodium acetate (2 mg, 24.4 mmol) in acetic acid (30 mL) and stirred at rt for 4 hours. Acetic acid is evaporated off *in vacuo*. The residue is dissolved in EtOAc (50 mL), washed with saturated aqueous Na_2CO_3 (10 mL), water (20 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vauo* to afford 2-bromo-3-amino-6-fluoropyridine (2.1 g) as a solid. MS: 190 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.04 (br, 2H), 6.77(dd, H), 7.17(dd, H).

Step 2: TFAA (8.31 g, 39.57 mmol) is added drop-wise to a stirred solution of 2-bromo-3-amino-6-fluoropyridine (6.30 g, 33.0 mmol) and pyridine (3.91 g, 49.46 mmol) in DCM (80 mL) at rt, and stirred at rt for an hour. Water (40 mL) is added. The organic layer is separated, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford N-(2-bromo-6-fluoropyridin-3-yl)-2,2,2-trifluoro-acetamide (9.37 g, >99%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06(m, H), 8.40 (br, N-H), 9.75(dd, H).

Step 3: A solution of N-(2-bromo-6-fluoropyridin-3-yl)-2,2,2-trifluoro-acetamide (9.16 g, 31.9 mmol), allyl bromide (6.18 g, 47.9 mmol) and sodium carbonate (8.82 g, 63.8 mmol) in CH_3CN (80 mL) is stirred at 80°C for 2 h. The reaction mixture is concentrated *in vacuo* and the residue is purified by silica gel chromatography eluting with 0-60% DCM in heptane to afford N-allyl-N-(2-bromo-6-fluoro-pyridin-3-yl)-2,2,2-trifluoro-acetamide (9.05 g) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (q, H), 5.01 (q, H), 5.17 (d, H), 5.29 (d, H), 6.85(m, H), 7.00 (dd, H), 7.64(t, H).

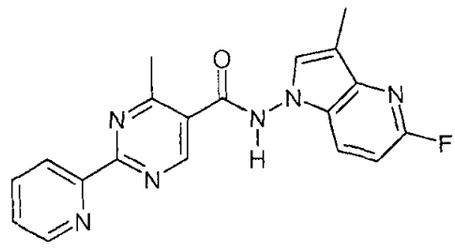
Step 4: A solution of N-allyl-N-(2-bromo-6-fluoro-pyridin-3-yl)-2,2,2-trifluoro-acetamide (3.41 g, 10.43 mmol), palladium acetate (94 mg, 0.42 mmol), tetra(n-butylammonium) chloride (3.19 g, 11.47 mmol) and triethylamine (2.37 g, 23.4 mmol) in anhydrous DMF (20 mL) is stirred at 100°C under N_2 for an hour. DMF is evaporated off and the residue is mixed with water (12 mL) and stirred at rt for an hour. EtOAc (15 mL) is added and stirred at rt overnight. The organic layer is separated and the aqueous layer is extracted with EtOAc (35 mL). The combined organic layer is dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 10-60% EtOAc in heptane to afford 5-fluoro-3-methyl-1H-pyrrolo[3,2-b]pyridine (1.5 g) as a solid. MS: 151 (M+ H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38(s, 3H), 6.77(d, H), 7.28(s, H), 7.74(dd, H).

Step 5: A solution of 5-fluoro-3-methyl-1H-pyrrolo[3,2-b]pyridine (10.7 mmol) in anhydrous DMF (15 mL) is added drop-wise to a stirred solution of NaH (60%, 160 mmol) in anhydrous DMF (25 mL) under N_2 at 0°C for 20 min and stirred at 0°C under N_2 for 30 minutes. HOSA (53.5 mmol) is added portion-wise for 30 minutes at 0°C, and stirred at 0°C for 1.5 hours. After quenching with ice-water (400 mL), the mixture is extracted with ether (3x 60 mL). The combined organic layer is washed with water (2x30 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue is purified by silica gel column chromatography eluting with 0-60% EtOAc in heptane to afford 5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-ylamine (570 mg). MS: 166 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.82 (br, 2N-H), 6.76 (d, H), 7.17 (s, H), 7.77 (dd, H).

Step 6: A solution of 2-pyrimidin-2-yl-4-methyl-pyrimidine-5-carboxylic acid (1.41 mmol), 5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-ylamine (1.41 mmol), DIPEA (158 mg, 4.22 mmol) and HATU (1.69 mmol) in anhydrous DMF (8 mL) is stirred at 90°C for 16 hours. DMF is evaporated off *in vacuo*. The residue is dissolved in EtOAc (40 mL), washed with water (3x10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with 1-20% MeOH in DCM to afford 4-methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide (125 mg) as a solid. MS: 364 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.31 (s, 3H), 2.87 (s, 3H), 6.87 (d, H), 7.50 (s, H), 7.66 (t, H), 7.96 (t, H), 9.04 (d, 2H), 9.27 (s, H).

Example 221

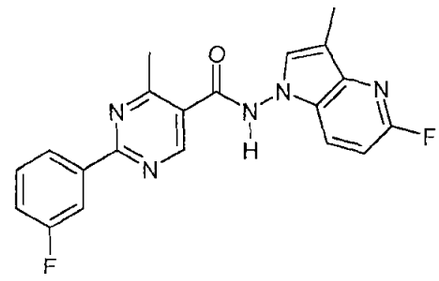
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide



A solution of 2-pyridin-2-yl-4-methyl-pyrimidine-5-carboxylic acid (1.36 mmol), 5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-ylamine (1.36 mmol), DIPEA (158 mg, 4.07 mmol) and HATU (1.63 mmol) in anhydrous DMF (8 mL) is stirred at 90°C for 15 hours. DMF is evaporated *in vacuo*. The residue is dissolved in EtOAc (40 mL), washed with water (3x15 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue is recrystallized from EtOAc to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide (285 mg) as a solid. MS: 363 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.35 (s, 3H), 2.87 (s, 3H), 6.92 (d, H), 7.51 (s, H), 7.60 (t, H), 7.97 (t, H), 8.05 (t, H), 8.65 (d, H), 8.78 (d, H), 9.23 (s, H).

Example 222

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide

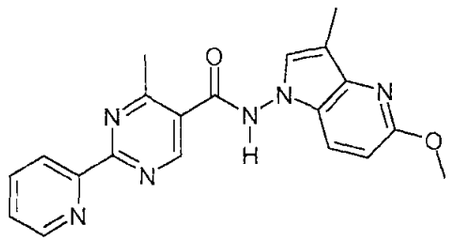


A solution of 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (1.34 mmol), 5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-ylamine (1.34 mmol), DIPEA (158 mg, 4.02 mmol) and HATU (1.60 mmol) in anhydrous DMF (8 mL) is stirred at 90°C for 16 h. DMF is evaporated off *in vacuo*. The residue is dissolved in EtOAc (40 mL), and washed with water (3x20 mL) and brine (10 mL). The organic layer is dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue is is purified by silica gel chromatography eluting with 0-60% EtOAc in heptane to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-

methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide (340 mg) as a solid. MS: 380 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.86 (s, 3H), 6.84 (d, H), 7.12-7.35 (m, 2H), 7.52 (q, H), 7.63 (t, H), 8.10-8.43 (m, 2H), 8.98 (br, N-H).

Example 223

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide



Step 1: Bromine (4.72 g, 29.5 mmol) is added to a mixture of 2-methoxy-5-aminopyridine (3.66 g, 29.5 mmol) and sodium acetate (4.84 g, 7.32 mmol) in acetic acid (50 mL) and stirred at rt for 20 minutes. Acetic acid is evaporated off *in vacuo*. The residue is dissolved in EtOAc (40 mL), and washed with water (40 mL), saturated sodium carbonate aqueous solution (20 mL), water (20 mL) and brine (20 mL). The organic layer is dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue is is purified by silica gel chromatography eluting with 0-40% EtOAc in heptane to afford 2-bromo-3-amino-6-methoxypyridine (4.35 g) as an oil. MS: 202 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.60(d, H), 7.07(d, H).

Step 2: TFAA (5.15 g, 24.5 mmol) is added drop-wise to a stirred solution of 2-bromo-3-amino-6-methoxypyridine (4.15 g, 20.5 mmol) and pyridine (1.94 g, 24.5 mmol) in DCM (60 mL) at rt and stirred at rt for 2.5 h. Water (40 mL) is added. The organic layer is separated, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford N-(2-bromo-6-methoxy-pyridin-3-yl)-2,2,2-trifluoro-acetamide (5.68 g) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (s,H), 6.80(s, H), 8.23 (br, N-H), 8.42(d, H).

Step 3: A mixture of N-(2-bromo-6-methoxy-pyridin-3-yl)-2,2,2-trifluoro-acetamide (5.52 g, 18.5 mmol), allyl bromide (3.57 g, 27.7 mmol) and sodium carbonate (5.1 g, 11 mmol) in CH_3CN (60 mL) is stirred at 80°C for 3 h. The mixture is filtered and the filtrate is

concentrated *in vacuo*. The residue is purified by silica gel column chromatography eluting with 0-60% DCM in heptane to afford N-allyl-N-(2-bromo-6-methoxy-pyridin-3-yl)-2,2,2-trifluoro-acetamide (5.55 g) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (q, H), 4.00 (s, H), 5.95 (q, H), 5.08-5.30 (q, 2H), 5.75-5.94 (m, H), 6.74 (d, H), 7.38 (d, H).

Step 4: A solution of N-allyl-N-(2-bromo-6-methoxy-pyridin-3-yl)-2,2,2-trifluoro-acetamide (5.54 g, 16.3 mmol), palladium acetate (147 mg, 0.65 mmol), tetra(n-butylammonium) chloride (4.99 g, 17.9 mmol) and triethylamine (3.72 g, 26.8 mmol) in anhydrous DMF (35 mL) is stirred at 100°C under N_2 for an hour. DMF is evaporated off, and the residue is mixed with water (20 mL) and stirred at rt overnight. EtOAc (50 mL) is added. The organic layer is separated, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue is is purified by silica gel column chromatography eluting with 30-70% EtOAc in heptane to afford 5-methoxy-3-methyl-1H-pyrrolo[3,2-b]pyridine (2.62 g) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H), 4.05 (s, 3H), 6.62 (s, H), 7.12 (s, H), 7.54 (d, H), 7.94 (br, N-H).

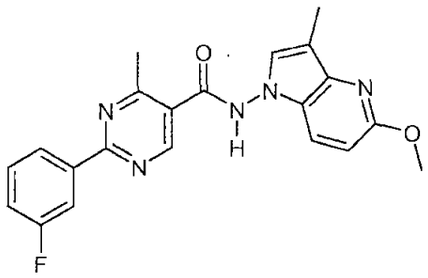
Step 5: A solution of 5-methoxy-3-methyl-1H-pyrrolo[3,2-b]pyridine (17.3 mmol) in anhydrous DMF (20 mL) is added drop-wise to a stirred solution of NaH (60%, 260 mmol) in anhydrous DMF (35 mL) under N_2 at 0°C for 40 min and then stirred at 0°C under nitrogen for 30 minutes. HOSA is added portion-wise for 45 minutes at 0°C and then stirred at 0°C for 2 hours. After quenching with ice-water (500 mL), the reaction mixture is extracted with ether (3 x 40 mL). The combined organic layer is washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue is purified by silica gel column chromatography eluting with 5-60% EtOAc in heptane to afford 5-methoxy-3-methyl-pyrrolo[3,2-b]pyridin-1-ylamine (1.73 g) as a solid. MS: 178 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 4.04(s, 3H), 4.75(br, 2N-H), 6.63(d, H), 7.04(s, H), 7.60(d, H).

Step 6: A solution of 2-pyridin-2-yl-4-methyl-pyrimidine-5-carboxylic acid (1.69 mmol), 5-methoxy-3-methyl-pyrrolo[3,2-b]pyridin-1-ylamine (1.69 mmol), DIPEA (5.01 mmol) and HATU (2.03 mmol) in anhydrous DMF (8 mL) is stirred at 90°C for 16 h. DMF is evaporated *in vacuo*. The residue is dissolved in EtOAc (40 mL), and washed with water (3x10 mL) and brine (10 mL). The organic layer is dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue is purified by silica gel column chromatography eluting with 0-15% MeOH in DCM to afford 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-

pyrrolo[3,2-b]pyridin-1-yl)-amide (295 mg) as a solid. MS: 375 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.40 (s, 3H), 2.84 (s, 3H), 4.02 (s, 3H), 6.70 (d, H), 7.13 (s, H), 7.41 (m, H), 7.50 (d, H), 7.85 (t, H), 8.51 (m, 2H), 8.78 (s,2H), 10.57 (br, N-H).

Example 224

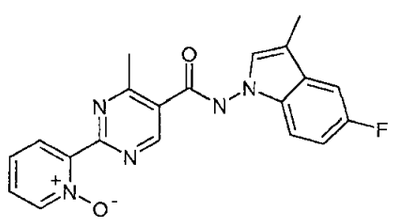
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide



A solution of 2-(3-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (1.13mmol), 5-methoxy-3-methyl-pyrrolo[3,2-b]pyridin-1-ylamine (1.13 mmol), DIPEA (3.39mmol) and HATU (1.36 mmol) in anhydrous DMF (8 mL) is stirred at 90°C for 16 h. DMF is evaporated off *in vacuo*. The residue is dissolved in EtOAc (45 mL), and washed with water (3x20 mL) and brine (10 mL). The organic layer is dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue is is triturated with DCM to afford 2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide (265 mg) as a solid. MS: 392 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ 2.33 (s, 3H), 2.79 (s, 3H), 3.97 (s, 3H), 6.67 (d, H), 7.20-7.60 (m, 2H), 7.53 (m, H), 7.64 (d, H), 8.17 (t, H), 8.34 (t, 2H), 9.05-9.20 (d, H).

Example 225

4-Methyl-2-(1-oxy-pyridin-2-yl)-pyrimidin-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide



Step 1: A solution of 2-cyanopyridine (1.67 g, 16 mmol), 30% H_2O_2 (3.2 mL) and methyltrioxorhenium (0.2 g, 0.8 mmol) in DCM (6.4 mL) is stirred at rt overnight. The reaction mixture is concentrated *in vacuo* and the residue is purified by silica gel chromatography eluting with 3-10% MeOH in DCM to afford 1-oxy-pyridine-2-carbonitrile (0.69 g) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (t, H), 7.49(t, H), 7.67(d, H), 8.30 (d, H).

Step 2: A solution of 1-oxy-pyridine-2-carbonitrile (532 mg, 4.43 mmol) and sodium methoxide (0.5 M in MeOH, 0.88 mL) in MeOH (1.8 mL) is stirred at rt overnight. Ammonium chloride (261 mg, 4.87 mmol) is added and stirred at 56°C for an hour, and then 7 N ammonia in MeOH (1.5 mL) is added. The reaction mixture is sealed in a tube and stirred at 40°C for an hour, and then cooled to 0°C. Sodium methoxide is added (0.5 M in MeOH, 8.86 mL). The mixture is filtered and the filtrate is concentrated in vacuo. The residue is recrystallized from ethanol to afford 1-oxy-pyridine-2-carboxamidine (370 mg) as a solid. ^{1}H NMR (300 MHz, CD_3OD): δ 7.52-7.68(m, 2H), 7.96(dd, H), 8.35 (d, H).

Step 3: A solution of 1-oxy-pyridine-2-carboxamidine (366 mg, 2.67 mmol) and N,N-dimethylaminomethylene acetoacetate (495 mg, 2.76 mmol) in ethanol (3 mL) and DMF (3 ml) is stirred at 90°C for 16 hours. The reaction mixture is concentrated *in vacuo* and the residue is purified by silica gel column chromatography eluting with 2.5 % MeOH in DCM to afford 4-methyl-2-(1-oxy-pyridin-2-yl)-pyrimidine-5-carboxylic acid ethyl ester (127 mg) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (t, 3H), 2.95 (s, 3H), 4.50 (q, 2H), 7.39 (m, H), 7.70(q, H), 8.36(q, H), 9.37 (s, H).

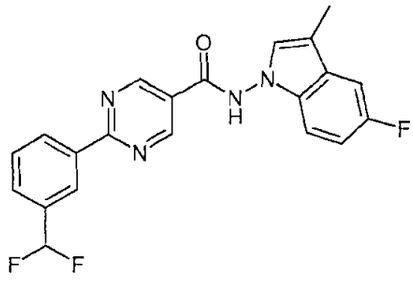
Step 4: A solution of 4-methyl-2-(-1oxy-pyridin-2-yl)-pyrimidine-5-carboxylic acid ethyl ester (123 mg, 0.48 mmol) and sodium hydroxide (123 mg, 3.07 mmol) in a mixture of MeOH/THF/H_2O (3 mL, 1:1:1) is stirred at 65°C for 5 minutes, and then stirred at rt overnight (16 hours). 1 N HCl aqueous solution (3.07 mL) is added. The resulting solution is concentrated to afford 4-methyl-2-(1-oxy-pyridin-2-yl)-pyrimidine-5-carboxylic acid and sodium chloride (313 mg), which is used in the next step without further purification.

Step 5: A solution of 4-methyl-2-(1-oxy-pyridin-2-yl)-pyrimidine-5-carboxylic acid and sodium chloride (313 mg), 3-methyl-5-fluoro-indol-1-ylamine (78 mg, 0.48 mmol), DIEA (92

mg, 0.71 mmol) and HATU (217 mg, 0.57 mmol) in anhydrous DMF (2.4 mL) is stirred at 150°C for 1 hour. DMF is vaporated off. The residue is purified by silica gel column chromatography eluting with 2.5-10% MeOH in DCM to afford 4-methyl-2-(1-oxy-pyridin-2-yl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide (169 mg) as a solid. MS: 378 (M+H); ^{1}H NMR (300 MHz, CD_3OD): δ =1.52(s, 3H), 2.84(s, 3H), 7.02(t, H), 7.18(s, H), 7.25 (d, H), 7.35(q, H), 7.62-7.80 (m, 2H), 7.85 (dd, H), 8.48 (d, H), 9.21(s, H). IC_{50} = 851.5 nM.

Example 226

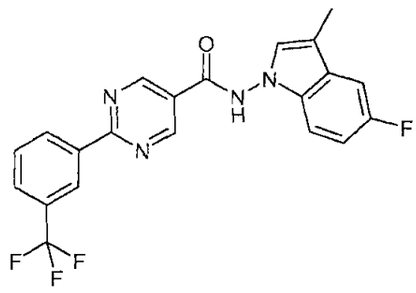
2-(3-Difluoromethyl-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide



Following procedures similar to those of Example 158, step 4, but substituting 2-(3-difluromethyl-phenyl)-2-yl-pyrimidine-5-carboxylic acid for 2-thiazol-2-yl-pyrimidine-5-carboxylic acid, there is prepared 2-(3-difluoromethyl-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide. MS: 397 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H), 7.04 (dt, 1H), 7.13 (d, 1H), 7.32 (s, 1H), 7.34-7.44 (m, 2H), 7.73-7.85 (m, 2H), 8.66 (d, 1H), 8.69 (s, 1H), 9.45 (s, 2H). IC_{50} = 17 nM.

Example 227

2-(3-Trifluoromethyl-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide



Following procedures similar to those of Example 158, step 4, but substituting 2-(3-trifluromethyl-phenyl)-2-yl-pyrimidine-5-carboxylic acid for 2-thiazol-2-yl-pyrimidine-5-carboxylic acid, there is prepared 2-(3-trifluoromethyl-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide. MS: 415 (M+H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H), 7.04 (dt, 1H), 7.33 (s, 1H), 7.34-7.44 (m, 2H), 7.86 (t, 1H), 8.00-8.02 (m, 1H), 8.75-8.79 (m, 2H), 9.47 (s, 2H). IC_{50} = 262 nM.

Following procedures similar to those described in the above examples, the following compounds are made:

2-Phenyl-pyrimidine-5-carboxylic acid (4-benzyl-piperazin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid piperazin-1-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid (4-methanesulfonyl-piperazin-1-yl)-amide,

2-(2-Methyl-thiazol-4-yl)-pyrimidine-5-carboxylic acid morpholin-4-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(1-methyl-1H-imidazole-2-carbonyl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(1-methyl-1H-imidazole-4-carbonyl)-piperazin-1-yl]-amide,

4-[(2-Phenyl-pyrimidine-5-carbonyl)-amino]-piperazine-1-carboxylic acid tert-butyl ester,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(4-trifluoromethyl-phenoxy)-piperidin-1-yl]-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid [4-(4-trifluoromethyl-phenoxy)-piperidin-1-yl]-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid morpholin-4-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid indol-1-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid (4-methoxy-piperidin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-benzo[1,4]oxazin-4-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-benzo[1,4]oxazin-4-yl)-amide,

1-{[2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-3-(2-morpholin-4-yl-ethyl)-1H-indole-6-carboxylic acid methyl ester,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(tetrahydro-pyran-4-yl)-indol-1-yl]-amide,

N-methyl-N-(5-fluoro)-indol-3-ylsulfonyl N'-[2-(3-fluoro)-phenyl-pyrimidine-5-carbonyl]-hydrazide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(tetrahydro-pyran-4-yl)-indol-1-yl]-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[3,2-c]pyridin-1-ylamide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)-amide.

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethy
l-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[3,2-c]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide.

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-(4-chloro -thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[3,2-c]pyridin-1-ylamide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-(4-Methyl-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-3-oxo-2,3-dihydro-indazol-1-yl)amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid(5-fluoro-indol-1-yl)amide)amide,

6-(4-Chloro-thiazol-2-yl)-2-methyl-N-pyrrolo[2,3-c]pyridin-1-yl-nicotinamide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid(5-methyl-4-oxo-4,5-dihydro-pyrrolo[3,2-c]pyridin-1-yl)amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (5-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (5-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluo ro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluo ro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluo ro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-difluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo [3,2-b]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo [3,2-b]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrro lo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-

pyrrolo[3,2-c]pyridin-1-yl]-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-2,2-diuoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-c] pyridin-1-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrro lo[2,3-c]pyridin-1-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo [2,3-c]pyridin-1-yl]-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo [2,3-c]pyridin-1-yl]-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b] pyridin-1-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b] pyridin-1-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo [2,3-b]pyridin-1-yl]-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo [2,3-b]pyridin-1-yl]-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-trifluoro methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-difluorom ethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoro methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoro methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoro methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl) -pyrrolo[3,2-b]pyridin-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-indol-1-yl)-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (3-difluoromethyl-indol-1-yl)-amide, and

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-indol-1-yl)-amide.

IN VITRO ASSAY PROTOCOLS TO IDENTIFY INHIBITORS OF HEMATOPOIETIC PGD2 SYNTHASE

The compounds of the present invention can be tested for enzymatic inhibiting activity against PGD2 Synthase according to either one of the following assays.

Assay 1: Fluorescence Polarization Assay

As described in PCT publication WO 2004/016223, Example II.

Assay 2: Enzyme Immunoassay (EIA) method

I. Assay solutions

a. Preparation of 0.1M K_2HPO_4/KH_2PO_4 buffer (pH 7.4)

Prepare 0.1 M KH_2PO_4 from 1M KH_2PO_4 (Sigma, Cat# P-8709)

Prepare 0.1 M K_2HPO_4 from powder of K_2HPO_4 (Fisher, BP363-500)

Mix 0.1 M K_2HPO_4 with 0.1 M KH_2PO_4 to adjust pH to 7.4.

b. Preparation of 0.5% γ-globulin

Add 0.1 g of γ-globulin (Sigma, Cat# G-5009) to 20 mL 0.1 M K_2HPO_4/KH_2PO_4 buffer (pH 7.4) and make 1-mL/vial aliquots and store in -80°C.

c. Preparation of 100 mM GSH

Add 307 mg of GSH (Sigma, Cat# G-6529) to 10 mL 0.1 M K_2HPO_4/ KH_2PO_4 buffer (pH 7.4) and store at - 80°C.

d. Preparation of Reaction buffer:

198 mL of 0.1M K_2HPO_4/KH_2PO_4 buffer (pH 7.4)

2 mM GSH – Prepared from 100 mM GSH

0.4 g Glycerol

2 mL of 0.5% γ-globulin

Add 0.4 g of glycerol and 2 mL of 0.5% γ-globulin to 198 mL of 0.1 M K_2HPO_4/KH_2PO_4 buffer (pH7.4).

Add 0.4 mL of 100 mM GSH to 19.6 mL reaction buffer before the assay (enough for two 96-well plates).

e. Preparation of $FeCl_2$/citric acid stopping solution: (8 mg/mL $FeCl_2$, 0.1 M citric acid)

Add 40 mg fresh $FeCl_2$ (IGN, Cat# 158046) to 5 mL 0.1 M citric acid (Sigma, Cat# C0759).

f. Preparation of MOX reagent:

10% EtOH - Add 1 mL of EtOH to 9 mL of ultra pure H_2O

Dissolve 0.1 g of methoxylamine (Cayman, Cat# 400036/) in 10% EtOH (10 mL).

Add 0.82 g of sodium acetate (Cayman, Cat#400037) to MOX solution and dissolve.

II. Materials and Method

Dimethylsulfoxide (DMSO; Sigma; Cat# D2650)

Prostaglandin D2-MOX express EIA kit (Caymen Chemical, Catalog No.500151)

Before the assay, cool down 10 mL of acetone in polypropylene tubes and empty 96 well plates in ice. All the procedures except compound dilution are performed on ice.

III. Compound dilution

1. Dilute compound in DMSO

Vol of DMSO stock solution (μL)	DMSO (μL)	Compound concentration (mM)
4 μL of 10 mM	6 μL	4
3 μL of 4 mM	6 μL	1.3333
3 μL of 1.33 mM	6 μL	0.4444
3 μL of 0.44 mM	6 μL	0.1481
3 μL of 0.148 mM	6 μL	0.0494
3 μL of 0.049 mM	6 μL	0.0165
3 μL of 0.016 mM	6 μL	0.0055

2. Dilute 2 μL of each above concentration of compound to 38 μL of reaction buffer in 96-well plates and mix.

IV. Enzyme and substrate solution preparation

1. Preparation of 0.39 ng/μL enzyme solution (0.35 ng/μL at final after compound addition).

   Mix 4 μL of 4 mg/mL human h-PGDS with 396 μL of reaction buffer (to give enzyme concentration 40 μg/mL). Add 46.8 μL of 40 μg/mL h-PGDS to 4.753 mL of reaction buffer to give a total volume of 4.8 mL
2. Preparation of Substrate Solution (PGH2): Add 0.375 mL of 0.1 mg/mL of PGH2 to 1.625mL acetone.

V. Enzyme reaction:

1. Add 60 μL of enzyme solution to compound well and positive control (without compound) in U-bottom polypropylene plate on ice.
2. Add 60 μL of reaction buffer and 6.6 μL of 5% DMSO in reaction buffer into negative control wells in the plate.
3. Add 6.6 μL of diluted compound in reaction buffer to the compound wells and mix.
4. Add 6.6 μL of 5% DMSO in reaction buffer to the positive control well.
5. Incubate the plate in ice for at least 30 min.

6. Add 20 μL of substrate (PGH2) solution to compound, negative and positive control wells in the U-bottom 96 well plate on ice.
7. Dry the plate in cold room for about 25-28 min.
8. Pipette 45 μL of enzyme solution (above) into 96-wells with dried PGH2 and mix 3 times. Incubate on the ice for 1 min.
9. Add 45 μL of $FeCl_2$ solution into each wells and mix.
10. Add 90 μL of MOX solution and mix.
11. Incubate for 30 min at 60^0C.
12. Dilute the samples 2500X with EIA buffer.

VI. EIA assay

Perform the assay according to the procedure in EIA kit provided by Cayman. Total PGD2 levels (pg/mL) were determined in the samples by EIA kits (Caymen Chemical, Catalog No. 500151)

Calculate amount of PGD2 as below

Calculated % Positive control according to the equation below;

%Positive control= (Compound value-Negative control)/(Positive value-Negative control value) ×100.

$$\%\text{Positive control} = \frac{(\text{Compound value} - \text{Negative control})}{(\text{Positive value} - \text{Negative control value})} \times 100$$

Compound value = PGD2 levels (pg/mL) obtained from the standard curve in EIA assay for the samples with compound

Negative control value = PGD2 levels (pg/mL) obtained from the standard curve in EIA assay for the samples without enzyme

Positive control value = PGD2 levels (pg/mL) obtained from the standard curve in EIA assay for the samples with enzyme but without compound

IC_{50}s are determined by excel fit to get the x value when y=1/2Ymax using 4 parameter logistic model for the IC_{50} curves.

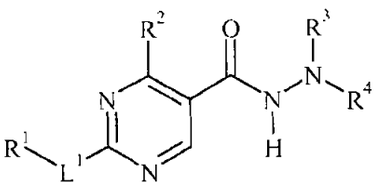
Results

Compounds within the scope of the invention produce 50% inhibition in the Fluorescence Polarization Assay or the EIA assay at concentrations within the range of about 1 nanomolar to about 30 micromolar, particularly about 1 nanomolar to about 1 micromolar, and more particularly about 1 nanomolar to about 100 nanomolar. IC_{50}s obtained by EIA assay for some of the examples are shown at the end of each of those examples.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

We claim:

1. A compound of formula (I):



(I)

wherein:

R^1 is $(C_1$-$C_6)$-alkyl optionally substituted one or more times independently by halo, hydroxy, $(C_1$-$C_6)$-alkoxy, or $(C_1$-$C_4)$-haloalkoxy, or
$(C_3$-$C_6)$-cycloalkyl, aryl or heteroaryl, each of which is optionally substituted one or more times independently by halo, $(C_1$-$C_6)$-alkyl, hydroxy, $(C_1$-$C_6)$-alkoxy, $(C_1$-$C_4)$-haloalkyl or $(C_1$-$C_4)$-haloalkoxy;

R^2 is hydrogen or $(C_1$-$C_4)$-alkyl optionally substituted one or more times by halogen;

R^3 is hydrogen, alkyl, aryl or heteroaryl,

R^4 is hydrogen, cycloalkyl, aryl, heterocyclyl, heteroaryl, arylsulfonyl, heteroarylsulfonyl, -C(=O)-NY^1Y^2, -C(=S)-NY^1Y^2, R^5, -C(=O)-R^5 or –C(=S)-R^5, wherein the aryl, heteroaryl or heterocyclyl moiety is optionally substituted one or more times independently by R^6, or

R^3 and R^4 together with the nitrogen atom to which they are attached form heterocyclyl, heterocyclenyl, heteroaryl, arylheterocyclyl, arylheterocyclenyl, heteroarylheterocyclyl, heteroarylheterocyclenyl, heterocyclylheteroaryl or heterocyclenylheteroaryl, each of which is optionally substituted one or more times independently by R^6;

R^5 is cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, or multicyclic alkaryl, each of which is optionally substituted one or more times independently by R^6;

L^1 is a bond, -O-, -C(=O)-, -NH-C(=O)-, or $(C_1$-$C_2)$-alkylene optionally substituted one or more times by halo;

R^6 is cyano, nitro, halo, hydroxy, carboxy, Y^1Y^2N-, Y^1Y^2N-C(=O)-, Y^1Y^2N-SO_2-, acyl, acyloxy, alkyl, alkenyl, alkynyl, alkoxy, alkoxycarbonyl, alkylthio, alkylsulfinyl, or alkylsulfonyl, each of which is optionally substituted one or more times independently by:
acyloxy, halo, alkoxy, haloalkoxy, hydroxy, carboxy, alkoxycarbonyl,

Y^1Y^2N-, Y^1Y^2N-C(=O)-, Y^1Y^2N-SO_2-,

aryl, aryloxy, aroyl, heteroaryl, heteroaryloxy, heteroaroyl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, or multicyclic alkaryl, each of which is optionally substituted one or more times independently by alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxycarbonyl, or

aryl, heteroaryl, aroyl, heteroaroyl, aryloxy, heteroaryloxy, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, or multicyclic alkaryl, each of which is optionally substituted one or more times independently by alkyl, haloalkyl, halo, alkoxy, haloalkoxy, hydroxy, carboxy, alkoxycarbonyl, Y^1Y^2N-, or Y^1Y^2N-SO_2-,

wherein the heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, or multicyclic alkaryl moiety of R^6 is also optionally substituted one or more times independently by oxo;

Y^1 and Y^2 are each independently:

hydrogen, alkylsulfonyl, aroyl, heteroaroyl, or

alkyl optionally substituted one or more times independently by hydroxy, carboxy, halo, amino, alkylamino, dialkylamino, alkoxy, heterocyclyl, aryl or heteroaryl, or

Y^1 and Y^2 together with the nitrogen atom to which they are attached form heterocyclyl;

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein R^1 is aryl or heteroaryl, each of which is optionally substituted one or more times independently by halo, (C_1-C_6)-alkyl, hydroxy, (C_1-C_6)-alkoxy, (C_1-C_4)-haloalkyl or (C_1-C_4)-haloalkoxy, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1, wherein R^1 is phenyl or five or six membered heteroaryl, each of which is optionally substituted one or more times independently by halo, (C_1-C_6)-alkyl, hydroxy, or (C_1-C_6)-alkoxy, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1, wherein R^1 is phenyl, pyridyl, pyrimidinyl, thiazolyl, or oxodiazolyl, each of which is optionally substituted one or more times independently by halo, $(C_1$-$C_6)$-alkyl, hydroxy, or $(C_1$-$C_6)$-alkoxy, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 1, wherein R^1 is phenyl, pyridyl or pyrimidnyl, each of which is optionally substituted independently at the ortho or meta position by halo, $(C_1$-$C_6)$-alkyl, hydroxy, or $(C_1$-$C_6)$-alkoxy, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1, wherein R^1 is phenyl optionally substituted independently at the ortho or meta position by halo, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1, wherein R^1 is pyridyl, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 1, wherein R^2 is hydrogen, methyl or trifluoromethyl, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 1, wherein R^2 is hydrogen, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 1, wherein R^2 is methyl, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 1, wherein L^1 is a bond, -O-, -C(=O)-, or -NH-C(=O)-, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

12. The compound according to claim 1, wherein L^1 is a bond, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 1, wherein:

R^3 and R^4 together with the nitrogen atom to which they are attached form heterocyclyl, heterocyclenyl, arylheterocyclyl, or heteroaryl, each of which is optionally substituted one or more times independently by R^6;

R^6 is alkoxy, hydroxyl, cycloalkyl, carboxy, cycloalkyl, halo, cyano, alkylsulfonyl, Y^1Y^2N-, Y^1Y^2N-SO_2-,

alkyl optionally substituted one or more times independently by acyloxy, hydorxy, alkoxycarbonyl, alkoxy, carboxy, aryl, halo, alkylsulfonyl, cyano, Y^1Y^2N-, or Y^1Y^2N-C(=O)-,

acyl or aryl, each of which is optionally substituted one or more times independently by halo,

alkoxycarbonyl optionally substituted one or more times independently by aryl,

heteroaroyl optionally substituted one or more times independently by alkyl,

heterocyclyl optionally substituted one or more times by oxo, or

aryloxy optionally substituted one or more times independently by haloalkyl; and

Y^1 and Y^2 are each independently hydrogen, alkylsulfonyl, aroyl, or alkyl optionally substituted by morpholinyl, or

Y^1 and Y^2 together with the nitrogen atom to which they are attached form morpholinyl;

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

14. The compound according to claim 1, wherein:

R^3 and R^4 together with the nitrogen atom to which they are attached form [1,2,4]triazolyl, pyrrolyl, indolyl, pyrrolo[2,3-b]pyridyl, pyrrolo[3,2-b]pyridyl, or pyrrolo[2,3-c]pyridyl, each of which is optionally substituted one or more times independently by R^6;

R^6 is alkoxy, carboxy, cycloalkyl, halo, cyano, alkylsulfonyl, Y^1Y^2N-SO_2-,

alkyl optionally substituted one or more times independently by Y^1Y^2N-C(=O)-, hydorxy, alkoxycarbonyl, alkoxy, carboxy, aryl, halo, heterocyclyl, cycloalkyl, alkylsulfonyl, cyano, heterocyclylcarbonyl,

acyl or aryl, each of which is optionally substituted one or more times independently by halo,

alkoxycarbonyl optionally substituted one or more times independently by aryl,

heteroaroyl optionally substituted one or more times independently by alkyl,

heterocyclyl optionally substituted one or more times by oxo, or

aryloxy optionally substituted one or more times independently by haloalkyl; and

Y^1 and Y^2 are each independently hydrogen, or alkyl optionally substituted by morpholinyl, or

Y^1 and Y^2 together with the nitrogen atom to which they are attached form morpholinyl;

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 1, wherein:

R^3 and R^4 together with the nitrogen atom to which they are attached form imidazolidinyl, [1,2,4]triazinanyl, piperazinyl, morpholinyl, pyrrolidinyl, 1,2,3,4-tetrahydro-pyrimidinyl, piperidinyl, oxazolidinyl, 2,3-dihydro-indolyl, octahydro-cyclopenta[c]pyrrolyl, or 3,4-dihydro-benzo[1,4]oxazine, each of which is optionally substituted one or more times independently by R^6;

R^6 is oxo, alkoxy, carboxy, cycloalkyl, halo, cyano, alkylsulfonyl, $Y^1Y^2N\text{-}SO_2\text{-}$,

alkyl optionally substituted one or more times independently by hydorxy, alkoxycarbonyl, alkoxy, carboxy, aryl, halo, heterocyclyl, cycloalkyl, alkylsulfonyl, cyano, heterocyclylcarbonyl,

acyl or aryl, each of which is optionally substituted one or more times independently by halo,

alkoxycarbonyl optionally substituted one or more times independently by aryl,

heteroaroyl optionally substituted one or more times independently by alkyl,

heterocyclyl optionally substituted one or more times by oxo, or

aryloxy optionally substituted one or more times independently by haloalkyl; and

Y^1 and Y^2 are each independently hydrogen, or alkyl optionally substituted by morpholinyl, or

Y^1 and Y^2 together with the nitrogen atom to which they are attached form morpholinyl;

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

16. The compound according to claim 1, wherein:

R^3 and R^4 together with the nitrogen atom to which they are attached form indolyl, optionally substituted one or more times independently by R^6;

R^6 is $Y^1Y^2N\text{-}SO_2\text{-}$, alkoxtcarbonyl, carboxyalkyl, cyano, halo, alkylsulfonyl, alkoxy, or acyl optionally substituted one or more times independently by halo; and

Y^1 and Y^2 are each independently independently hydrogen, or alkyl optionally substituted by morpholinyl, or

Y^1 and Y^2 together with the nitrogen atom to which they are attached form morpholinyl;
or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

17. The compound according to claim 1, wherein:

R^5 is phenyl, pyridyl, or benzo[1,3]dioxolyl, each of which is optionally substituted one or more times independently by R^6;

R^6 is $Y^1Y^2N\text{-}SO_2\text{-}$, hydroxy, alkoxy, halo, alkyl, or haloalkyl; and

Y^1 and Y^2 are each independently hydrogen or alkyl,

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

18. The compound according to claim 1, which is

2-Pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-Pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide,

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-3,3-dimethyl-2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2,3-dimethyl-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-chloro-2-methyl-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-bromo-indol-1-yl)-amide,
3-Oxo-4-[(2-phenyl-pyrimidine-5-carbonyl)-amino]-piperazine-1-carboxylic acid benzyl ester,
2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-(3-dimethylsulfamoyl-5-fluoro-indol-1-yl)amide,
2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-(3-dimethylsulfamoyl-5-fluoroindol-1-yl)amide,
2-(3-Fluorophenyl)pyrimidine-5-carboxylicacid-[5-fluoro-3-(morpholine-4-sulfonyl)indol-1-yl] amide,
2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3- (morpholine-4-sulfonyl) indol-1-yl] amide,
2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-sulfamoylindol-1-yl)amide,
2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-methylsulfamoyl)indol-1-yl)amide,
2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-[5-fluoro-3-(2-morpholin-4-ylethylsulfamoyl)indol-1-yl)amide,
2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3-methylsulfamoyl)indol-1-yl)amide,
2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-{5-fluoro-[(3-tetrahydropyran-4-ylmethyl)sulfamoyl]indol-1-yl}amide,
2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-[5-fluoro-3-(2-morpholin-4-ylethylsulfamoyl)indol-1-yl)amide,
2-(3-Fluorophenyl)pyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide,
2-(3-Fluorophenyl)-4-methylpyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide,
2-(Pyridin-2-yl)-pyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide,
2-(Pyridin-2-yl)-4-methylpyrimidine-5-carboxylic acid-(4-fluoroindol-1-yl)amide,
2-Phenyl-pyrimidine-5-carboxylic acid [6-(4-fluoro-phenyl)-3-oxo-2,5-dihydro-3H-1,2,4-triazin-4-yl]-amide,
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid[5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1-yl]-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(2-hydroxy-2-methyl-propyl)-indol-1 yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-cyano-5-fluoro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(1H-tetrazol-5-yl)-indol-1-yl]-amide,

2- Phenyl-pyrimidine-5-carboxylic acid [1,2,4] triazol-4-ylamide,

2-phenyl-pyrimidine-5-carboxylic acid piperidin-1-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-(2-fluoro-phenyl)-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid N`-ethyl-N'-tolyl-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid (3-oxo-morpholin-4-yl)-amide,

2-(5-Methyl-[1,2,4]oxadiazol-3-yl)-pyrimidine-5-carboxylic acid morpholin-4-ylamide,

2-Benzoyl-pyrimidine-5-carboxylic acid morpholin-4-ylamide,

2-Benzoyl-pyrimidine-5-carboxylic acid [4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid N`-methyl-N`-[5-trifluoromethyl-pyridin-2-yl]-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid N`-methyl-N'-[4-trifluoromethyl-pyridin-2-yl]-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid N`-pyridin-2-yl-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-(2-chloro-phenyl)-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-(2-oxo-piperidin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid N`-cyclohexyl-N`-methyl-hydrazide,

2-Phenyoxy-pyrimidine-5-carboxylic acid N`-morpholin-4-yl-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (2,6-dimethyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (6-tert-butyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-tert-butyl-3-oxo-2,5-dihydro-3H-1,2,4-triazine-4-yl)-amide,

3-{2,4-Dioxo-3-[(2-pheyl-pyrimidine-5-carbonyl)-amino]-1,2,3,4-tetrahydro-pyrimidin-5-yl}-propionic acid methyl ester,

3-{2,4-Dioxo-3-[(2-pheyl-pyrimidine-5-carbonyl)-amino]-1,2,3,4-tetrahydro-pyrimidin-5-yl}-propionic acid,

2-Phenyl-pyrimidine-5-carboxylic acid (4-methyl-piperazin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid morpholin-4-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-hydroxy-ethyl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid ((s)-2-methoxymethyl)-pyrrolidin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid ((R)-2-methoxymethyl)-pyrrolidin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (5-bromo-2, 4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (3-isopropyl-5-oxo-1,5-dihydro-[1,2,4]triazol-4-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid pyrrol-1-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid (5-morpholin-4-ylmethyl-2-oxo-oxazolidin-3-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (4-cyclopentyl-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (2-oxo-oxazolidin-3-yl)-amide,

4-Methyl-2-phenyl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl]-amide,

[N'-(2-Phenyl-pyrimidine-5-carbonyl)-hydrazino]-acetic acid ethyl ester,

2-[N'-(2-Phenyl-pyrimidine-5-carbonyl)-hydrazino]-acetamide,

4-[3-(4-Morpholino)propyl]-1-(2-phenyl-pyrimidine-5-carbonyl)-3-thiosemicarbazide,

2-Phenyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

{4-[2-Phenyl-pyrimidine-5-carbonyl)-amino]-piperazin-1-yl}-acetic acid methyl ester,

2-Phenyl-pyrimidine-5-carboxylic acid (4-cyanomethyl-piperazin-1-yl)-amide,

Acetic acid 2-{4-[(2-phenyl-pyrimidine-5-carbonyl)-amino]-piperazin-1-yl}-ethyl ester,

2-Phenyl-pyrimidine-5-carboxylic acid (4-acetyl-piperazin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-oxo-tetrahydro-furan-3-yl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(2,2,2-trifluoro-acetyl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-methoxy-ethyl)-piperazin-1-yl]-amide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazin-1-yl]-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid piperadin-1-yl-amide,

2-Phenyl-pyrimidine-5-carboxylic acid piperadin-1-yl-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (hexahydro-cyclopenta[c]pyrrol-2-yl)-amide,

4-Methyl-2-phenyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid pyrrolidin-1-yl-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (2,6-dimethyl-piperadin-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (4-cyclopentyl-piperazin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid N'-methyl-N'-pyridin-2-yl-hydrazide,

2-Phenyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid indol-1-yl-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid indol-1-yl-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-2,3-dihydro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid indol-1-ylamide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (2,3-dihydro-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid indol-1-ylamide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-methanesulfonyl-indol-1-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide,

2-Pyridin-3-yl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl-4-methyl)-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,

2-Pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridine-1-ylamide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid pyrrolo[3,2-b]pyridin-1-ylamide,

4-Methyl-2-pyridin-3-yl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-cyano-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (4-cyano-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [4-(1H-tetrazol-5-yl)-indol-1-yl]-amide,

1-{[2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-4-carboxylic acid methyl ester,

1-{[2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-4-carboxylic acid,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-cyanomethyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methoxy-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(1H-tetrazol-5-ylmethyl)-indol-1-yl]-amide,

2-(2-Phenyl-pyrimidine-5-carbonyl)-1-hydrazinecarboxamide,

2-(2-Phenyl-pyrimidine-5-carbonyl)-1-hydrazine-1-carbothioamide,
2-Phenyl-pyrimidine-5-carboxylic acid (2,4-dioxo-imidazolidin-1-yl)-amide,
2-Phenyl-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-Phenyl-pyrimidine-5-carboxylic acid N'-phenyl-hydrazide,
Pyridine-2-carboxylic acid N`-(2-phenyl-pyrimidine-5-carbonyl)-hydrazide,
4-[N`-(2-Phenyl-pyrimidine-5-carbonyl)-hydrazino]-benzenesulfonamide,
3-Hydroxy-benzoic acid N'-(2-phenyl-pyrimidine-5-carbonyl)-hydrazide,
Benzo[1,3]dioxo-5-carboxylic acid N`-(phenyl-pyrimidine-5-carbonyl)-hydrazide,
3,4-Dimethoxy-benzoic acid N`-(phenyl-pyrimidine-5-carbonyl)-hydrazide,
2-Phenyl-pyrimidine-5-carboxylic acid N`-methyl-N`-phenyl-hydrazide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-indol-1-yl)-amide,
2-(3-Methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-(2-Methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-(4-Methoxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-(3-Hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-(2-Hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
2-(4-Hydroxy-phenyl)-pyrimidine-5-carboxylic acid (6-methyl-3-oxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,
2-Thiazol-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,
[2,2']Bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylicacid(3chloro-5-fluoro-indol-1-yl)-amide,
5-Fluoro-1-{[2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indole-3-carboxylic acid amide,

2-{5-Fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indol-3-yl}-2-methyl-propionic acid,

2-(5-Fluoro-1-{[2-(3-fluoro-phenyl) -4-methyl-pyrimidine-5-carbonyl]-amino}-1H-indol-3-yl)-2-methyl-propionic acid,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3- (3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3- (2-pyridin-3-yl-ethyl)-indol-1-yl]- amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-formyl-indol-1-yl)-amide,

5-Fluoro-1-[(4-methyl-2-pyridin-2-yl-pyrimidine-5-carbonyl)-amino]-1H-indole-3-carboxylic acid,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-hydroxymethyl-indol-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(3-hydroxy-3-methyl-butyl)-indol-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethoxy-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (6-trifluoromethyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-ethyl-5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid *N',N'*-diphenyl-hydrazide

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (7-fluoro-3-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methanesulfonyl-3-methyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3c] pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-5-trifluoromethyl-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3c]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-nitro-indol-1-yl)-amide,

2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-amino-indol-1-yl)-amide,

2-(3-fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-(dimethanesulfonyl)-amino-indol-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-benzoylamino-indol-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-indol-1-yl]-amide,

2-Pyridin-2-yl-4-trifluoromethyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-indol-1-yl)-amide,

2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-1,4-benzoxazin-4-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-1,4-benzoxazin-4-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-ethyl-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (2-cyclopropyl-5-fluoro-indol-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (2-cyclopropyl-5-fluoro-indol-1-yl)-amide,

2-Pyrimidin-2-yl-4-methyl-pyrimidine-5-carboxylic acid (5-methoxyl-indol-1-yl)-amide,

4-Methyl-[2,2`]bipyrimidinyl-5-carboxylic acid (5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-methoxy-3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(1-oxy-pyridin-2-yl)-pyrimidin-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-(3-Difluoromethyl-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide, or

2-(3-Trifluoromethyl-phenyl)-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

19. The compound accordin to claim 1, which is:

2-Phenyl-pyrimidine-5-carboxylic acid (4-benzyl-piperazin-1-yl)-amide,

2-Phenyl-pyrimidine-5-carboxylic acid piperazin-1-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid (4-methanesulfonyl-piperazin-1-yl)-amide,

2-(2-Methyl-thiazol-4-yl)-pyrimidine-5-carboxylic acid morpholin-4-ylamide,

2-Phenyl-pyrimidine-5-carboxylic acid [4-(1-methyl-1H-imidazole-2-carbonyl)-piperazin-1-yl]-amide.

2-Phenyl-pyrimidine-5-carboxylic acid [4-(1-methyl-1H-imidazole-4-carbonyl)-piperazin-1-yl]-amide,

4-[(2-Phenyl-pyrimidine-5-carbonyl)-amino]-piperazine-1-carboxylic acid tert-butyl ester,
2-Phenyl-pyrimidine-5-carboxylic acid [4-(4-trifluoromethyl-phenoxy)-piperidin-1-yl]-amide,
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid [4-(4-trifluoromethyl-phenoxy)-piperidin-1-yl]-amide,
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid morpholin-4-ylamide,
2-Phenyl-pyrimidine-5-carboxylic acid indol-1-ylamide,
2-Phenyl-pyrimidine-5-carboxylic acid (4-methoxy-piperidin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-indol-1-yl)-amide,
2-(3-Fluoro-phenyl)-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-benzo[1,4]oxazin-4-yl)-amide,
2-Phenyl-pyrimidine-5-carboxylic acid (6-fluoro-2,3-dihydro-benzo[1,4]oxazin-4-yl)-amide,
1-{[2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carbonyl]-amino}-3-(2-morpholin-4-yl-ethyl)-1H-indole-6-carboxylic acid methyl ester,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [5-fluoro-3-(tetrahydro-pyran-4-yl)-indol-1-yl]-amide,
N-methyl-N-(5-fluoro)-indol-3-ylsulfonyl N`-[2-(3-fluoro)-phenyl-pyrimidine-5-carbonyl]-hydrazide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid [5-fluoro-3-(tetrahydro-pyran-4-yl)-indol-1-yl]-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[3,2-c]pyridin-1-ylamide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethy l-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid pyrrolo[3,2-c]pyridin-1-ylamide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-b]pyridin-1-ylamide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[2,3-c]pyridin-1-ylamide,

4-Methyl-2-(4-chloro -thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid pyrrolo[3,2-c]pyridin-1-ylamide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-isopropyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-chloro-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide,

2-(4-Methyl-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-fluoro-3-methyl-indol-1-yl)-amide.

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (2-methyl-3-oxo-2,3-dihydro-indazol-1-yl)amide,

2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid(5-fluoro-indol-1-yl)amide)amide,

6-(4-Chloro-thiazol-2-yl)-2-methyl-N-pyrrolo[2,3-c]pyridin-1-yl-nicotinamide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid(5-methyl-4-oxo-4,5-dihydro-pyrrolo[3,2-c]pyridin-1-yl)amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (5-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,

4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (5-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluo ro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluo ro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,

4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-

ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluo ro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
4-Methyl-2-(4-methyl-thiazol-2-yl)-pyrimidine-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[2,3-b]pyridin-1-yl]-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-trifluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,
4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (5-difluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrrolo[3,2-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo [3,2-b]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo [3,2-b]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[3,2-c] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrro lo[3,2-c]pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-2,2-diuoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-c] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrro lo[2,3-c]pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo [2,3-c]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo [2,3-c]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid (3-difluoromethyl-pyrrolo[2,3-b] pyridin-1-yl)-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo [2,3-b]pyridin-1-yl]-amide,

4-Methyl-[2,2']bipyrimidinyl-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo [2,3-b]pyridin-1-yl]-amide,

2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-trifluoro

methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (5-difluorom
ethyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoro
methyl-pyrrolo[3,2-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoro
methyl-pyrrolo[3,2-c]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoro
methyl-pyrrolo[2,3-c]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid (3-trifluoromethyl-pyrrolo[2,3-b]pyridin-1-yl)-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2-difluoro-ethyl)-pyrrolo[3,2-b]pyridin-1-yl]-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)
-pyrrolo[3,2-b]pyridin-1-yl]-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[3,2-c]pyridin-1-yl]-amide,
2-(3-Fluoro-phenyl)-4-methyl-pyrimidine-5-carboxylic acid [3-(2,2,2-trifluoro-ethyl)-pyrrolo[2,3-c]pyridin-1-yl]-amide,
4-Methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-indol-1-yl)-amide,
2-(4-Chloro-thiazol-2-yl)-4-methyl-pyrimidine-5-carboxylic acid (3-difluoromethyl-indol-1-yl)-amide, or
4-Methyl-2-thiazol-2-yl-pyrimidine-5-carboxylic acid (3-difluoromethyl-indol-1-yl)-amide,
or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising the compound according to claim 1, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

21. A method for treating an allergic or inflammatory disorder in a patient in need thereof, comprising administering to the patient a pharmaceutically effective amount of the compound according to claim 1, or a hydrate, solvate or N-oxide thereof, or a pharmaceutically acceptable salt thereof.

22. The method according to claim 21, wherein the allergic or inflammatory disorder is allergic rhinitis.

23. The method according to claim 21, wherein the allergic or inflammatory disorder is asthma.

24. The method according to claim 21, wherein the allergic or inflammatory disorder is chronic obstructive pulmonary disease.

COMPUESTOS DE PIRIMIDINA HIDRAZIDA COMO INHIBIDORES DE PGDS

CAMPO DE LA INVENCIÓN

La presente invención se refiere a compuestos de pirimidina, a su preparación, a composiciones farmacéuticas que contienen estos compuestos y a su uso farmacéutico en el tratamiento de patologías que pueden modularse por la inhibición de la prostaglandina D2 sintasa.

ANTECEDENTES DE LA INVENCIÓN

La rinitis alérgica, la enfermedad atópica más común, tiene una prevalencia estimada que varía entre aproximadamente 5 y aproximadamente 22 por ciento de la población humana general y se caracteriza por los síntomas de estornudos, descarga nasal y congestión nasal. Se cree que estos síntomas se desencadenan por múltiples mediadores liberados por los mastocitos y otras células inflamatorias. Las terapias actuales, tales como antihistamínicos, tratan eficazmente los estornudos y la descarga nasal, pero tienen poco efecto sobre la congestión, que es un síntoma clave que afecta a la calidad de vida de los pacientes.

Se ha demostrado que la exposición local a alérgenos en pacientes con rinitis alérgica, asma bronquial, conjuntivitis alérgica y dermatitis atópica produce una rápida elevación de los niveles de prostaglandina D2 "(PGD2)" en los fluidos de lavado nasal y bronquial, lágrimas y fluidos de cámaras cutáneas. La PGD2 tiene muchas acciones inflamatorias, tales como aumentar la permeabilidad vascular en la conjuntiva y la piel, aumentar la resistencia de las vías respiratorias nasales, el estrechamiento de las vías respiratorias y la infiltración de eosinófilos en la conjuntiva y la tráquea. La PGD2 es el principal producto de la reacción catalizada por la ciclooxigenasa del ácido araquidónico producido a partir de los mastocitos con desafío inmunológico [Lewis, RA, Soter NA, Diamond PT, Austen KF, Oates JA, Roberts LJ II, Prostaglandin D2 generation after activation of rat and human mast cells with anti-IgE, *J. Immunol.* **129**, 1627-1631, 1982]. Los mastocitos activados, una fuente muy importante de PGD2, son uno de los participantes claves para dirigir la respuesta alérgica en enfermedades tales como asma, rinitis alérgica, conjuntivitis alérgica, dermatitis alérgica y otras enfermedades [Brightling CE, Bradding P, Pavord ID, Wardlaw AJ, New Insights en the role of the mast cell in asthma, *Clin. Exp. Allergy* **33**, 550-556, 2003].

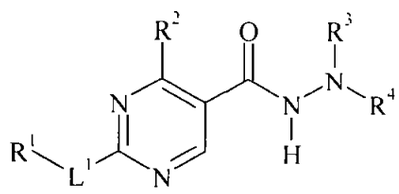
En presencia de compuestos de sulfhidrilo, se forma PGD2 por la isomerización de PGH2, un precursor común de prostanoides, por acción catalítica de la prostaglandina D sintasa "(PGDS)". Existen dos isoformas de la enzima PGDS: L-PGDS; y H-PGDS. La H-PGDS es una enzima citosólica que se distribuye en los tejidos periféricos, y que se localiza en las células presentadoras de antígenos, mastocitos, megacariocitos y linfocitos Th2. La acción de la PGD2 producida está mediada por receptores acoplados a proteínas G: prostaglandina D "(DP)" y crTH2. Véase (1) Prostaglandin D Synthase: Structure and Function. T. Urade y O. Hayaishi, *Vitamin and Hormones*, 2000, 58, 89-120, (2) J. J. Murray, *N. Engl. J. Med.*, 1986 Sept. 25; 315(13):800, y (3) Urade et. al., *J. Immunology* 168: 443-449, 2002.

Los presentes inventores creen que la inhibición de la formación de PGD2 debe tener un efecto sobre la congestión nasal y, por lo tanto, debe tener un efecto terapéutico beneficioso en la rinitis alérgica. Además, los presentes inventores creen que un inhibidor de la PGDS debe tener un efecto terapéutico beneficioso en varias indicaciones distintas tales como el asma bronquial.

Se ha informado sobre inhibidores de PGDS. El compuesto HQL-79, se presenta como un inhibidor débil de PGDS y es antiasmático en modelos de cobaya y rata (Matsusshita, et al., Jpn. J. Pharmacol. 78: 11, 1998). El compuesto Tranilast se describe como un inhibidor de la PGDS. (Inhibitory Effect of Tranilast on Prostaglandin D Synthetase. K. Ikai, M. Jihara, k. Fujii, e Y. Urade. *Biochemical Pharmacology*, 1989, 28, 2773-2676).

SUMARIO DE LA INVENCIÓN

La presente invención se refiere a un compuesto de fórmula (I):



(I)

en la que:

R^1 es alquilo (C_1-C_6) opcionalmente sustituido una o más veces independientemente con halo, hidroxi, alcoxi (C_1-C_6) o haloalcoxi (C_1-C_4) o

cicloalquilo (C_3-C_6), arilo o heteroarilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), haloalquilo (C_1-C_4) o haloalcoxi (C_1-C_4);

R^2 es hidrógeno o alquilo (C_1-C_4) opcionalmente sustituido una o más veces con halo;

R^3 es hidrógeno, alquilo, arilo o heteroarilo,

R^4 es hidrógeno, cicloalquilo, arilo, heteroarilo, heterociclilo, arilsulfonilo, heteroarilsulfonilo,

$-C(=O)-NY^1Y^2$, $-C(=S)-NY^1Y^2$, R^5, $-C(=O)-R^5$ o $-C(=S)-R^5$, donde el resto arilo, heteroarilo o heterociclilo está opcionalmente sustituido una o más veces independientemente con R^6, o

R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman heterociclilo, heterociclenilo, heteroarilo, arilheterociclilo, arilheterociclenilo, heteroarilheterociclilo, heteroarilheterociclenilo, heterociclilheteroarilo o heterociclenilheteroarilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

R^5 es cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclilo, heterociclenilo, o alcarilo multicíclico, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

L^1 es un enlace, -O-, -C(=O)-, -NH-C(=O)- o alquileno (C_1-C_2) opcionalmente sustituido una o más veces con halo;

R^6 es ciano, nitro, halo, hidroxi, carboxi, Y^1Y^2N-, Y^1Y^2N-C(=O)-, Y^1Y^2N-SO_2-,

acilo, aciloxi, alquilo, alquenilo, alquinilo, alcoxi, alcoxicarbonilo, alquiltio, alquilsulfinilo o alquilsulfonilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con:

aciloxi, halo, alcoxi, haloalcoxi, hidroxi, carboxi, alcoxicarbonilo, Y^1Y^2N-, Y^1Y^2N-C(=O)-, Y^1Y^2N-SO_2-,

arilo, ariloxi, aroílo, heteroarilo, heteroariloxi, heteroaroílo, heterociclilo, heterociclenilo, cicloalquilo, cicloalquenilo o alcarilo multicíclico, cada uno de ellos opcionalmente sustituido una o más veces independientemente con alquilo, halo, haloalquilo, alcoxi, haloalcoxi, hidroxi, amino, alquilamino, dialquilamino, carboxi o alcoxicarbonilo, o

arilo, heteroarilo, aroílo, heteroaroílo, ariloxi, heteroariloxi, heterociclilo, heterociclenilo, cicloalquilo, cicloalquenilo o alcarilo multicíclico, cada uno de ellos opcionalmente sustituido una o más veces independientemente con

alquilo, haloalquilo, halo, alcoxi, haloalcoxi, hidroxi, carboxi, alcoxicarbonilo, Y^1Y^2N- o Y^1Y^2N-SO_2-,

donde el resto heterociclilo, heterociclenilo, cicloalquilo, cicloalquenilo o alcarilo multicíclico de R^6 también está opcionalmente sustituido una o más veces independientemente con oxo;

cada uno de Y^1 e Y^2 es independientemente:

hidrógeno, alquilsulfonilo, aroílo, heteroaroílo o

alquilo opcionalmente sustituido una o más veces independientemente con hidroxi, carboxi, halo, amino, alquilamino, dialquilamino, alcoxi, heterociclilo, arilo o heteroarilo, o

Y^1 e Y^2 junto con el átomo de nitrógeno al que están unidos forman heterociclilo;

o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otro aspecto de la presente invención es una composición farmacéutica que comprende una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con la fórmula (I), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo, mezclada con un vehículo farmacéuticamente aceptable.

Otro aspecto de la presente invención se refiere a un método para tratar trastornos alérgicos y/o inflamatorios, particularmente trastornos tales como rinitis alérgica, asma y/o enfermedad pulmonar obstructiva crónica (COPD) en un paciente que lo necesita, mediante la administración al paciente de un compuesto de acuerdo con la fórmula (I), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Definición de Expresiones

Como se ha usado anteriormente, y a lo largo de la descripción de la invención, debe entenderse que las siguientes expresiones, a menos que se indique otra cosa, tienen los siguientes significados:

"Acilo" significa H-CO- o (grupo alifático o ciclil)-CO-. Un acilo particular incluye alcanoílo inferior que contiene un alquilo inferior. Los ejemplos de acilo incluyen formilo,

acetilo, propanoílo, 2-metilpropanoílo, butanoílo, palmitoílo, acriloílo, propinoílo y ciclohexilcarbonilo.

"Aciloxi" significa acil-O-.

"Alquenilo" significa un grupo hidrocarburo alifático lineal o ramificado que contiene un doble enlace carbono-carbono y que tiene de 2 a aproximadamente 15 átomos de carbono. Un alquenilo particular tiene de 2 a aproximadamente 12 átomos de carbono. Un alquenilo más particular tiene de 2 a aproximadamente 4 átomos de carbono. Ramificado significa que uno o más de los grupos alquilo inferior tales como metilo, etilo o propilo se unen a una cadena de alquenilo lineal. "*Alquenilo inferior*" significa de aproximadamente 2 a aproximadamente 4 átomos de carbono en la cadena que puede ser lineal o ramificada. Los ejemplos de alquenilo incluyen etenilo, propenilo, *n*-butenilo, *i*-butenilo, 3-metilbut-2-enilo, *n*-pentenilo, heptenilo, octenilo, ciclohexilbutenilo y decenilo.

"Alcoxi" significa alquil-O-. Los ejemplos de alcoxi incluyen metoxi, etoxi, *n*-propoxi, *i*-propoxi, *n*-butoxi y heptoxi.

"Alcoxicarbonilo" significa alquil-O-CO-. Los ejemplos de alcoxicarbonilo incluyen metoxicarbonilo, etoxicarbonilo y *t*-butiloxicarbonilo.

"Alquilo" significa un hidrocarburo alifático lineal o ramificado que tiene de 1 a aproximadamente 20 átomos de carbono. Un alquilo *particular* tiene de 1 a aproximadamente 12 átomos de carbono. Un alquilo más particular es alquilo inferior. Ramificado significa que uno o más de los grupos alquilo inferior tales como metilo, etilo o propilo se unen a una cadena de alquilo lineal. "Alquilo inferior" significa de 1 a aproximadamente 4 átomos de carbono en una cadena de alquilo lineal que puede ser lineal o ramificada.

"Alquilamino" significa alquil-NH-. Un alquilamino particular es alquilamino (C_1-C_6). Los ejemplos de alquilamino incluyen metilamino y etilamino.

"Alquilsulfinilo" significa alquil-SO-. Un alquilsulfonilo particular es alquilsulfinilo (C_1-C_6). El grupo alquilsulfinilo ejemplar incluye CH_3-SO- y CH_3CH_2-SO-.

"Alquilsulfonilo" significa alquil-SO_2-. Un alquilsulfonilo particular es alquilsulfonilo (C_1-C_6). Los ejemplos de alquilsulfonilo incluyen CH_3-SO_2- y CH_3CH_2-SO_2-.

"Alquiltio" significa un alquil-S-. Los ejemplos de alquiltio incluyen CH_3-S-.

"Alquinilo" significa un hidrocarburo alifático lineal o ramificado que contiene un triple enlace carbono-carbono y que tiene de 2 a aproximadamente 15 átomos de carbono. Un alquinilo particular tiene de 2 a aproximadamente 12 átomos de carbono. Un alquinilo más particular tiene de 2 a aproximadamente 6 átomos de carbono. Ramificado significa que uno o más de los grupos alquilo inferior tales como metilo, etilo o propilo se unen a una cadena alquinilo lineal. "Alquinilo inferior" significa de 2 a aproximadamente 4 átomos de carbono en una cadena de alquinilo lineal que puede ser lineal o ramificada. Los ejemplos de alquinilo incluyen etinilo, propinilo, *n*-butinilo, 2-butinilo, 3-metilbutinilo, *n*-pentinilo, heptinilo, octinilo y decinilo.

"Aroilo" significa aril-CO-. Los ejemplos de aroílo incluyen benzoílo y 1- y 2-naftoílo.

"Arilo" significa un sistema de anillos monocíclicos o multicíclicos aromáticos de aproximadamente 6 a aproximadamente 14 átomos de carbono. Un arilo particular incluye de aproximadamente 6 a aproximadamente 10 átomos de carbono. Los ejemplos de arilo incluyen fenilo y naftilo.

"Arilcicloalquenilo" significa un arilo y cicloalquenilo condensados. Un arilcicloalquenilo particular es aquel en el que su arilo es fenilo y el cicloalquenilo se compone de aproximadamente 5 a aproximadamente 7 átomos en el anillo. Un arilcicloalquenilo se une a través de cualquier átomo del resto cicloalquenilo del mismo capaz de tal unión. Los ejemplos de arilcicloalquenilo incluyen 1,2-dihidronaftileno e indeno.

"Arilcicloalquilo" significa un arilo y cicloalquilo condensados. Un arilcicloalquilo particular es aquel en el que su arilo es fenilo y el cicloalquenilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un arilcicloalquilo se une a través de cualquier átomo del resto cicloalquilo del mismo capaz de tal unión. Los ejemplos de arilcicloalquilo incluyen 1,2,3,4-tetrahidro-naftileno.

"Arilheterociclenilo" significa un arilo y heterociclenilo condensados. Un arilheterociclenilo particular es aquel en el que su arilo es fenilo y el heterociclenilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un arilheterociclenilo se une a través de cualquier átomo del heterociclenilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heterociclenilo del arilheterociclenilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un arilheterociclenilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre de la porción heterociclenilo del arilheterociclenilo puede oxidarse también opcionalmente hasta el N-óxido, S-óxido o S,S-dióxido correspondiente. Los ejemplos de arilheterociclenilo incluyen 3H-indolinilo, 1H-2-oxoquinolilo, 2H-1-oxoisoquinolilo, 1,2-dihidroquinolinilo, 3,4-dihidroquinolinilo, 1,2-dihidroisoquinolinilo y 3,4-dihidroisoquinolinilo.

"Arilheterociclilo" significa un arilo y heterociclilo condensados. Un heterociclilarilo particular es aquel en el que su arilo es fenilo y el heterociclilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un arilheterociclilo se une a través de cualquier átomo del resto heterociclilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heterociclilo del arilheterociclilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un arilheterociclilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre de la porción heterociclilo del arilheterociclilo puede oxidarse también opcionalmente hasta el N-óxido, S-óxido o S,S-dióxido correspondiente. Los ejemplos de arilheterociclilo incluyen indolinilo, 1,2,3,4-tetrahidroisoquinolina, 1,2,3,4-tetrahidroquinolina, 1H-2,3-dihidroisoindol-2-ilo, 2,3-dihidrobenz[f]isoindol-2-ilo y 1,2,3,4-tetrahidrobenz[g]-isoquinolin-2-ilo.

"Ariloxi" significa un aril-O-. Los ejemplos de ariloxi incluyen fenoxi y naftoxi.

"Compuestos de la presente invención" y expresiones equivalentes pretenden incluir los compuestos de Fórmula (I) que se han descrito anteriormente en este documento, los hidratos, solvatos y N-óxidos de los mismos, y las sales farmacéuticamente aceptables de los mismos, cuando el contexto así lo permita. Análogamente, la referencia a intermedios, reivindicados o no por sí mismos, pretende incluir sus sales, N-óxidos y solvatos, cuando el contexto así lo permita.

"Cicloalquenilo" significa un sistema de anillos mono- o multicíclicos no aromáticos de aproximadamente 3 a aproximadamente 10 átomos de carbono, particularmente de aproximadamente 5 a aproximadamente 10 átomos de carbono y que contiene al menos un doble enlace carbono-carbono. Los anillos particulares del sistema de anillos de aproximadamente 5 a aproximadamente 6 átomos en el anillo; y tales tamaños de anillo particulares se denominan también "inferiores". Los ejemplos de cicloalquenilo monocíclico incluyen ciclopentenilo, ciclohexenilo y cicloheptenilo. Un ejemplo de cicloalquenilo multicíclico es norbornilenilo.

"Cicloalquenilarilo" significa un arilo y cicloalquenilo condensados. Un cicloalquenilarilo particular es aquel en el que su arilo es fenilo y el cicloalquenilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un cicloalquenilarilo se une a través de cualquier átomo del resto arilo del mismo capaz de tal unión. Los ejemplos de cicloalquenilarilo incluyen 1,2-dihidronaftileno e indeno.

"Cicloalquenilheteroarilo" significa un heteroarilo y cicloalquenilo condensados. Un cicloalquenilheteroarilo particular es aquel en el que su heteroarilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo y el cicloalquenilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un cicloalquenilheteroarilo se une a través de cualquier átomo del heteroarilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heteroarilo del cicloalquenilheteroarilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un cicloalquenilheteroarilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno de la porcion heteroarilo del cicloalquenilheteroarilo puede oxidarse también opcionalmente hasta el N-óxido correspondiente. Los ejemplos de cicloalquenilheteroarilo incluyen 5,6-dihidroquinolilo, 5,6-dihidroisoquinolilo, 5,6-dihidroquinoxalinilo, 5,6-dihidroquinazolinilo, 4,5-dihidro-1H-bencimidazolilo y 4,5-dihidrobenzoxazolilo.

"Cicloalquilo" significa un sistema de anillos saturados mono- o multicíclicos no aromáticos de aproximadamente 3 a aproximadamente 10 átomos de carbono, particularmente de aproximadamente 5 a aproximadamente 10 átomos de carbono. Los sistemas de anillos particulares de aproximadamente 5 a aproximadamente 7 átomos en el anillo; y tales sistemas de anillos particulares se denominan también "inferiores". Los ejemplos de

cicloalquilo monocíclico incluyen ciclopentilo, ciclohexilo y cicloheptilo. Los ejemplos de cicloalquilo multicíclico incluyen 1-decalina, norbornilo y adamant-(1- o 2-)ilo.

"Cicloalquilarilo" significa un arilo y cicloalquilo condensados. Un cicloalquilarilo particular es aquel en el que su arilo es fenilo y el cicloalquilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un cicloalquilarilo se une a través de cualquier átomo del resto cicloalquilo del mismo capaz de tal unión. Los ejemplos de cicloalquilarilo incluyen 1,2,3,4-tetrahidro-naftileno.

"Cicloalquilheteroarilo" significa heteroarilo y cicloalquilo condensados. Un cicloalquilheteroarilo particular es aquel en el que su heteroarilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo y el cicloalquilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un cicloalquilheteroarilo se une a través de cualquier átomo del heteroarilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heteroarilo del cicloalquilheteroarilo condensado define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un cicloalquilheteroarilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno de la porción heteroarilo del cicloalquilheteroarilo también puede oxidarse opcionalmente hasta el N-óxido correspondiente. Los ejemplos de cicloalquilheteroarilo incluyen 5,6,7,8-tetrahidroquinolinilo, 5,6,7,8-tetra-hidroisoquinolilo, 5,6,7,8-tetrahidroquinoxalinilo, 5,6,7,8-tetrahidroquinazolilo, 4,5,6,7-tetrahidro-1H-bencimidazolilo y 4,5,6,7-tetrahidrobenzoxazolilo.

"Ciclilo" significa cicloalquilo, cicloalquenilo, heterociclilo o heterociclenilo.

"Dialquilamino" significa (alquil)$_2$-N-. Un dialquilamino particular es (alquil C_1-C_6)$_2$-N-. Los ejemplos de grupos incluyen dialquilamino dimetilamino, dietilamino y metiletilamino.

"Halo" o ""halógeno" significa flúor, cloro, bromo o yodo. El halo o halógeno particular es flúor o cloro.

"Haloalcoxi" significa alcoxi sustituido con uno a tres grupos halo. Los haloalcoxi particulares son los alcoxi inferiores sustituidos con uno a tres halógenos. Los haloalcoxi más particulares son los alcoxi inferiores sustituidos con un halógeno.

El término "haloalquilo" se refiere a alquilo sustituido con uno a tres grupos halo. Los haloalquilos particulares son alquilo inferior sustituido con uno a tres halógenos. Los haloalquilos más particulares son alquilo inferior sustituido con un halógeno.

"Heteroaroílo" significa heteroaril-CO-. Los ejemplos de heteroaroílo incluyen tiofenoílo, nicotinoílo, pirrol-2-ilcarbonilo, y piridinoílo.

"Heteroarilo" significa un sistema de anillos aromáticos monocíclicos o multicíclicos de aproximadamente 5 a aproximadamente 14 átomos de carbono, en el que uno o más de los átomos de carbono en el sistema de anillos es/son heteroelemento(s) diferentes de carbono, por ejemplo nitrógeno, oxígeno o azufre. Los sistemas de anillos aromáticos particulares incluyen de aproximadamente 5 a aproximadamente 10 átomos de carbono, e incluyen de 1 a 3 heteroátomos. Los tamaños de anillo más particulares de los anillos del sistema de anillos incluyen de aproximadamente 5 a aproximadamente 6 átomos en el anillo. La designación de aza, oxa o tio como prefijo antes del heteroarilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. Un átomo de nitrógeno de un heteroarilo puede ser un átomo de nitrógeno básico y puede oxidarse también opcionalmente hasta el N-óxido correspondiente. Cuando un heteroarilo está sustituido con un grupo hidroxi, también incluye su tautómero correspondiente. Los ejemplos de heteroarilo incluyen pirazinilo, tienilo, isotiazolilo, oxazolilo, pirazolilo, furanilo, pirrolilo, 1,2,4-tiadiazolilo, piridazinilo, quinoxalinilo, ftalazinilo, imidazo[1,2-a]piridina, imidazo[2,1-b]tiazolilo, benzofuranilo, azaindolilo, bencimidazolilo, benzotienilo, tienopiridilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo, imidazolilo, indolilo, indolizinilo, isoxazolilo, isoquinolinilo, isotiazolilo, oxadiazolilo, pirazinilo, piridazinilo, pirazolilo, piridilo, pirimidinilo, pirrolilo, quinazolinilo, quinolinilo, 1,3,4-tiadiazolilo, tiazolilo, tienilo y triazolilo.

"Heteroarilalquilo" significa heteroaril-alquil-. Un heteroarilalquilo particular contiene un resto alquilo (C_1-C_4). Los ejemplos de heteroarilalquilo incluyen tetrazol-5-ilmetilo.

"Heteroarilcicloalquenilo" significa un heteroarilo y cicloalquenilo condensados. Un heteroarilcicloalquenilo particular es aquel en el que su heteroarilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo y el cicloalquenilo se compone

de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un heteroarilcicloalquenilo se une a través de cualquier átomo del cicloalquenilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heteroarilo del heteroarilcicloalquenilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un heteroarilcicloalquenilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno de la porción heteroarilo del heteroarilcicloalquenilo puede oxidarse también opcionalmente hasta el N-óxido correspondiente. Los ejemplos de heteroarilcicloalquenilo incluyen 5,6-dihidroquinolilo, 5,6-dihidroisoquinolilo, 5,6-dihidroquinoxalinilo, 5,6-dihidroquinazolinilo, 4,5-dihidro-1H-bencimidazolilo y 4,5-dihidrobenzoxazolilo.

"Heteroarilcicloalquilo" significa un heteroarilo y cicloalquilo condensados. Un heteroarilcicloalquilo particular es aquel en el que su heteroarilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo y el cicloalquilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un heteroarilcicloalquilo se une a través de cualquier átomo del cicloalquilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heteroarilo del heteroarilcicloalquilo condensado define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un heteroarilcicloalquilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno de la porción heteroarilo del heteroarilcicloalquilo también puede oxidarse opcionalmente hasta el N-óxido correspondiente. Los ejemplos de heteroarilcicloalquilo incluyen 5,6,7,8-tetrahidroquinolinilo, 5,6,7,8-tetra-hidroisoquinolilo, 5,6,7,8-tetrahidroquinoxalinilo, 5,6,7,8-tetrahidroquinazolilo, 4,5,6,7-tetrahidro-1H-bencimidazolilo y 4,5,6,7-tetrahidrobenzoxazolilo.

"Heteroarilheterociclenilo" significa un heteroarilo y heterociclenilo condensados. Un heteroarilheterociclenilo particular es aquel en el que su heteroarilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo y el heterociclenilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un heteroarilheterociclenilo se une a través de cualquier átomo del heterociclenilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heteroarilo o heterociclenilo del heteroarilheterociclenilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un heteroarilazaheterociclenilo puede ser un átomo de nitrógeno

básico. El átomo de nitrógeno o azufre de la porción heteroarilo o heterociclenilo del heteroarilheterociclenilo también puede oxidarse opcionalmente para dar el N-óxido, S-óxido o S,S-dióxido correspondiente. Los ejemplos de heteroarilheterociclenilo incluyen 7,8-dihidro[1,7]naftiridinilo, 1,2-dihidro[2,7]-naftiridinilo, 6,7-dihidro-3H-imidazo[4,5-c]piridilo, 1,2-dihidro-1,5-naftiridinilo, 1,2-dihidro-1,6-naftiridinilo, 1,2-dihidro-1,7-naftiridinilo, 1,2-dihidro-1,8-naftiridinilo y 1,2-dihidro-2,6-naftiridinilo.

"Heteroarilheterociclilo" significa un heteroarilo y heterociclilo condensados. Un heteroarilheterociclilo particular es aquel en el que su heteroarilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo y el heterociclilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un heteroarilheterociclilo se une a través de cualquier átomo del heterociclilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heteroarilo o heterociclilo del heteroarilheterociclilo condensado define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un heteroarilheterociclilo condensado puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre de la porción heteroarilo o heterociclilo del heteroarilheterociclilo puede oxidarse también opcionalmente hasta el N-óxido, S-óxido o S,S-dióxido correspondiente. Los ejemplos de heteroarilheterociclilo incluyen 2,3-dihidro-1H-pirrol[3,4-b]quinolin-2-ilo, 1,2,3,4-tetrahidrobenz[b][1,7]naftiridin-2-ilo, 1,2,3,4-tetrahidrobenz[b][1,6]naftiridin-2-ilo, 1,2,3,4-tetra-hidro-9H-pirido[3,4-b]indol-2-ilo, 1,2,3,4-tetrahidro-9H-pirido[4,3-b]indol-2-ilo, 2,3-dihidro-1H-pirrolo[3,4-b]indol-2-ilo, 1H-2,3,4,5-tetrahidroazepino[3,4-b]indol-2-ilo, 1H-2,3,4,5-tetra-hidroazepino[4,3-b]indol-3-ilo, 1H-2,3,4,5-tetrahidroazepino[4,5-b]indol-2-ilo, 5,6,7,8-tetra-hidro[1,7]naftiridilo, 1,2,3,4-tetrahidro[2,7]naftiridilo, 2,3-dihidro[1,4]dioxino[2,3-b]piridilo, 2,3-dihidro-[1,4]dioxino[2,3-b]piridilo, 3,4-dihidro-2H-1-oxa[4,6]diazanaftalenilo, 4,5,6,7-tetrahidro-3H-imidazo[4,5-c]piridilo, 6,7-dihidro[5,8]diazanaftalenilo, 1,2,3,4-tetrahidro[1,5]-naftiridinilo, 1,2,3,4-tetrahidro[1,6]naftiridinilo, 1,2,3,4-tetrahidro[1,7]naftiridinilo, 1,2,3,4-tetrahidro[1,8]naftiridinilo y 1,2,3,4-tetra-hidro[2,6]naftiridinilo.

"Heteroariloxi" significa heteroaril-O-. Los ejemplos de heteroariloxi incluyen piridiloxi.

"Heterociclenilo" significa un sistema de anillos de hidrocarburos monocíclicos o multicíclicos no aromáticos de aproximadamente 3 a aproximadamente 10 átomos de carbono, en el que uno o más de los átomos de carbono en el sistema de anillos es/son

heteroelemento(s) diferentes de carbono, por ejemplo átomos de nitrógeno, oxígeno o azufre, y que contiene al menos un doble enlace carbono-carbono o carbono-nitrógeno. Un sistema de anillos no aromáticos particular incluye de aproximadamente 5 a aproximadamente 10 átomos de carbono y de 1 a 3 heteroátomos. Los tamaños de anillo más particulares de los anillos del sistema de anillos incluyen de aproximadamente 5 a aproximadamente 6 átomos en el anillo; y tales tamaños de anillo particulares se denominan también "inferiores". La designación de aza, oxa o tio como prefijo antes de heterociclenilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un heterociclenilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre del heterociclenilo puede oxidarse también opcionalmente hasta el N-óxido, S-óxido o S,S-dióxido correspondiente. Los ejemplos de azaheterociclenilo monocíclico incluyen 1,2,3,4-tetrahidrohidropiridilo, 1,2-dihidropiridilo, 1,4-dihidropiridilo, 1,2,3,6-tetra-hidropiridilo, 1,4,5,6-tetrahidro-pirimidina, 2-pirrolinilo, 3-pirrolinilo, 2-imidazolinilo y 2-pirazolinilo. Los ejemplos de oxaheterociclenilo incluyen 3,4-dihidro-2H-pirano, dihidrofuranilo y fluorodihidro-furanilo. Un ejemplo de oxaheterociclenilo multicíclico es 7-oxabiciclo[2,2,1]heptenilo. Los ejemplos de tioheterociclenilo monocíclico incluyen dihidrotiofenilo y dihidrotiopiranilo.

"Heterociclenilarilo" significa un arilo y heterociclenilo condensados. Un heterociclenilarilo particular es aquel en el que su arilo es fenilo y el heterociclenilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un heterociclenilarilo se une a través de cualquier átomo del arilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heterociclenilo del heterociclenilarilo condensado define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un heterociclenilarilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre de la porción heterociclenilo del heterociclenilarilo puede oxidarse también opcionalmente hasta el N-óxido, S-óxido o S,S-dióxido correspondiente. Los ejemplos de heterociclenilarilo incluyen 3H-indolinilo, 1H-2-oxoquinolilo, 2H-1-oxoisoquinolilo, 1,2-dihidroquinolinilo, 3,4-dihidroquinolinilo, 1,2-dihidroisoquinolinilo y 3,4-dihidroisoquinolinilo.

"Heterociclenilheteroarilo" significa un heteroarilo y heterociclenilo condensados. Un heterociclenilheteroarilo particular es aquel en el que su heteroarilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo y el heterociclenilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un

heterociclenilheteroarilo se une a través de cualquier átomo del heteroarilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heteroarilo o heterociclenilo del heterociclenilheteroarilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un azaheterociclenilheteroarilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre de la porción heteroarilo o heterociclenilo del heterociclenilheteroarilo también puede oxidarse opcionalmente para dar el N-óxido, S-óxido o S,S-dióxido correspondiente. Los ejemplos de heterociclenilheteroarilo incluyen 7,8-dihidro[1,7]naftiridinilo, 1,2-dihidro[2,7]-naftiridinilo, 6,7-dihidro-3H-imidazo[4,5-c]piridilo, 1,2-dihidro-1,5-naftiridinilo, 1,2-dihidro-1,6-naftiridinilo, 1,2-dihidro-1,7-naftiridinilo, 1,2-dihidro-1,8-naftiridinilo y 1,2-dihidro-2,6-naftiridinilo.

"Heterociclilo" significa un sistema de anillos monocíclicos o multicíclicos saturados no aromáticos de aproximadamente 3 a aproximadamente 10 átomos de carbono, en el que uno o más de los átomos del sistema de anillos es/son heteroelemento(s) diferentes de carbono, por ejemplo nitrógeno, oxígeno o azufre. Un sistema de anillos particular contiene de aproximadamente 5 a aproximadamente 10 átomos de carbono y de 1 a 3 heteroátomos. Los tamaños de los anillos particulares del sistema de anillos incluyen de aproximadamente 5 a aproximadamente 6 átomos en el anillo; y tales tamaños de anillo particulares se denominan también "inferiores". La designación de aza, oxa o tio como prefijo antes de heterociclilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre respectivamente como un átomo del anillo. El átomo de nitrógeno de un heterociclilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre del heterociclilo puede oxidarse también opcionalmente para dar el N-óxido, S-óxido o S,S-dióxido correspondiente. Los ejemplos de heterociclilo monocíclico incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,3-dioxolanilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo y tetrahidrotiopiranilo.

"Heterociclilarilo" significa un arilo y heterociclilo condensados. Un heterociclilarilo particular es aquel en el que su arilo es fenilo y el heterociclilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un heterociclilarilo se une a través de cualquier átomo del resto arilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heterociclilo del heterociclilarilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un heterociclilarilo puede ser un átomo de

nitrógeno básico. El átomo de nitrógeno o azufre de la porción heterociclilo del heterociclilarilo también puede oxidarse opcionalmente hasta el N-óxido, S-óxido o S,S-dióxido correspondiente. Los ejemplos de heterociclilarilo incluyen indolinilo, 1,2,3,4-tetrahidroisoquinolina, 1,2,3,4-tetrahidroquinolina, 1H-2,3-dihidroisoindol-2-ilo y 2,3-dihidrobenz[f]isoindol-2-ilo y 1,2,3,4-tetrahidrobenz[g]-isoquinolin-2-ilo.

"Heterociclilheteroarilo" significa un heteroarilo y heterociclilo condensados. Un heterociclilheteroarilo particular es aquel en el que su heteroarilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo y el heterociclilo se compone de aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un heterociclilheteroarilo se une a través de cualquier átomo del heteroarilo del mismo capaz de tal unión. La designación de aza, oxa o tio como prefijo antes de la porción heteroarilo o heterociclilo del heterociclilheteroarilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. El átomo de nitrógeno de un heterociclilheteroarilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre de la porción heteroarilo o heterociclilo del heterociclilheteroarilo también puede oxidarse opcionalmente hasta el N-óxido, S-óxido o S,S-dióxido correspondiente. Los ejemplos de heterociclilheteroarilo incluyen 2,3-dihidro-1H-pirrol[3,4-b]quinolin-2-ilo, 1,2,3,4-tetrahidrobenz[b][1,7]naftiridin-2-ilo, 1,2,3,4-tetrahidrobenz[b][1,6]naftiridin-2-ilo, 1,2,3,4-tetra-hidro-9H-pirido[3,4-b]indol-2-ilo, 1,2,3,4-tetrahidro-9H-pirido[4,3-b]indol-2-ilo, 2,3-dihidro-1H-pirrolo[3,4-b]indol-2-ilo, 1H-2,3,4,5-tetrahidroazepino[3,4-b]indol-2-ilo, 1H-2,3,4,5-tetra-hidroazepino[4,3-b]indol-3-ilo, 1H-2,3,4,5-tetrahidroazepino[4,5-b]indol-2-ilo, 5,6,7,8-tetra-hidro[1,7]naftiridilo, 1,2,3,4-tetrahidro[2,7]naftiridilo, 2,3-dihidro[1,4]dioxino[2,3-b]piridilo, 2,3-dihidro-[1,4]dioxino[2,3-b]piridilo, 3,4-dihidro-2H-1-oxa[4,6]diazanaftalenilo, 4,5,6,7-tetrahidro-3H-imidazo[4,5-c]piridilo, 6,7-dihidro[5,8]diazanaftalenilo, 1,2,3,4-tetrahidro[1,5]-naftiridinilo, 1,2,3,4-tetrahidro[1,6]naftiridinilo, 1,2,3,4-tetrahidro[1,7]naftiridinilo, 1,2,3,4-tetrahidro[1,8]naftiridinilo y 1,2,3,4-tetra-hidro[2,6]naftiridinilo.

"Alcarilo multicíclico" significa un sistema de anillos multicíclicos que incluye al menos un anillo aromático condensado con al menos un anillo no aromático que puede estar saturado o insaturado, y también puede contener en el sistema de anillos uno o más heteroátomos, tales como nitrógeno, oxígeno o azufre. Los ejemplos de alcarilo multicíclico incluyen arilcicloalquenilo, arilcicloalquilo, arilheterociclenilo, arilheterociclilo, cicloalquenilarilo, cicloalquilarilo, cicloalquenilheteroarilo, cicloalquilheteroarilo, heteroarilcicloalquenilo,

heteroarilcicloalquilo, heteroarilheterociclenilo, heteroarilheterociclilo, heterociclenilarilo, heterociclenilheteroarilo, heterociclilarilo y heterociclilheteroarilo. Los grupos alcarilo multicíclico particulares son anillos bicíclicos que incluyen un anillo aromático condensado con un anillo no aromático y que pueden contener también en el sistema de anillos uno o más heteroátomos, tales como nitrógeno, oxígeno o azufre.

El término "paciente" incluye seres humanos y otros mamíferos.

"Sales farmacéuticamente aceptables" se refiere a las sales de adición de ácidos orgánicos e inorgánicos y a las sales de adición de bases, no tóxicas, de los compuestos de la presente invención. Estas sales pueden prepararse *in situ* durante el aislamiento y purificación finales de los compuestos o haciendo reaccionar por separado el compuesto purificado en su forma de base libre con un ácido orgánico o inorgánico adecuado y aislando la sal formada de esta manera. En algunos casos, los propios compuestos pueden autoprotonar sitios básicos de la molécula y formar una sal anfótera interna.

Los ejemplos de sales de adición de ácidos incluyen las sales hidrobromuro, hidrocloruro, sulfato, bisulfato, fosfato, nitrato, acetato, oxalato, valerato, oleato, palmitato, estearato, laurato, borato, benzoato, lactato, fosfato, tosilato, citrato, maleato, fumarato, succinato, tartrato, naftilato, mesilato, glucoheptonato, lactiobionato, sulfamatos, malonatos, salicilatos, propionatos, metileno-bis-ß-hidroxinaftoatos, gentisatos, isetionatos, di-p-toluoiltartratos, metanosulfonatos, etanosulfonatos, bencenosulfonatos, p-toluenosulfonatos, ciclohexilsulfamatos y laurilsulfonato. Véase, por ejemplo, S.M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66, 1-19 (1977) que se incorpora en este documento como referencia. También pueden prepararse sales de adición de bases haciendo reaccionar por separado el compuesto purificado en su forma de ácido con una base orgánica o inorgánica adecuada y aislando la sal formada de esta manera. Las sales de adición de bases incluyen sales de metales y sales de aminas farmacéuticamente aceptables. Las sales de metales adecuadas incluyen las sales de sodio, potasio, calcio, bario, cinc, magnesio y aluminio. Una sal de adición de bases particular es la sal de sodio o la sal de potasio. Las sales de adición de bases inorgánicas adecuadas se preparan a partir de bases de metales que incluyen hidruro sódico, hidróxido sódico, hidróxido potásico, hidróxido de calcio, hidróxido de aluminio, hidróxido de litio, hidróxido de magnesio e hidróxido de cinc. Las sales de adición de bases de aminas adecuadas se preparan a partir de aminas que tienen suficiente basicidad para formar una sal estable y particularmente incluyen las aminas que se usan

frecuentemente en la química médica por su baja toxicidad y aceptabilidad para el uso médico. La amina ejemplar incluye amonio, etilendiamina, N-metil-glucamina, lisina, arginina, onitina, colina, N,N'-dibenciletilendiamina, cloroprocaína, dietanolamina, procaína, N-bencilfenetilamina, dietilamina, piperazina, tris(hidroximetil)-aminometano, hidróxido de tetrametilamonio, trietilamina, dibencilamina, efenamina, deshidroabietilamina, N-etilpiperidina, bencilamina, tetrametilamonio, tetraetilamonio, metilamina, dimetilamina, trimetilamina, etilamina, aminoácidos básicos, por ejemplo, lisina y arginina y diciclohexilamina.

"Solvato" se refiere a una asociación física de un compuesto de la presente invención con una o más moléculas de disolvente. Esta asociación física incluye un enlace de hidrógeno. En ciertos casos, el solvato podrá aislarse, por ejemplo cuando se incorporan una o más moléculas disolventes en la estructura cristalina del sólido cristalino. "Solvato" incluye tanto solvatos en fase de solución como solvatos insolubles. Los solvatos particulares incluyen hidratos, etanolatos y metanolatos.

"Sustituido una o más veces independientemente" significa sustituido una o más veces con los mismos o diferentes grupos de sustituyentes, particularmente sustituido una, dos o tres veces con los mismos o diferentes grupos de sustituyentes.

Realizaciones Particulares de la Invención

Una realización particular de la invención es un compuesto de fórmula (I) en la que R^1 es arilo o heteroarilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), haloalquilo (C_1-C_4) o haloalcoxi (C_1-C_4), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que R^1 es fenilo o heteroarilo de cinco o seis miembros, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo, alquilo (C_1-C_6), hidroxi o alcoxi (C_1-C_6), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que R^1 es fenilo, piridilo, pirimidinilo, tiazolilo u oxadiazolilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo, alquilo (C_1-C_6), hidroxi o alcoxi

(C_1-C_6), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que R^1 es fenilo, piridilo o pirimidinilo, cada uno de ellos opcionalmente sustituido independientemente en la posición orto o meta con halo, alquilo (C_1-C_6), hidroxi o alcoxi (C_1-C_6), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que R^1 es fenilo opcionalmente sustituido independientemente en la posición orto o meta con halo, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que R^1 es piridilo, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que R^2 es hidrógeno, metilo o trifluorometilo, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que R^2 es hidrógeno, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que R^2 es metilo, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que L^1 es un enlace, -O-, -C(=O)- o -NH-C(=O), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que L^1 es un enlace, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que:

R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman heterociclilo, heterociclenilo, arilheterociclilo o heteroarilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

R^6 es alcoxi, hidroxilo, cicloalquilo, carboxi, cicloalquilo, halo, ciano, alquilsulfonilo, Y^1Y^2N-, Y^1Y^2N-SO_2-,

alquilo opcionalmente sustituido una o más veces independientemente con aciloxi, hidroxi, alcoxicarbonilo, alcoxi, carboxi, arilo, halo, alquilsulfonilo, ciano, Y^1Y^2N- o Y^1Y^2N-C(=O)-,

acilo o arilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo,

alcoxicarbonilo opcionalmente sustituido una o más veces independientemente con arilo,

heteroaroílo opcionalmente sustituido una o más veces independientemente con alquilo,

heterociclilo opcionalmente sustituido una o más veces con oxo, o

ariloxi opcionalmente sustituido una o más veces independientemente con haloalquilo, y

cada uno de Y^1 e Y^2 es independientemente hidrógeno, alquilsulfonilo, aroílo o alquilo opcionalmente sustituido con morfolinilo o

Y^1 e Y^2 junto con el átomo de nitrógeno al que están unidos forman morfolinilo;

o un hidrato, solvato o N-óxido de los mismos, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que:

R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman [1,2,4]triazolilo, pirrolilo, indolilo, pirrolo[2,3-b]piridilo, pirrolo[3,2-b]piridilo o pirrolo[2,3-c]piridilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

R^6 es alcoxi, carboxi, cicloalquilo, halo, ciano, alquilsulfonilo, Y^1Y^2N-SO_2-,

alquilo opcionalmente sustituido una o más veces independientemente con aciloxi, hidroxi, alcoxicarbonilo, alcoxi, carboxi, arilo, halo, heterociclilo, alquilsulfonilo, ciano, heterociclilcarbonilo,

acilo o arilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo,

alcoxicarbonilo opcionalmente sustituido una o más veces independientemente con arilo,

heteroaroílo opcionalmente sustituido una o más veces independientemente con alquilo,

heterociclilo opcionalmente sustituido una o más veces con oxo, o

ariloxi opcionalmente sustituido una o más veces independientemente con haloalquilo, y

cada uno de Y^1 e Y^2 es independientemente hidrógeno o alquilo opcionalmente sustituido con morfolinilo o

Y^1 e Y^2 junto con el átomo de nitrógeno al que están unidos forman morfolinilo;

o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que:

R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman imidazolidinilo, [1,2,4]triazinanilo, piperazinilo, morfolinilo, pirrolidinilo, 1,2,3,4-tetrahidro-pirimidinilo, piperidinilo, oxazolidinilo, 2,3-dihidro-indolilo, octahidro-ciclopenta[c]pirrolilo o 3,4-dihidro-benzo[1,4]oxazina, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

R^6 es oxo, alcoxi, carboxi, cicloalquilo, halo, ciano, alquilsulfonilo, $Y^1Y^2N\text{-}SO_2\text{-}$,

alquilo opcionalmente sustituido una o más veces independientemente con hidroxi, alcoxicarbonilo, alcoxi, carboxi, arilo, halo, heterociclilo, alquilsulfonilo, ciano, heterociclilcarbonilo,

acilo o arilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo,

alcoxicarbonilo opcionalmente sustituido una o más veces independientemente con arilo,

heteroaroílo opcionalmente sustituido una o más veces independientemente con alquilo,

heterociclilo opcionalmente sustituido una o más veces con oxo, o

ariloxi opcionalmente sustituido una o más veces independientemente con haloalquilo, y

cada uno de Y^1 e Y^2 es independientemente hidrógeno o alquilo opcionalmente sustituido con morfolinilo o

Y^1 e Y^2 junto con el átomo de nitrógeno al que están unidos forman morfolinilo;

o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que:

R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman indolilo, opcionalmente sustituido una o más veces independientemente con R^6;

R^6 es $Y^1Y^2N\text{-}SO_2\text{-}$, alcoxicarbonilo, carboxialquilo, ciano, halo, alquilsulfonilo, alcoxi o acilo opcionalmente sustituido una o más veces independientemente con halo; y

cada uno de Y^1 e Y^2 es independientemente hidrógeno o alquilo opcionalmente sustituido con morfolinilo, o

Y^1 e Y^2 junto con el átomo de nitrógeno al que están unidos forman morfolinilo;

o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de fórmula (I) en la que:

R^5 es fenilo, piridilo o benzo[1,3]dioxolilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

R^6 es $Y^1Y^2N\text{-}SO_2\text{-}$, hidroxi, alcoxi, halo, alquilo o haloalquilo; y

cada uno de Y^1 e Y^2 es, independientemente, hidrógeno o alquilo;

o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Otra realización particular de la invención es un compuesto de Fórmula (I), que es

(5-fluoro-2-metil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico,

(5-fluoro-2-metil-indol-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico,

(5-fluoro-2-metil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,
(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
(5-fluoro-2-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico,
(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-fluoro-2-metil-indol-1-il)amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
(5-fluoro-2-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
[3-(2,2,2-trifluoro-acetil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico,
(2,3-dimetil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-cloro-2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-bromo-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
éster bencílico del ácido 3-oxo-4-[(2-fenil-pirimidina-5-carbonil)-amino]-piperazina-1-carboxílico,
(3-dimetilsulfamoil-5-fluoro-indol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,
(3-dimetilsulfamoil-5-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,
[5-fluoro-3-(morfolina-4-sulfonil)indol-1-il]amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,
[5-fluoro-3-(morfolina-4-sulfonil)indol-1-il]amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,
[5-fluoro-3-sulfamoilindol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,
[5-fluoro-3-metilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,
[5-fluoro-3-(2-morfolin-4-iletilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,

[5-fluoro-3-metilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,

{5-fluoro-[(3-tetrahidropiran-4-ilmetil)sulfamoil]indol-1-il}amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,

[5-fluoro-3-(2-morfolin-4-iletilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,

(4-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,

(4-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,

(4-fluoroindol-1-il)amida del ácido 2-(piridin-2-il)-pirimidina-5-carboxílico,

(4-fluoroindol-1-il)amida del ácido 2-(piridin-2-il)-4-metilpirimidina-5-carboxílico,

[6-(4-fluoro-fenil)-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

[5-fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

[5-fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[5-fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-ciano-5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[5-fluoro-3-(1H-tetrazol-5-il)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[1,2,4] triazol-4-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

piperidin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

N`-(2-fluoro-fenil)-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N`-etil-N`-tolil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

(3-oxo-morfolin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

morfolin-4-ilamida del ácido 2-(5-metil-[1,2,4]oxadiazol-3-il)-pirimidina-5-carboxílico,

morfolin-4-ilamida del ácido 2-benzoil-pirimidina-5-carboxílico,

[4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-benzoil-pirimidina-5-carboxílico.

N'-metil-N'-[5-trifluorometil-piridin-2-il]-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-metil-N'-[4-trifluorometil-piridin-2-il]-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-piridin-2-il-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-(2-cloro-fenil)-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-(2-oxo-piperidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-ciclohexil-N'-metil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-morfolin-4-il-amida del ácido 2-fenoxi-pirimidina-5-carboxílico,

(2,6-dimetil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(6-terc-butil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,

(6-terc-butil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

éster metílico del ácido 3-{2,4-dioxo-3-[(2-fenil-pirimidina-5-carbonil)-amino]-1,2,3,4-tetrahidro-pirimidin-5-il}-propiónico,

ácido 3-{2,4-dioxo-3-[(2-fenil-pirimidina-5-carbonil)-amino]-1,2,3,4-tetrahidro-pirimidin-5-il}-propiónico,

(4-metil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

morfolin-4-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

((S)-2-metoximetil)-pirrolidin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

((R)-2-metoximetil)-pirrolidin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(5-bromo-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(3-isopropil-5-oxo-1,5-dihidro-[1,2,4]triazol-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

pirrol-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

(5-morfolin-4-ilmetil-2-oxo-oxazolidin-3-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(4-ciclopentil-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(2-oxo-oxazolidin-3-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il]-amida del ácido 4-metil-2-fenil-pirimidina-5-carboxílico,

éster etílico del ácido [N'-(2-fenil-pirimidina-5-carbonil)-hidrazino]-acético,

2-[N'-(2-fenil-pirimidina-5-carbonil)-hidrazino]-acetamida,

4-[3-(4-morfolino)propil]-1-(2-fenil-pirimidina-5-carbonil)-3-tiosemicarbazida,

(2,3-dihidro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

éster metílico del ácido {4-[2-fenil-pirimidina-5-carbonil)-amino]-piperazin-1-il}-acético,

(4-cianometil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

2-{4-[(2-fenil-pirimidina-5-carbonil)-amino]-piperazin-1-il}-etil éster del ácido acético,

(4-acetil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(2-oxo-tetrahidro-furan-3-il)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(2,2,2-trifluoro-acetil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(2-metoxi-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(2-morfolin-4-il-2-oxo-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

piperidin-1-il-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

piperidin-1-il-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(hexahidro-ciclopenta[c]pirrol-2-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-fenil-pirimidina-5-carboxílico,

pirrolidin-1-il-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(2,6-dimetil-piperidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(4-ciclopentil-piperazin-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(2-metil-2,3-dihidro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(2-metil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

N`-metil-N`-piridin-2-il-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

(5-fluoro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(2,3-dihidro-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,

indol-1-il-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,

indol-1-il-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(2-metil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

indol-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
indol-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(5-metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
(6-metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
(5-metanosulfonil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,
(5-metanosulfonil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico,
(5-metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
pirrolo[2,3-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
pirrolo[3,2-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
(5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
(5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil-4-metil)-pirimidina-5-carboxílico,
pirrolo[3,2-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
pirrolo[2,3-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-fluoro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(5-fluoro-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,
pirrolo[2,3-b]piridina-1-ilamida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,
pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
pirrolo[3,2-b]piridin-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
pirrolo[2,3-c]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
pirrolo[3,2-b]piridin-1-ilamida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico,
(5-fluoro-indol-1-il)-amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico,
(5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-metoxi-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-ciano-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(4-ciano-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
[4-(1H-tetrazol-5-il)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
éster metílico del ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-4-carboxílico,
ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-4-carboxílico,
(3-cianometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-metoxi-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

[3-(1H-tetrazol-5-ilmetil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

2-(2-fenil-pirimidina-5-carbonil)-1-hidrazinacarboxamida,

2-(2-fenil-pirimidina-5-carbonil)-1-hidrazina-1-carbotioamida,

(2,4-dioxo-imidazolidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-fenil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-(2-fenil-pirimidina-5-carbonil)-hidrazida del ácido piridina-2-carboxílico,

4-[N'-(2-fenil-pirimidina-5-carbonil)-hidrazino]-bencenosulfonamida,

N'-(2-fenil-pirimidina-5-carbonil)-hidrazida del ácido 3-hidroxi-benzoico,

N'-(fenil-pirimidina-5-carbonil)-hidrazida del ácido benzo[1,3]dioxo-5-carboxílico,

N'-(fenil-pirimidina-5-carbonil)-hidrazida del ácido 3,4-dimetoxi-benzoico,

N'-metil-N'-fenil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

(5-metoxi-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(2-metoxi-fenil)-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(4-metoxi-fenil)-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-hidroxi-fenil)-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(2-hidroxi-fenil)-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(4-hidroxi-fenil)-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-tiazol-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido [2,2']bipirimidinil-5-carboxílico,

(3-cloro-5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

amida del ácido 5-fluoro-1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indolo-3-carboxílico,

ácido 2-{5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indol-3-il}-2-metil-propiónico,

ácido 2-(5-fluoro-1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-3-il)-2-metil-propiónico,

[5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

[5-fluoro-3-(2-piridin-3-il-etil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-3-formil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

ácido 5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indolo-3-carboxílico,

(5-fluoro-3-hidroximetil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

[5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(6-trifluorometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(6-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(6-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(6-trifluorometil-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(5-metoxi-2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

N',N'-difenil-hidrazida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(7-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-metanosulfonil-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-etil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-pirrolo[2,3-c] piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-metil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-nitro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-amino-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[5-(dimetanosulfonil)-amino-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-benzoilamino-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[5-fluoro-3-(1,2,3,6-tetrahidro-piridin-4-il)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-2-il-4-trifluorometil-pirimidina-5-carboxílico,

(2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(6-fluoro-2,3-dihidro-1,4-benzoxazin-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(6-fluoro-2,3-dihidro-1,4-benzoxazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(3-etil-5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-etil-5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(2-ciclopropil-5-fluoro-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(2-ciclopropil-5-fluoro-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(5-metoxil-indol-1-il)-amida del ácido 2-pirimidin-2-il-4-metil-pirimidina-5-carboxílico,
(5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,
(5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-metoxi-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(5-metoxi-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-(1-oxi-piridin-2-il)-pirimidin-5-carboxílico,
(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-difluorometil-fenil)-pirimidina-5-carboxílico, o
(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-trifluorometil-fenil)-pirimidina-5-carboxílico,
o un hidrato, solvato o N-óxido de los mismos, o una sal farmacéuticamente aceptable de los mismos.

Otra realización particular de la invención es un compuesto de fórmula (I), que es:
(4-bencil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,
piperazin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,
(4-metanosulfonil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,
morfolin-4-ilamida del ácido 2-(2-metil-tiazol-4-il)-pirimidina-5-carboxílico,
[4-(1-metil-1H-imidazol-2-carbonil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,
[4-(1-metil-1H-imidazol-4-carbonil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,
éster terc-butílico del ácido 4-[(2-fenil-pirimidina-5-carbonil)-amino]-piperazina-1-carboxílico,
[4-(4-trifluorometil-fenoxi)-piperidin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,
[4-(4-trifluorometil-fenoxi)-piperidin-1-il]-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
morfolin-4-ilamida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

indol-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

(4-metoxi-piperidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(6-fluoro-2,3-dihidro-benzo[1,4]oxazin-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(6-fluoro-2,3-dihidro-benzo[1,4]oxazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

éster metílico del ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-3-(2-morfolin-4-il-etil)-1H-indolo-6-carboxílico,

[5-fluoro-3-(tetrahidro-piran-4-il)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

N-metil-N-(5-fluoro)-indol-3-ilsulfonil-N`-[2-(3-fluoro)-fenil-pirimidina-5-carbonil]-hidrazida,

[5-fluoro-3-(tetrahidro-piran-4-il)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-(1-oxi)-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[3,2-c]piridin-1-ilamida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[3,2-c]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[3,2-c]piridin-1-ilamida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(4-metil-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(2-metil-3-oxo-2,3-dihidro-indazol-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-indol-1-il)amida)amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

6-(4-cloro-tiazol-2-il)-2-metil-N-pirrolo[2,3-c]piridin-1-il-nicotinamida,

(5-metil-4-oxo-4,5-dihidro-pirrolo[3,2-c]piridin-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(3-difluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(3-difluorometil-indol-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico, o
(3-difluorometil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,
o un hidrato, solvato o N-óxido de los mismos, o una sal farmacéuticamente aceptable de los mismos.

Se debe entender que esta invención cubre todas las combinaciones apropiadas de las realizaciones particulares indicadas en este documento.

La presente invención también incluye dentro de su alcance una composición farmacéutica que comprende una cantidad farmacéuticamente eficaz de un compuesto de la invención en mezcla con un vehículo farmacéuticamente aceptable.

Los compuestos de la presente invención son inhibidores de PGDS y, por lo tanto, son útiles para tratar trastornos alérgicos y/o inflamatorios, particularmente trastornos tales como rinitis alérgica, asma y/o enfermedad pulmonar obstructiva crónica (COPD). Por consiguiente, otra invención de este documento se refiere a un método para tratar a un paciente que padece rinitis alérgica, asma y/o enfermedad pulmonar obstructiva crónica (COPD) que comprende administrar al paciente una cantidad farmacéuticamente eficaz de compuesto de fórmula (I), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

Debe apreciarse que las referencias de este documento dirigidas al tratamiento incluyen terapia profiláctica para inhibir PGDS, así como para tratar afecciones agudas, crónicas o fisiológicas establecidas asociadas con PGDS para curar esencialmente a un paciente que las padece, o mejorar las afecciones fisiológicas asociadas con ellas. Las condiciones fisiológicas descritas en este documento incluyen algunas, pero no todas, las posibles

situaciones clínicas en las que se justifica un tratamiento contra la rinitis alérgica y/o el asma. Los especialistas en este campo conocen bien las circunstancias que requieren tratamiento.

En la práctica, el compuesto de la presente invención se puede administrar en una forma de dosificación farmacéutica farmacéuticamente aceptable para seres humanos y otros mamíferos por administración tópica o sistémica, que incluye administración oral, por inhalación, rectal, nasal; bucal, sublingual, vaginal, colónica, parenteral (incluyendo subcutánea, intramuscular, intravenosa, intradérmica, intratecal y epidural), intracisternal e intraperitoneal. Se apreciará que la ruta particular puede variar, por ejemplo, con el estado fisiológico del destinatario.

"Formas de dosificación farmacéuticamente aceptables" se refiere a formas de dosificación del compuesto de la invención e incluye, por ejemplo, comprimidos, grageas, polvos, elixires, jarabes, preparaciones líquidas, incluyendo suspensiones, pulverizaciones, inhalantes, comprimidos, pastillas, emulsiones, soluciones, gránulos, cápsulas y supositorios, así como preparaciones líquidas para inyecciones, incluyendo preparaciones de liposomas. Las técnicas y formulaciones pueden encontrarse, en general, en Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, última edición.

Un aspecto particular de la invención proporciona el compuesto de la invención para ser administrado en forma de una composición farmacéutica.

Los vehículos farmacéuticamente aceptables incluyen al menos un componente seleccionado entre el grupo que consiste en soportes, diluyentes, recubrimientos, adyuvantes, excipientes o vehículos farmacéuticamente aceptables, tales como agentes conservantes, cargas, agentes disgregantes, agentes humectantes, agentes emulsionantes, agentes para estabilizar la emulsión, agentes de suspensión, agentes isotónicos, agentes edulcorantes, agentes aromatizantes, agentes de perfume, agentes colorantes, agentes antibacterianos, agentes antifúngicos, otros agentes terapéuticos, agentes lubricantes, agentes para retrasar o promover la adsorción y agentes de administración, dependiendo de la naturaleza del modo de administración y de las formas de dosificación.

Los ejemplos de agentes de suspensión incluyen alcoholes isoestearílicos etoxilados, ésteres de polioxietileno sorbitol y sorbitán, celulosa microcristalina, metahidróxido de aluminio, bentonita, agar-agar y tragacanto, o mezclas de estas sustancias.

Los ejemplos de agentes antibacterianos y antifúngicos para la prevención de la acción de microorganismos incluyen parabenos, clorobutanol, fenol, ácido sórbico y similares.

Los agentes isotónicos ejemplares incluyen azúcares, cloruro sódico y similares.

Los ejemplos de agentes que retrasan la adsorción para prolongar la absorción incluyen monoestearato de aluminio y gelatina.

Los ejemplos de agentes que promueven la adsorción para mejorar la absorción incluyen dimetilsulfóxido y análogos relacionados.

Los ejemplos de diluyentes, disolventes, vehículos, agentes solubilizantes, emulsionantes y estabilizadores de emulsión incluyen agua, cloroformo, sacarosa, etanol, alcohol isopropílico, carbonato de etilo, acetato de etilo, alcohol bencílico, alcohol tetrahidrofurfurílico, benzoato de bencilo, polioles, propilenglicol, 1,3-butilenglicol, glicerol, polietilenglicoles, dimetilformamida, Tween® 60, Span® 60, alcohol cetoestearílico, alcohol miristílico, mono-estearato de glicerilo y lauril sulfato sódico, ésteres de ácidos grasos de sorbitán, aceites vegetales (tales como aceite de semilla de algodón, aceite de cacahuete, aceite de oliva, aceite de ricino y aceite de sésamo) y ésteres orgánicos inyectables tales como oleato de etilo, y similares, o mezclas adecuadas de estas sustancias.

Los ejemplos de excipientes incluyen lactosa, azúcar de leche, citrato sódico, carbonato cálcico y fosfato dicálcico.

Los ejemplos de agentes disgregantes incluyen almidón, ácidos algínicos y ciertos silicatos complejos.

Los ejemplos de lubricantes incluyen estearato de magnesio, laurilsulfato sódico, talco, así como polietilenglicoles de alto peso molecular.

En general, la elección del vehículo farmacéutico aceptable se determina de acuerdo con las propiedades químicas del compuesto activo tales como solubilidad, el modo particular de administración y las condiciones a tener en cuenta en la práctica farmacéutica.

Las composiciones farmacéuticas de la presente invención adecuadas para administración oral pueden presentarse como unidades discretas tales como una forma de dosificación sólida, tal como cápsulas, obleas o comprimidos que contienen, cada una, una cantidad predeterminada del ingrediente activo o como un polvo o granulado; como una forma de dosificación líquida tal como una solución o una suspensión en un líquido acuoso o un líquido no acuoso, o como una emulsión líquida de agua en aceite o de aceite en agua. El ingrediente activo también puede presentarse como una inyección en embolada, electuario o pasta.

"Forma de dosificación sólida" significa que la forma de dosificación del compuesto de la invención es una forma sólida, por ejemplo, cápsulas, comprimidos, píldoras, polvos, grageas o gránulos. En tales formas de dosificación sólidas, el compuesto de la invención se mezcla, por lo menos, con un excipiente (o vehículo) inerte habitual tal como citrato sódico o fosfato dicálcico o: (a) materiales de carga o diluyentes, como por ejemplo, almidones, lactosa, sacarosa, glucosa, manitol y ácido silícico, (b) aglutinantes, como por ejemplo, carboximetilcelulosa, alginatos, gelatina, polivinilpirrolidona, sacarosa y goma arábiga, (c) humectantes, como por ejemplo, glicerol, (d) agentes disgregantes, como por ejemplo, agar-agar, carbonato cálcico, almidón de patata o tapioca, ácido algínico, ciertos silicatos complejos y carbonato sódico, (e) retardantes de disolución, como por ejemplo la parafina, (f) aceleradores de absorción, como por ejemplo, compuestos de amonio cuaternario, (g) agentes humectantes, como por ejemplo, alcohol cetílico y monoestearato de glicerol, (h) adsorbentes, como por ejemplo caolín y bentonita, (i) lubricantes, como por ejemplo, talco, estearato de calcio, estearato de magnesio, polietilenglicoles sólidos, lauril sulfato sódico, (j) agentes opacificantes, (k) agentes de tamponamiento, y agentes que liberan el compuesto de la invención en una cierta parte del tracto intestinal de una manera retardada.

Un comprimido puede prepararse por compresión o por moldeo, opcionalmente con uno o más ingredientes auxiliares. Los comprimidos de compresión se pueden preparar comprimiendo en una máquina adecuada el principio activo en una forma que fluye libremente tal como un polvo o gránulos, opcionalmente mezclado con un aglutinante, lubricante, diluyente inerte, conservante, agente tensioactivo o agente dispersante. Pueden usarse excipientes tales como lactosa, citrato sódico, carbonato cálcico, fosfato dicálcico y agentes disgregantes tales como almidón, ácidos algínicos y ciertos silicatos complejos combinados con lubricantes tales como estearato de magnesio, laurilsulfato sódico y talco. Los comprimidos de moldeo se pueden obtener moldeando en una máquina adecuada una

mezcla de los compuestos en polvo humedecidos con un diluyente líquido inerte. Los comprimidos opcionalmente pueden recubrirse o ranurarse para proporcionar una liberación lenta o controlada del ingrediente activo presente en su interior.

Las composiciones sólidas también pueden emplearse como cargas en cápsulas de gelatina rellenas blandas y duras usando excipientes tales como lactosa o azúcar de leche, así como polietilenglicoles de alto peso molecular y similares.

Si se desea, y para una distribución más eficaz, el compuesto se puede microencapsular en, o se puede unir a, sistemas de liberación lenta o de administración dirigida tales como matrices poliméricas biocompatibles y biodegradables (por ejemplo, poli(d,l-lactida co-glicolida)), liposomas, y microesferas y se puede inyectar por vía subcutánea o intramuscular mediante una técnica llamada depósito subcutáneo o intramuscular para proporcionar una liberación lenta continua del compuesto o compuestos durante un periodo de 2 semanas o más largo. Los compuestos pueden esterilizarse, por ejemplo, por filtración a través de un filtro de retención de bacterias o por medio de la incorporación de agentes de esterilización en forma de composiciones sólidas estériles que pueden disolverse en agua estéril o algún otro medio inyectable estéril inmediatamente antes del uso.

"Forma de dosificación líquida" significa que la dosis de un compuesto activo que se va a administrar al paciente está en forma líquida, por ejemplo, emulsiones, soluciones, suspensiones, jarabes y elixires farmacéuticamente aceptables. Además del compuesto activo, las formas de dosificación líquidas pueden contener diluyentes inertes comúnmente utilizados en la técnica, tales como disolventes, agentes solubilizantes y emulsionantes.

Cuando se usan suspensiones acuosas, éstas pueden contener agentes emulsionantes o agentes que facilitan la suspensión.

Las composiciones farmacéuticas adecuadas para administración tópica se refieren a formulaciones que están en una forma adecuada para administrarse a un paciente por vía tópica. La formulación puede presentarse como una pomada tópica, ungüento, polvos, pulverizaciones e inhalantes, geles (basados en agua o en alcohol), cremas, como se conoce generalmente en la técnica, o incorporarse en una base de matriz para aplicarse en un parche, que permitiría la liberación controlada del compuesto a través de la barrera transdérmica. Cuando se formulan en una pomada, los ingredientes activos pueden emplearse con una base

parafínica o con una base de pomada miscible en agua. Como alternativa, los ingredientes activos pueden formularse en una crema con una base de crema de aceite en agua. Las formulaciones adecuadas para administración tópica en el ojo incluyen gotas oftálmicas en las que el ingrediente activo está disuelto o suspendido en un vehículo adecuado, especialmente un disolvente acuoso para el ingrediente activo. Las formulaciones adecuadas para la administración tópica en la boca incluyen comprimidos para chupar que comprenden el ingrediente activo en una base aromatizada, normalmente sacarosa y goma arábiga o tragacanto; pastillas que comprenden el ingrediente activo en una base inerte tal como gelatina y glicerina, o sacarosa y goma arábiga; y enjuagues bucales que comprenden el ingrediente activo en un vehículo líquido adecuado.

La fase oleosa de la composición farmacéutica en emulsión se puede constituir a partir de ingredientes conocidos, de una manera conocida. Aunque la fase puede comprender simplemente un emulsionante (conocido de otra manera como un emulgente), deseablemente comprende una mezcla de al menos un emulsionante con una grasa o un aceite o con una grasa y un aceite. En una realización particular, se incluye un emulsionante hidrófilo junto con un emulsionante lipófilo que actúa como estabilizante. Juntos, el emulsionante o emulsionantes con, o sin, el estabilizante o estabilizantes constituyen la cera emulsionante, y junto con el aceite y la grasa constituyen la base de pomada emulsionante que forma la fase oleosa dispersa de las formulaciones en crema.

Si se desea, la fase acuosa de la base de crema puede incluir, por ejemplo, por lo menos 30% p/p de un alcohol polihidroxílico, es decir un alcohol que tiene dos o más grupos hidroxilo tal como, propilenglicol, butano-1,3-diol, manitol, sorbitol, glicerol y polietilenglicol (incluyendo PEG 400) y sus mezclas. Las formulaciones tópicas pueden incluir deseablemente un compuesto que potencie la absorción, o penetración del principio activo a través de la piel, o de otras áreas afectadas.

La elección de aceites o grasas adecuadas para una composición se basa en la obtención de las propiedades deseadas. Así una crema debe ser especialmente un producto no graso, que no manche y lavable con consistencia adecuada para evitar fugas de los tubos u otros recipientes. Pueden usarse ésteres de alquilo mono- o dibásicos de cadena lineal o ramificada tales como miristato de diisopropilo, oleato de decilo, palmitato de isopropilo, estearato de butilo, palmitato de 2-etilhexilo o una mezcla de ésteres de cadena ramificada conocida como Crodamol CAP. Éstos pueden usarse solos o en combinación dependiendo de las

propiedades requeridas. Como alternativa, pueden usarse lípidos de alto punto de fusión tales como parafina blanda blanca y/o parafina líquida u otros aceites minerales.

Las composiciones farmacéuticas adecuadas para administraciones rectal o vaginal implican formulaciones que están en una forma adecuada para administrarse por vía rectal o vaginal a un paciente y que contienen por lo menos un compuesto de la invención. Los supositorios son una forma particular para tales formulaciones que pueden prepararse mezclando los compuestos de esta invención con excipientes o vehículos no irritantes adecuados tales como manteca de cacao, polietilenglicol o una cera de supositorios, que son sólidos a las temperaturas habituales pero líquidos a la temperatura corporal y, por lo tanto, se funden en el recto o en la cavidad vaginal y liberan el componente activo.

Las composiciones farmacéuticas administradas por inyección pueden administrarse por inyección transmuscular, intravenosa, intraperitoneal y/o subcutánea. Las composiciones de la presente invención se formulan en soluciones líquidas, en particular en tampones fisiológicamente compatibles tales como solución de Hank o solución de Ringer. Además, las composiciones pueden formularse en forma sólida y redisolverse o suspenderse inmediatamente antes del uso. También se incluyen las formas liofilizadas. Las formulaciones son estériles e emulsiones, suspensiones o soluciones de inyección acuosas o no acuosas, que pueden contener agentes de suspensión y agentes espesantes y antioxidantes, tampones, bacteriostáticos y solutos que hacen que las formulaciones sean isotónicas y tengan un pH ajustado convenientemente, con la sangre del receptor deseado.

Una composición farmacéutica de la presente invención adecuada para administración nasal o por inhalación se refiere a composiciones que están en una forma adecuada para administrarse por vía nasal o por inhalación a un paciente. La composición puede contener un vehículo, en forma de polvo, que tenga un tamaño de partículas, por ejemplo, en el intervalo de 1 a 500 micrómetros (incluyendo tamaños de partículas en un intervalo comprendido entre 20 y 500 micrómetros en incrementos de 5 micrómetros tales como 30 micrómetros, 35 micrómetros, etc.). Las composiciones adecuadas en las que el vehículo es un líquido, para administración, por ejemplo, como una pulverización nasal o como gotas nasales, incluyen soluciones acuosas u oleosas del ingrediente activo. Las composiciones adecuadas para la administración en aerosol pueden prepararse de acuerdo con métodos convencionales, y pueden administrarse con otros agentes terapéuticos. La terapia por inhalación se administra fácilmente mediante inhaladores dosificadores o cualquier inhalador

de polvo seco adecuado, tal como el Eclipse, Spinhaler®, o Ultrahaler® según se describe en la solicitud de patente WO2004/026380, y en la patente de Estados Unidos N° 5.176.132.

Los niveles de dosificación reales del(de los) ingrediente(s) activo(s) en las composiciones de la invención pueden variarse para obtener una cantidad del(de los) ingrediente(s) activo(s) que sea(n) eficaz(eficaces) para obtener una respuesta terapéutica deseada para una composición concreta y un método de administración al paciente. Un nivel de dosificación seleccionado para cualquier paciente concreto, por lo tanto, depende de una diversidad de factores, incluyendo el efecto terapéutico deseado, la vía de administración, la duración deseada del tratamiento, la etiología y gravedad de la enfermedad, el estado, peso, sexo, dieta y edad del paciente, el tipo y potencia de cada ingrediente activo, las velocidades de absorción, metabolismo y/o excreción y otros factores.

La dosis diaria total del compuesto de esta invención administrada a un paciente en una sola dosis o en dosis divididas puede ser en cantidades, por ejemplo, desde aproximadamente 0,001 a aproximadamente 100 mg/kg de peso corporal al día y particularmente de 0,01 a 10 mg/kg/día. Por ejemplo, en un adulto, las dosis son generalmente desde aproximadamente 0,01 a aproximadamente 100, particularmente de aproximadamente 0,01 a aproximadamente 10 mg/kg de peso corporal por día mediante inhalación, de aproximadamente 0,01 a aproximadamente 100, particularmente de 0,1 a 70, más especialmente de 0,5 a 10 mg/kg de peso corporal por día mediante administración oral, y de aproximadamente 0,01 a aproximadamente 50, particularmente de 0,01 a 10 mg/kg de peso corporal por día mediante administración intravenosa. El porcentaje de ingrediente activo en una composición puede variarse, aunque debería constituir una proporción de modo que se obtenga una dosificación adecuada. Las composiciones de dosificación unitaria pueden contener tales cantidades o tales submúltiplos de las mismas como puedan usarse para constituir la dosis diaria. Obviamente, pueden administrarse varias formas de dosificación unitaria aproximadamente al mismo tiempo. Una dosis puede administrarse con tanta frecuencia como sea necesario para obtener el efecto terapéutico deseado. Algunos pacientes pueden responder rápidamente a una dosis más alta o más baja y pueden encontrar adecuadas dosis de mantenimiento mucho más bajas. Para otros pacientes, puede ser necesario proporcionar tratamientos a largo plazo en la proporción de 1 a 4 dosis al día, de acuerdo con los requisitos fisiológicos de cada paciente en particular. Se entiende que, para otros pacientes, será necesario prescribir no más de una o dos dosis diarias.

Las formulaciones pueden prepararse en forma de dosificación unitaria mediante cualquier método conocido en la técnica farmacéutica. Tales métodos incluyen la etapa de asociar el principio farmacéuticamente activo con el vehículo que constituye uno o más de los ingredientes accesorios. En general, las formulaciones se preparan asociando de manera uniforme e íntima el ingrediente activo con vehículos líquidos o vehículos sólidos finamente divididos, o ambos, y después, si es necesario, dando forma al producto.

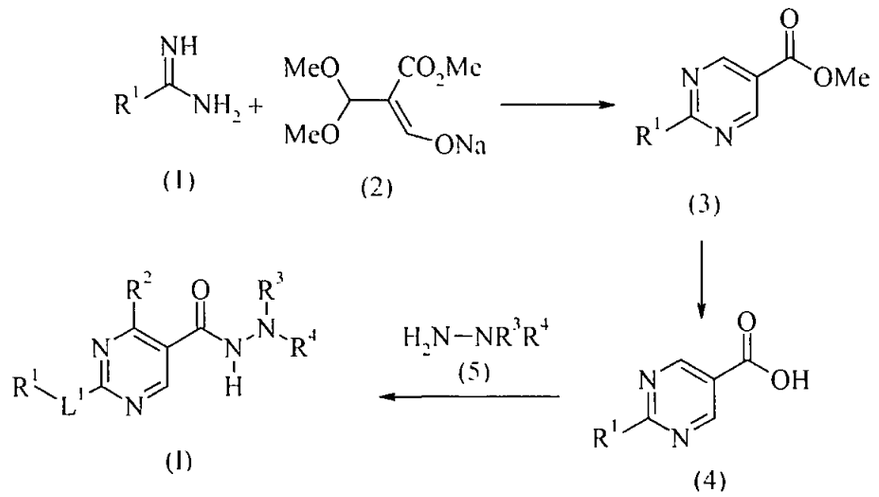
Las formulaciones pueden presentarse en recipientes de una sola dosis o de múltiples dosis, por ejemplo, ampollas y viales sellados con tapones elastoméricos, y pueden conservarse en un estado secado por congelación (liofilizado) que sólo requiere la adición del vehículo líquido estéril, por ejemplo, agua para inyección, inmediatamente antes del uso. Las soluciones y suspensiones para inyección improvisada pueden prepararse a partir de polvos estériles, gránulos y comprimidos del tipo descrito previamente.

Los compuestos de la invención pueden prepararse mediante la aplicación o adaptación de métodos conocidos, y esto significa los métodos usados hasta la fecha o descritos en la bibliografía, por ejemplo, los descritos por R.C. Larock en Comprehensive Organic Transformations, VCH publishers, 1989.

En las reacciones descritas más adelante puede ser necesario proteger los grupos funcionales reactivos, por ejemplo grupos hidroxi, amino, imino, tio o carboxi, cuando se desea que estén en el producto final, para evitar su participación indeseada en las reacciones. Los grupos protectores convencionales pueden usarse según la práctica convencional, véase por ejemplo T.W. Greene y P.G.M. Wuts, *Protecting Groups in Organic Synthesis*, 3ª edition, John Wiley & Sons, Inc., 1999.

Un compuesto de fórmula (I), en la que R^2 es hidrógeno, L^1 es un enlace, –NH-C(=O)- o alquileno (C_1-C_2) opcionalmente sustituido una o más veces con halo, y R^1, R^3 y R^4 son como se han definido en este documento, puede prepararse, como se muestra en el Esquema I a continuación, (i) haciendo reaccionar un compuesto de amidina correspondiente de fórmula (1), con un reactivo de fórmula (2) para proporcionar un compuesto de fórmula (3), (ii) hidrolizando el compuesto de fórmula (3) para proporcionar un compuesto de fórmula (4), y (iii) acoplando el compuesto de (4) con un compuesto correspondiente de fórmula (5).

Esquema I



R^2 = hidrógeno, $\mathcal{F}$

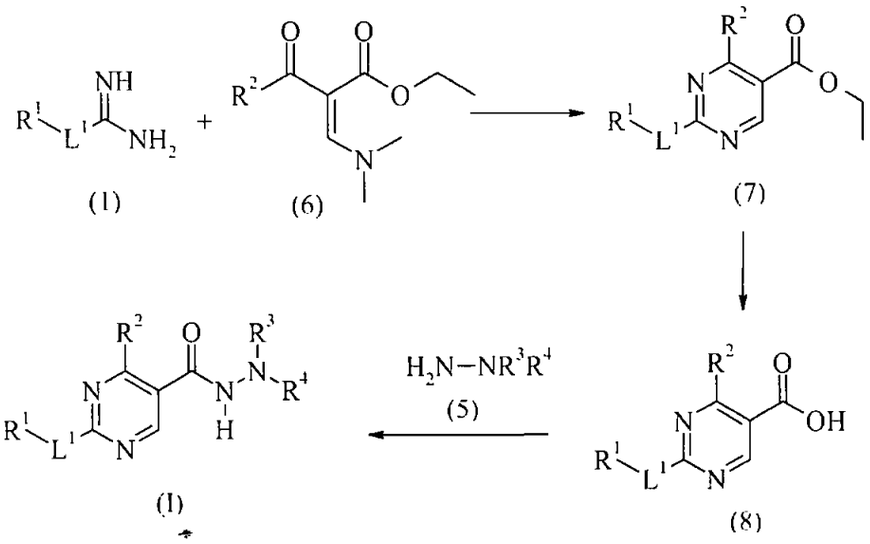
L^1 es un enlace, -NH-C(=O)- o alquileno (C_1-C_2) opcionalmente sustituido una o más veces con halo

La reacción de la primera etapa puede realizarse convenientemente, por ejemplo, a una temperatura de aproximadamente 100°C, en un disolvente inerte, tal como DMF. La reacción de la segunda etapa puede realizarse convenientemente, por ejemplo, a temperatura ambiente, en presencia de una base inorgánica, tal como LiOH, KOH o NaOH, en un disolvente, tal como THF, MeOH, agua o una mezcla de los mismos. La reacción de la tercera etapa puede realizarse convenientemente, por ejemplo, de aproximadamente la temperatura ambiente a 100°C, en presencia de un agente de acoplamiento, tal como HCTU, HOTT, PyBrOP, DMTMM, o HATU con HOAt, y una base, tal como DIPEA o Et_3N, en un disolvente inerte, tal como DMF. La reacción de la tercera etapa puede realizarse convenientemente, por ejemplo, aproximadamente a una temperatura de aproximadamente 0°C a la temperatura ambiente, haciendo reaccionar primero el compuesto de fórmula (4) con cloruro de oxalilo, y después añadiendo el compuesto de fórmula (5) y una base tal como DIPEA, Et_3N, K_2CO_3 o Na_2CO_3, en un disolvente inerte, tal como DCM o DMF.

Un compuesto de fórmula (I), en la que R^2 es alquilo (C_1-C_4) opcionalmente sustituido una o más veces con halo, L^1 es un enlace, –NH-C(=O)- o alquileno (C_1-C_2) opcionalmente sustituido una o más veces con halo, y R^1, R^3 y R^4 son como se han definido en este documento, también puede prepararse, como se muestra en el Esquema II a continuación, (i) haciendo reaccionar un compuesto de amidina correspondiente de fórmula (1), con un

reactivo de fórmula (6) para proporcionar un compuesto de fórmula (7), (ii) hidrolizando el compuesto de fórmula (7) para proporcionar un compuesto de fórmula (8), y (iii) acoplando el compuesto de fórmula (8) con un compuesto correspondiente de fórmula (5).

Esquema II



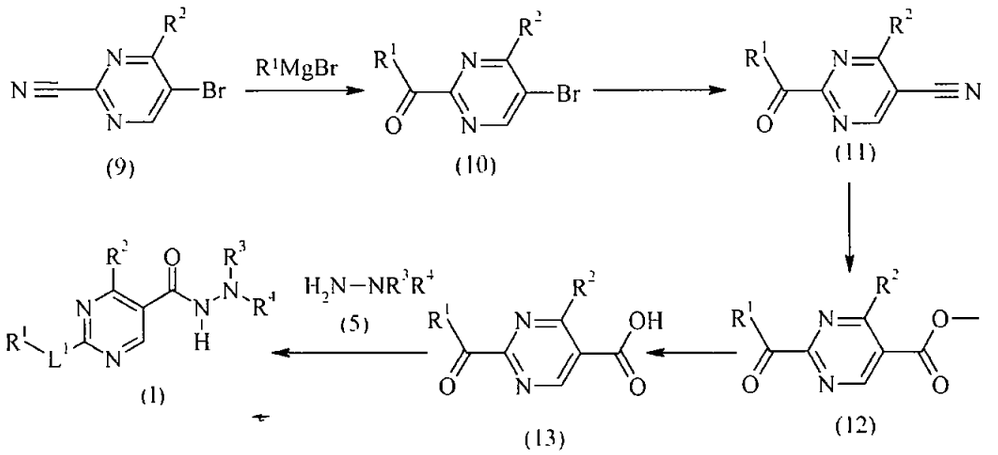
R^2 = alquilo (C_1-C_4) opcionalmente sustituido una o más veces con halo, y

L^1 es un enlace, -NH-C(=O)- o alquileno (C_1-C_2) opcionalmente sustituido una o más veces con halo

La reacción de la primera etapa puede realizarse convenientemente, por ejemplo, a una temperatura de aproximadamente 100°C, en presencia de metal sodio, en un disolvente, tal como EtOH. La reacción de la segunda etapa puede realizarse convenientemente, por ejemplo, a temperatura ambiente, en presencia de una base inorgánica, tal como LiOH, KOH o NaOH, en un disolvente, tal como THF, MeOH, agua o una mezcla de los mismos. La reacción de la tercera etapa puede realizarse convenientemente, por ejemplo, de aproximadamente la temperatura ambiente a 100°C, en presencia de un agente de acoplamiento, tal como HCTU, HOTT, PyBrOP, DMTMM, o HATU con HOAt, y una base, tal como DIPEA o Et_3N, en un disolvente inerte, tal como DMF. La reacción de la tercera etapa puede realizarse convenientemente, por ejemplo, aproximadamente a una temperatura de aproximadamente 0°C a la temperatura ambiente, haciendo reaccionar primero el compuesto de fórmula (8) con cloruro de oxalilo, y después añadiendo el compuesto de fórmula (5) y una base tal como DIPEA, Et_3N, K_2CO_3 o Na_2CO_3, en un disolvente inerte, tal como DCM o DMF.

Un compuesto de fórmula (I), en la que L^1 es -C(=O)-, y R^1, R^2, R^3 y R^4 son como se han definido en este documento, puede prepararse, como se muestra en el Esquema III a continuación, (1) haciendo reaccionar un compuesto correspondiente de fórmula (9), con un reactivo de Grignard de fórmula R^1MgBr para proporcionar un compuesto de fórmula (10), (2) convirtiendo the compuesto de fórmula (10) en un compuesto de fórmula (11), y (3) hidrolizando el compuesto de fórmula (11) para proporcionar un compuesto de fórmula (12), (4) hidrolizando el compuesto de fórmula (12) para proporcionar un compuesto de fórmula (13) y (5) acoplando el compuesto de fórmula (13) con un compuesto correspondiente de fórmula (5).

Esquema III



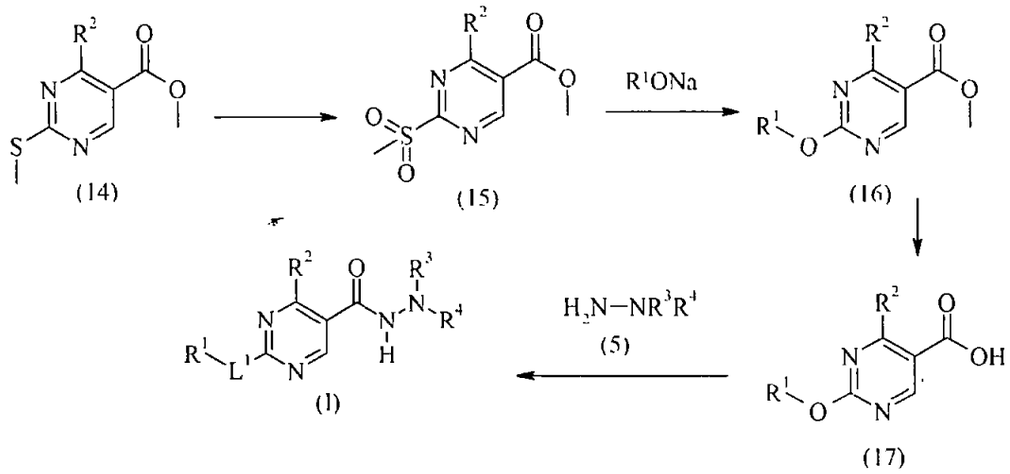
L^1 es -C(=O)-

La reacción de la primera etapa puede realizarse convenientemente, por ejemplo, a una temperatura de aproximadamente la temperatura ambiente a 50°C, en un disolvente inerte, tal como Et_2O. La reacción de la segunda etapa puede realizarse convenientemente, por ejemplo, a una temperatura de aproximadamente 150°C, en presencia de hexacianoferrato potásico (II) trihidrato, acetato de paladio (II) y una base, tal como Na_2CO_3 o K_2CO_3, en un disolvente inerte, tal como dimetilacetamida o DMF. La reacción de la tercera etapa puede realizarse convenientemente, por ejemplo, aproximadamente a una temperatura de aproximadamente 0°C a la temperatura ambiente, en presencia de una base inorgánica, tal como KOH, NaOH o LiOH, en un disolvente, tal como MeOH, o una mezcla de MeOH y agua. La reacción de la cuarta etapa puede realizarse convenientemente, por ejemplo, a temperatura ambiente, en presencia de una base inorgánica, tal como LiOH, KOH o NaOH,

en un disolvente, tal como THF, MeOH, agua o una mezcla de los mismos. La reacción de la quinta etapa puede realizarse convenientemente, por ejemplo, de aproximadamente la temperatura ambiente a 100°C, en presencia de un agente de acoplamiento, tal como HCTU, HOTT, PyBrOP, DMTMM, o HATU con HOAt, y una base, tal como DIPEA o Et_3N, en un disolvente inerte, tal como DMF. La reacción de la tercera etapa puede realizarse convenientemente, por ejemplo, aproximadamente a una temperatura de aproximadamente 0°C a la temperatura ambiente, haciendo reaccionar primero el compuesto de fórmula (4) con cloruro de oxalilo, y después añadiendo el compuesto de fórmula (5) y una base tal como DIPEA, Et_3N, K_2CO_3 o Na_2CO_3, en un disolvente inerte, tal como DCM o DMF.

Un compuesto de fórmula (I), en la que L^1 es -O-, y R^1, R^2, R^3 y R^4 son como se han definido en este documento, puede prepararse, como se muestra en el Esquema IV a continuación, (i) oxidando un compuesto de fórmula (14) para proporcionar un compuesto de fórmula (15), (ii) haciendo reaccionar el compuesto de fórmula (15) con un compuesto correspondiente que tiene la fórmula R^1ONa para proporcionar un compuesto de fórmula (16), (iii) hidrolizando el compuesto de fórmula (16) para proporcionar un compuesto de fórmula (17), y (iv) acoplando el compuesto de fórmula (17) con un compuesto correspondiente de fórmula (5).

Esquema IV



L^1 es -O-

La reacción de oxidación de la primera etapa puede realizarse convenientemente, por ejemplo, a temperatura ambiente, en presencia de MCPBA y $Na_2S_2O_3$, en un disolvente

inerte, tal como DCM. La reacción de la segunda etapa puede realizarse convenientemente, por ejemplo, en un microondas calentado a una temperatura de aproximadamente 100°C, en un disolvente inerte, tal como NMP. La reacción de la tercera etapa puede realizarse convenientemente, por ejemplo, aproximadamente a una temperatura de aproximadamente 0°C a la temperatura ambiente, en presencia de una base inorgánica, tal como KOH, NaOH o LiOH, en un disolvente, tal como THF, MEOH o una mezcla de los mismos. La reacción de la cuarta etapa puede realizarse convenientemente, por ejemplo, de aproximadamente la temperatura ambiente a 100°C, en presencia de un agente de acoplamiento, tal como HCTU, HOTT, PyBrOP, DMTMM, o HATU con HOAt, y una base, tal como DIPEA o Et_3N, en un disolvente inerte, tal como DMF. La reacción de la tercera etapa puede realizarse convenientemente, por ejemplo, aproximadamente a una temperatura de aproximadamente 0°C a la temperatura ambiente, haciendo reaccionar primero el compuesto de fórmula (17) con cloruro de oxalilo, y después añadiendo el compuesto de fórmula (5) y una base tal como DIPEA, Et_3N, K_2CO_3 o Na_2CO_3, en un disolvente inerte, tal como DCM o DMF.

Los compuestos de la invención también pueden prepararse por interconversión de otros compuestos de la invención.

Se apreciará que los compuestos de la presente invención pueden contener centros asimétricos. Estos centros asimétricos pueden estar independientemente en la configuración R o S. Será obvio para los especialistas en la técnica que ciertos compuestos de la invención también pueden mostrar isomería geométrica. Se entiende que la presente invención incluye los isómeros geométricos individuales, los estereoisómeros y las mezclas de los mismos, incluyendo mezclas racémicas, de los compuestos de la fórmula (I) descritos anteriormente en este documento. Tales isómeros pueden separarse de sus mezclas mediante la aplicación o adaptación de métodos conocidos, por ejemplo, técnicas cromatográficas y técnicas de recristalización, o se preparan de forma separada a partir de los isómeros apropiados de sus intermedios.

Los compuestos de la invención, sus métodos de preparación y su actividad biológica serán más evidentes a partir del examen de los siguientes ejemplos que se presentan solamente como una ilustración y no deben considerarse como limitantes del alcance de la invención. Los compuestos de la invención se identifican, por ejemplo, por los siguientes métodos analíticos.

Los espectros de masas (MS) se registran usando un espectrómetro de masas Micromass LCT. El método es ionización por electronebulización positiva, masa de barrido m/z de 100 a 1000.

Los espectros de resonancia magnética nuclear de ^1H (^1H RMN) a 300 MHz se registran a temperatura ambiente usando un espectrómetro Varian Mercury (300 MHz) con una sonda de 5 mm ASW. En la ^1H RMN, los valores de los desplazamientos químicos se indican en partes por millón (ppm) con respecto al tetrametilsilano (TMS) como patrón interno.

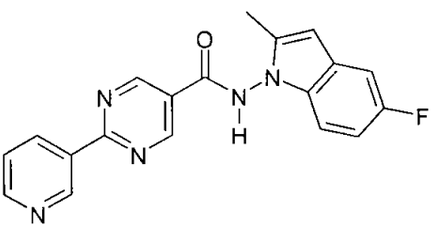
Como se usan en los ejemplos y preparaciones que se muestran a continuación, así como en el resto de la solicitud, los términos usados tendrán los significados indicados: "kg" = kilogramos, "g" = gramos, "mg" = miligramos, "µg" = microgramos, "mol" = moles, "mmol" = milimoles, "M" = molar, "mM" = milimolar, "µM" = micromolar, "nM" = nanomolar, "l" = litros, "ml" = mililitros, "µl" = microlitros, "ºC" = grados centígrados, "pf" o "p.f." = punto de fusión, "pe" o "p.e." = punto de ebullición, "mm de Hg" = presión en milímetros de mercurio, "cm" = centímetros, "nm" = nanómetros, "abs." = absoluto, "conc." = concentrado, "c" = concentración en g/ml, "ta" = temperatura ambiente, "TLC" = cromatografía de capa fina, "HPLC" = cromatografía líquida de alta resolución, "i.p." = por vía intraperitoneal, "i.v." = por vía intravenosa, "s" = singlete, "d" = doblete; "t" = triplete; "c" = cuadruplete; "m" = multiplete, "dd" = doblete de dobletes; "a" = ancho, "LC" = cromatografía líquida, "MS" = espectroscopía de masas, "ESI/MS" = ionización por electronebulización/espectroscopía de masas, "T_R" = tiempo de retención, "M" = ion molecular, "PSI" = libras por pulgada cuadrada, "DMSO" = dimetilsulfóxido, "DMF" = N,N-dimetilformamida, "DCM" = diclorometano, "HCl" = ácido clorhídrico, "SPA" = Ensayo de Proximidad por Centelleo, "EtOAc" = acetato de etilo, "PBS"= Solución Salina Tamponada con Fosfato, "IUPAC" = Unión Internacional de Química Pura y Aplicada, "MHz" = megahertzios, "MeOH " = metanol, "N" = normalidad, "THF" = tetrahidrofurano, "min" = minuto(s), "N_2" = gas nitrógeno, "MeCN" o "CH_3CN" = acetonitrilo, "Et_2O" = éter etílico, "TFA" = ácido trifluoroacético, "~" = aproximadamente, "$MgSO_4$" = sulfato de magnesio, "Na_2SO_4" = sulfato sódico, "$NaHCO_3$" = bicarbonato sódico, "Na_2CO_3" = carbonato sódico, "MCPBA" = ácido 3-cloroperoxibenzoico, "NMP" = N-metilpirrolidona, "PS-DCC" = diciclohexilcarbodiimida soportada con polímero, "LiOH" = hidróxido de litio, "PS-trisamina" = trisamina soportada con polímero, "PGH2" = prostaglandina H2, "PGD2" = prostaglandina D2; "PGE2" = prostaglandina E2, "hPGDS" = PGD2 sintasa hematopoyética, "GSH" = glutatión (reducido), "EIA" = inmunoensayo enzimático,

"KH_2PO_4" = fosfato potásico, monobásico, "K_2HPO_4" = fosfato potásico, dibásico, "$FeCl_2$" = cloruro de hierro, "MOX" = metoxilamina; "EtOH" = etanol, "DMSO" = dimetilsulfóxido, "Ag_2O" = óxido de plata (I), "HATU" = hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio, "HOAt" = 1-hidroxi-7-azabenzotriazol, "DIPEA" = *N*,*N*-diisopropiletilamina, "HOTT" = hexafluorofosfato de *S*-(1-oxido-2-piridil)-*N*,*N*,*N*',*N*'-tetrametiltiuronio, "HCTU" = hexafluorofosfato de *N*,*N*,*N*',*N*'-tetrametil-*O*-(6-cloro-1*H*-benzotriazol-1-il)uronio, "PyBrOP" = hexafluorofosfato de bromo-*tris*-pirrolidinofosfonio, "LiAlH4" = hidruro de litio y aluminio, "PyAOP" = hexafluorofosfato de (7-azabenzotriazol-1-iloxi)-tripirrolidinofosfonio, "TBTU" = tetrafluoroborato de O-benzotriazol-1-il-N,N,N,N-tetrametiluronio, "NaHMDS" = bis(trimetilsilil)amida sódica, "NMP" = N-metil-2-pirrolidinona, "HOSA" = ácido hidroxilamina-O-sulfónico, "DMTMM" = cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolinio, "$TMSN_3$" = trimetilsilil azida, "TBAF" = fluoruro de tetrabutilamonio, "TFAA" = anhídrido trifluoroacético.

EJEMPLOS

Ejemplo 1

(5-Fluoro-2-metil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico



Etapa 1: Una solución de *terc*-butóxido potásico (1,84 g, 16,43 mmol) y 5-fluoro-2-metilindol (1,21 g, 8,09 mmol) en DMF (20 ml) se agita en una atmósfera de N_2 a ta durante 60 min. Se añade una solución de monocloroamina en éter (65 ml, 9,75 mmol) mediante un embudo de adición durante 10 min. La mezcla resultante se agita a 23°C durante 2 horas y después se concentra al vacío. El residuo se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10% en heptano para producir 5-fluoro-2-metil-indol-1-ilamina (290 mg, 22%) en forma de un sólido. MS: 165 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,24-7,19 (m, 1H), 7,12 (dd, 1H), 6,92 (dt, 1H), 6,12 (s, 1H), 4,23 (s a, 2 H), 2,39 (s, 3H).

Etapa 2: Un matraz de fondo redondo, de tres bocas, de 250 ml, equipado con un agitador magnético y un condensador de reflujo se purga con N_2. El matraz se carga secuencialmente con 3,3-dimetoxipropionato de metilo (5,22 g, 35,3 mmol), 1,2-dimetoxietano anhidro (25 ml), formiato de metilo anhidro (5 ml) e hidruro sódico al 60% (1,70 g, 42,5 mmol), y la mezcla se calienta a 40 – 50°C hasta que se detiene el desprendimiento de gas hidrógeno. La mezcla de reacción se enfría en un baño de hielo/agua y se deja que alcance lentamente la temperatura ambiente durante una noche con agitación. Se añade éter anhidro (25 ml) y la suspensión resultante se filtra en una atmósfera de N_2, se lava con éter anhidro (10 ml) y se seca al vacío durante 2 horas para producir la sal sódica de éster metílico del ácido 2-dimetoximetil-3-hidroxi-acrílico (3,51 g, 50%) en forma de un polvo. ^{1}H RMN (CD_3OD): δ 3,33 (s, 6H), 3,60 (s, 3H), 5,31 (s, 1H), 8,89 (s, 1H). (Véase: P. Zhichkin, D.J. Fairfax, S.A. Eisenbeis, Synthesis, 2002, 720-722).

Etapa 3: A una solución de hidrocloruro de nicotinamidina (1 g, 6,35 mmol) en DMF anhidra (12 ml) se le añade la sal sódica de éster metílico del ácido 2-dimetoximetil-3-hidroxi-acrílico (1,46 g, 7,36 mmol) y la mezcla de reacción se calienta a 100°C en una atmósfera de N_2 durante 3 horas. Después de este tiempo, la reacción se enfría a temperatura ambiente y se añade agua (48 ml). El precipitado se recoge por filtración, se lava con agua y se seca al vacío para producir éster metílico del ácido 2-piridin-3-il-pirimidina-5-carboxílico (0,7 g, 51%). MS: 216 (M+H).

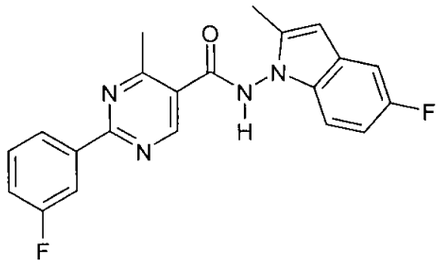
Etapa 4: Una solución de éster metílico del ácido 2-piridin-3-il-pirimidina-5-carboxílico (0,73 g, 3,32 mmol) y LiOH acuoso 1 M (3,32 ml) en MeOH (5 ml) se agita a ta durante una noche. El MeOH se retira al vacío y la solución acuosa se trata con HCl acuoso 3 N para ajustar el valor del pH a ~2-3. El sólido se retira por filtración, se lava con agua y se seca al vacío para producir ácido 2-piridin-3-il-pirimidina-5-carboxílico (0,2 g, 30%) en forma de un sólido. MS: 202 (M+H).

Etapa 5: Una solución de ácido 2-piridin-3-il-pirimidina-5-carboxílico (506 mg, 2,13 mmol), HCTU (970 mg, 2,34 mmol) y DIPEA (1 ml, 5,72 mmol) en DMF (10 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-fluoro-2-metil-indol-1-ilamina (311 mg, 1,89 mmol). La mezcla resultante se agita a 75°C durante una noche. La mezcla se enfría y se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 45% en heptano para

producir (5-fluoro-2-metil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico (300 mg, 46%) en forma de un sólido. MS: 348 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,02 (s, 1H), 9,60 (d, 1H), 9,49 (s, 2H), 8,82-8,76 (m, 2H), 7,64 (dd, 1H), 7,39 (dd, 1H), 7,29 (dd, 1H), 6,94 (dt, 1H), 6,35 (s, 1H), 2,33 (s, 3H).

Ejemplo 2

(5-Fluoro-2-metil-indol-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,



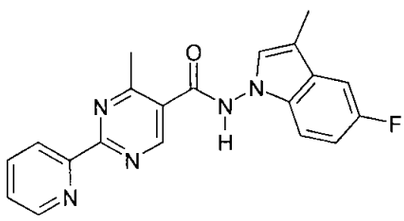
Etapa 1: Se añade Na^0 (0,66 g, 28,6 mmol) a EtOH anhidro (100 ml) y la mezcla se agita a ta durante 15 min. Se añade hidrocloruro de 3-fluorobenzamidina (4,87 g, 27,8 mmol) y la solución se agita durante 15 min. Se añade éster etílico del ácido 2-dimetilaminometileno-3-oxo-butírico (5,3 g, 28,6 mmol) y la mezcla de reacción se calienta a reflujo en una atmósfera de N_2 durante 1 horas. La reacción se enfría a ta y se concentra al vacío. El residuo se disuelve en EtOAc (300 ml), se lava con salmuera (2 x 100 ml), se seca (Na_2SO_4), se filtra y se concentra para producir éster etílico del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (6,8 g, 99%). MS: 261 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,43 (t, J = 7,0 Hz, 3H), 2,92 (s, 3H), 4,42 (c, J = 7,0 Hz, 2H), 7,24 (m, 1H), 7,45 (m, 1H), 8,27 (m, 1H), 8,37 (m, 1H), 9,21 (s, 1H).

Etapa 2: Una solución de éster etílico del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (6,7 g, 27,2 mmol) y NaOH (2,1 g, 54,4 mmol) en una solución 1:1:1 de THF, MeOH y agua (300 ml) se calienta a reflujo durante 45 min. El THF/MeOH se evapora y la solución acuosa se trata con HCl 3 N para ajustar el pH entre 2 y 3. El sólido se retira por filtración, se lava con agua y se seca al vacío para producir ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (5,4 g, 91%) en forma de un sólido. MS: 233 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,85 (s, 3H), 7,24 (m, 1H), 7,50 (m, 1H), 8,17 (m, 1H), 8,32 (m, 1H), 9,20 (s, 1H).

Etapa 3: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (340 mg, 1,46 mmol, preparado de acuerdo con el procedimiento general descrito en el Ejemplo 1, etapas 3 y 4), HOAt (248 mg, 1,82 mmol) y HATU (645 mg, 1,70 mmol) en DMF (15 ml) se agita a ta en una atmósfera de N_2 durante 20 min. Se añaden 5-fluoro-2-metil-indol-1-ilamina (237 mg, 1,44 mmol) y DIPEA (380 µl, 2,18 mmol). La mezcla resultante se agita a 80°C durante una noche. La mezcla se enfría y se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 20% en heptano para producir (5-fluoro-2-metil-indol-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (300 mg, 55%) en forma de un sólido. MS: 379 (M+H). ^{1}H RMN (300 MHz, CD_3OD): δ 9,14 (s, 1H), 8,38-8,20 (m, 3H), 7,56-7,52 (m, 1H), 7,30-7,27 (m, 2H), 7,19-7,16 (m, 1H), 6,96-6,90 (m, 1H), 6,32 (s, 1H), 2,83 (s, 3H), 2,42 (s, 3H).

Ejemplo 3

(5-Fluoro-3-metil-indol-1-il)amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Etapa 1: Una suspensión de NaH (2,01 g, 50,3 mmol, al 60% en aceite mineral) en DMF (45 ml) a 0°C se trata con 5-fluoro-3-metil-1H-indol (500 mg, 3,55 mmol) y la mezcla se agita a 0°C durante 1 h. Se añade en porciones NH_2OSO_3H (1,9 g, 16,75 mmol) y después la mezcla se calienta a ta y se agita durante 2 h. La mezcla se inactiva con MeOH, se diluye con agua, se extrae con EtOAc, se seca (Na_2SO_4), se filtra y se concentra para producir 5-fluoro-3-metil-indol-1-ilamina. MS: 165 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,22 (s, 3H), 6,86 (m, 1H), 6,99 (s, 1H), 7,08 (m, 1H), 7,36 (m, 1H).

Etapa 2: Se añade Na^0 (31,7 mmol) a EtOH anhidro (100 ml) y la mezcla se agita a ta durante 15 min. Se añade hidrocloruro de piridina-2-carboxamidina (31,7 mmol) y la solución se agita durante 15 min. Se añade éster etílico del ácido 2-dimetilaminometileno-3-oxo-butírico (31,7 mmol) y la mezcla de reacción se calienta a reflujo en una atmósfera de N_2 durante 1 h. La reacción se enfría a ta y se concentra al vacío. El residuo se disuelve en EtOAc (200 ml), se lava con salmuera (2 x 100 ml), se seca (Na_2SO_4), se filtra y se concentra

para producir éster etílico del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (6,77 g, 88%). MS: 261 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,44 (t, 3H), 2,97 (s, 3H), 4,44 (c, 2H), 7,44 (m, 1H), 7,91 (m, 1H), 8,60 (m, 1H), 8,90 (m, 1H), 9,31 (s, 1H).

Etapa 3: Una solución de éster etílico del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico 26,7 mmol) y LiOH (53,4 mmol) en una solución 1:1:1 de THF, MeOH y agua (200 ml) se agita a ta durante una noche. El THF/MeOH se evapora y la solución acuosa se trata con HCl acuoso al 10% para ajustar el pH entre 1,5 y 2,5. El sólido se retira por filtración, se lava con agua y se seca al vacío para producir ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (5,50 g, 96%) en forma de un sólido. MS: 233 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ = 2,93 (s, 3H), 7,59 (m, 1H), 8,05 (t, 1H), 8,62 (d, 1H), 8,76 (d, 1H), 9,28 (s, 1H).

Etapa 4, Método A:

Una solución de ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (335 mg, 1,56 mmol), HOTT (638 mg, 1,72 mmol) y DIPEA (700 µl, 4,01 mmol) en DMF (6 ml) se agita a ta en una atmósfera de N_2 durante 20 min. Se añade 5-fluoro-3-metil-indol-1-ilamina (241 mg, 1,47 mmol). La mezcla resultante se agita a ta durante una noche. La mezcla se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 60% en heptano para producir (5-fluoro-3-metil-indol-1-il)amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (193 mg, 36%) en forma de un sólido. MS: 362 (M+H). ^{1}H RMN (300 MHz, $CDCl_3$): δ 10,41 (s, 1H), 8,84 (s, 1H), 8,55 (s, 1H), 8,48-8,45 (m, 1H), 7,86 (t, 1H), 7,40-7,36 (m, 1H), 7,24-7,20 (m, 2H), 7,05-7,01 (m, 2H), 2,82 (s, 3H), 2,32 (s, 3H).

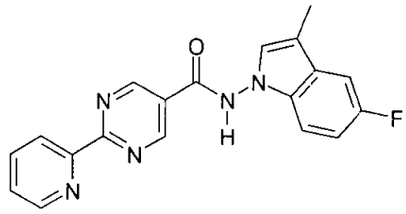
Etapa 4, Método B:

Se trata 5-fluoro-3-metil-indol-1-ilamina (10,6 mmol) con ácido 4-metil-2-piridin-2-ilpirimidina-5-carboxílico (2,75 g, 12,8 mmol) en DMF (75 ml) y la mezcla se agita a ta durante 10 min. Después, la mezcla se trata con cloruro de 2,4-dimetoxi-6-(4-metilmorfolin-4-il)-[1,3,5]triazina (3,82 g, 13,85 mmol) y se agita a 60°C durante 1 h. La mezcla se concentra al vacío. El residuo se diluye con Et_2O (50 ml) y $NaHCO_3$ al 10% (50 ml) y la mezcla se agita a ta durante 20 min. El sólido resultante se filtra, se lava y se seca para producir (5-fluoro-3-metil-indol-1-il)amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-

carboxílico (3,2 g, 83%). El sólido se cristaliza con MeOH:agua (4:1) para producir (5-fluoro-3-metil-indol-1-il)amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico en forma de un cristal. MS: 362 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,27 (s, 3H), 2,78 (s, 3H), 7,06 (m, 1H), 7,34 (m, 1H), 7,37 (s, 1H), 7,44 (m, 1H), 7,59 (m, 1H), 8,05 (m, 1H), 8,45 (m, 1H), 8,80 (m, 1H), 9,25 (s, 1H). CI_{50} = 7 nM.

Ejemplo 4

(5-Fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico



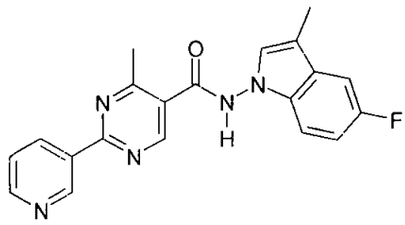
Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 1, etapa 3, pero sustituyendo hidrocloruro de nicotinamidina por hidrocloruro de piridina-2-carboxamidina, se prepara éster metílico del ácido 2-piridin-2-il-pirimidina-5-carboxílico .

Etapa 2: Siguiendo procedimientos similares a los del Ejemplo 2, etapa 1, pero sustituyendo éster metílico del ácido 2-piridin-3-il-pirimidina-5-carboxílico por éster metílico del ácido 2-piridin-2-il-pirimidina-5-carboxílico, se prepara ácido 2-piridin-2-il-pirimidina-5-carboxílico.

Etapa 3: Una solución de ácido 2-piridin-2-il-pirimidina-5-carboxílico (209 mg, 0,88 mmol), HOTT (435 mg, 1,17 mmol) y DIPEA (400 µl, 2,29 mmol) en DMF (10 ml) se agita a ta en una atmósfera de N_2 durante 20 min. Se añade 5-fluoro-3-metil-indol-1-ilamina (125 mg, 0,76 mmol). La mezcla resultante se agita a ta durante una noche. La mezcla se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 70% en heptano para producir (5-fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico (180 mg, 68%) en forma de un sólido. MS: 348 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,12 (s, 1H), 9,47 (s, 2H), 8,82 (d, 1H), 8,51 (d, 1H), 8,05 (td, 1H), 7,62 (dd, 1H), 7,42 (dd, 1H), 7,35 (dd, 1H), 7,33 (s, 1H), 7,03 (td, 1H), 2,27 (s, 3H).

Ejemplo 5

(5-Fluoro-3-metil-indol-1-il)amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico



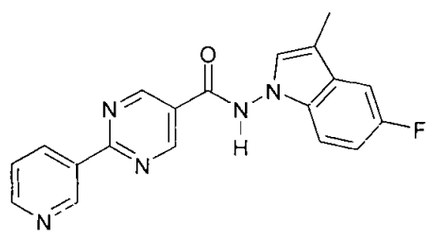
Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 2, etapa 1, pero sustituyendo hidrocloruro de 3-fluorobenzamidina por hidrocloruro de nicotinamidina, se prepara éster etílico del ácido 2-piridin-3-il-4-metil-pirimidina-5-carboxílico.

Etapa 2: Siguiendo procedimientos similares a los del Ejemplo 2, etapa 1, pero sustituyendo éster etílico del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico por éster etílico del ácido 2-piridin-3-il-4-metil-pirimidina-5-carboxílico, se prepara ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico.

Etapa 3: Una solución de ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico (502 mg, 2,33 mmol), HCTU (1,054 g, 2,55 mmol) y DIPEA (1,10 ml, 6,30 mmol) en DMF (10 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-fluoro-3-metil-indol-1-ilamina (341 mg, 2,08 mmol). La mezcla resultante se agita a ta durante una noche. La mezcla se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se tritura en éter (4 veces) para producir (5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico (160 mg, 21%) en forma de un sólido. MS: 362 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,86 (s, 1H), 9,58 (s, 1H), 9,24 (s, 1H), 8,79-8,78 (m, 1H), 8,74 (td, 1H), 7,62 (dd, 1H), 7,44 (dd, 1H), 7,37-7,36 (m, 2H), 7,06 (td, 1H), 2,78 (s, 3H), 2,27 (s, 3H).

Ejemplo 6

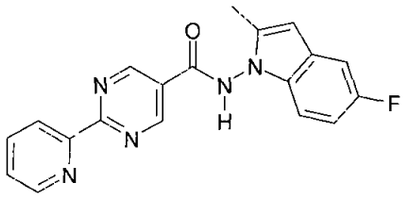
(5-Fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico



Una solución de ácido 2-piridin-3-il-pirimidina-5-carboxílico (664 mg, 2,79 mmol), HCTU (1,27 g, 3,07 mmol) y DIPEA (1,4 ml, 8,02 mmol) en DMF (15 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-fluoro-3-metil-indol-1-ilamina (491 mg, 2,55 mmol). La mezcla resultante se agita a ta durante una noche. La mezcla se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se tritura en éter (3 veces) y metanol para producir (5-fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico (375 mg, 42%) en forma de un sólido. MS: 348 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,10 (s, 1H), 9,61-9,60 (m, 1H), 9,45 (s, 2H), 8,81-8,80 (m, 1H), 8,77 (dt, 1H), 7,64 (dd, 1H), 7,41 (dd, 1H), 7,35 (dd, 1H), 7,32 (s, 1H), 7,03 (td, 1H), 2,27 (s, 3H). CI_{50} = 10 nM.

Ejemplo 7

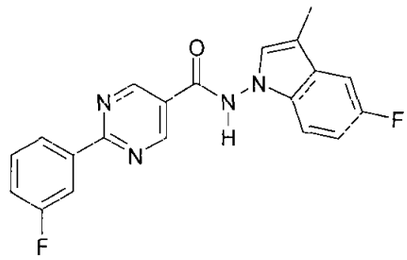
(5-Fluoro-2-metil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico



Una solución de ácido 2-piridin-3-il-pirimidina-5-carboxílico (485 mg, 2,04 mmol), HCTU (909 mg, 2,2 mmol) y DIPEA (1 ml, 5,72 mmol) en DMF (15 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-fluoro-2-metil-indol-1-ilamina (299 mg, 1,82 mmol). La mezcla resultante se agita a ta durante una noche. La mezcla se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 70% en heptano para producir (5-fluoro-2-metil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico (112 mg, 18%) en forma de un sólido. MS: 348 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,03 (s, 1H), 9,51 (s, 2H), 8,83 (d, 1H), 8,50 (d, 1H), 8,05 (dt, 1H), 7,62 (dd, 1H), 7,39 (dd, 1H), 7,28 (dd, 1H), 6,94 (dt, 1H), 6,35 (s, 1H), 2,33 (s, 3H).

Ejemplo 8

(5-Fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



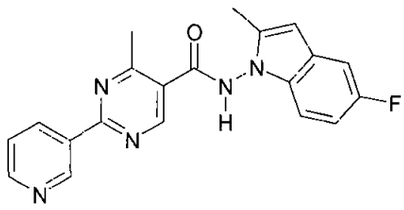
Etapa 1: A una solución de hidrocloruro de 3-fluoro-benzamidina (4 g, 22,6 mmol) en DMF anhidra (35 ml) se le añade 3,3-dimetoxi-2-carbometoxiprop-1-en-1-óxido sódico (4,99 g, 25,2 mmol). La mezcla de reacción se calienta a 100ºC en una atmósfera de N_2 durante 3 h y después se enfría a ta. Se añade agua (150 ml) y la mezcla se extrae con EtOAc. La capa orgánica se lava con salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío para producir éster metílico del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (1,76 g, 34%). MS: 233 (M+H).

Etapa 2: A una solución de éster metílico del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (1,76 g, 7,58 mmol) en MeOH anhidro (35 ml) se le añade LiOH (0,38 g, 15,9 mmol) y la mezcla de reacción se agita a ta durante una noche. La mezcla se concentra al vacío y el residuo se reparte entre EtOAc y HCl acuoso 3 N (7,6 ml). La mezcla se extrae con EtOAc y la capa orgánica se lava con salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío para producir ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (1,62 g, 98%) en forma de un sólido. MS: 219 (M+H).

Etapa 3: Una solución de ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (372 mg, 1,7 mmol), HCTU (757 mg, 1,83 mmol) y DIPEA (780 µl, 4,47 mmol) en DMF (10 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-fluoro-3-metil-indol-1-ilamina (250 mg, 1,52 mmol). La mezcla resultante se agita a ta durante una noche. La mezcla se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se tritura en éter para producir (5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (332 mg, 60%) en forma de un sólido. MS: 365 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,08 (s, 1H), 9,43 (s, 2H), 8,36 (d, 1H), 8,20 (dt, 1H), 7,70-7,62 (m, 1H), 7,48 (dt, 1H), 7,40 (dd, 1H), 7,35 (dd, 1H), 7,32 (s, 1H), 7,03 (dt, 1H), 2,27 (s, 3H).

Ejemplo 9

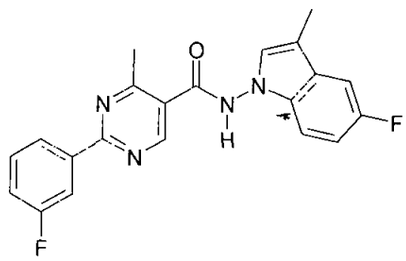
(5-Fluoro-2-metil-indol-1-il)amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico



Una solución de ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico (504 mg, 2,34 mmol), HCTU (1,06 g, 2,55 mmol) y DIPEA (1,1 ml, 6,30 mmol) en DMF (15 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-fluoro-2-metil-indol-1-ilamina (346 mg, 2,11 mmol). La mezcla resultante se agita a ta durante una noche. La mezcla se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 70% en heptano para producir (5-fluoro-2-metil-indol-1-il)amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico (82 mg, -11%) en forma de un sólido. MS: 362 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,80 (s, 1H), 9,59 (d, 1H), 9,29 (s, 1H), 8,80-8,73 (m, 2H), 7,63 (dd, 1H), 7,22 (dd, 1H), 7,28 (dd, 1H), 6,97 (dt, 1H), 6,35 (s, 1H), 2,79 (s, 3H), 2,37 (s, 3H).

Ejemplo 10

(5-Fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

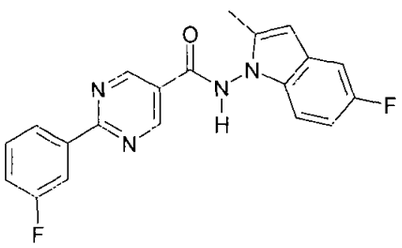


Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (645 mg, 2,78 mmol), HCTU (1,25 g, 3,02 mmol) y DIPEA (1,35 ml, 7,73 mmol) en DMF (15 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-fluoro-3-metil-indol-1-ilamina (380 mg, 2,31 mmol). La mezcla resultante se agita a ta durante una noche. La mezcla se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se tritura en éter para producir (5-fluoro-3-metil-indol-1-il)-amida de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (533 mg, 61%) en forma de un sólido. MS: 379 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,84 (s, 1H), 9,21 (s, 1H), 8,32 (d, 1H), 8,17-8,15 (m, 1H), 7,66-

7,61 (m, 1H), 7,47-41 (m, 2H), 7,36-7,34 (m, 2H), 7,05 (dt, 1H), 2,76 (s, 3H), 2,26 (s, 3H). CI_{50} = 6 nM.

Ejemplo 11

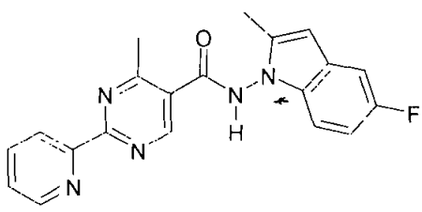
(5-Fluoro-2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



Una solución de ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (389 mg, 1,78 mmol), HOAt (290 mg, 2,13 mmol) y HATU (811 mg, 2,13 mmol) en DMF (20 ml) se agita a ta en una atmósfera de N_2 durante 20 min. Se añade 5-fluoro-2-metil-indol-1-ilamina (290 mg, 1,77 mmol) y DIPEA (450 µl, 2,58 mmol). La mezcla resultante se agita a 80ºC durante una noche. La mezcla se enfría y se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con DCM al 25% en heptano para producir (5-fluoro-2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (300 mg, 47%) en forma de un sólido. MS: 365 (M+H). ^{1}H RMN (300 MHz, $CDCl_3$): δ 9,23 (s, 1H), 8,76 (s, 1H), 8,35-8,22 (m, 2H), 7,54-7,45 (m, 1H), 7,19-6,86 (m, 5H), 6,25 (s, 1H), 2,29 (s, 3H).

Ejemplo 12

(5-Fluoro-2-metil-indol-1-il)amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico

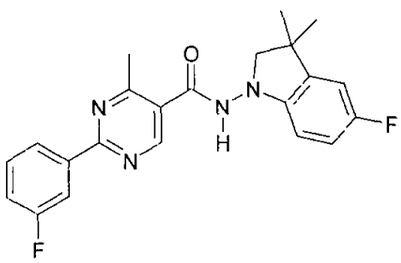


Una solución de ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (810 mg, 3,76 mmol), PyBrOP (1,76 g, 3,78 mmol) y DIPEA (1,9 ml, 10,89 mmol) en DMF (15 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-fluoro-2-metil-indol-1-ilamina (560 mg, 3,41 mmol). La mezcla resultante se agita a ta durante una noche. La mezcla se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por

cromatografía sobre gel de sílice eluyendo con MeOH al 3% en DCM para producir (5-fluoro-2-metil-indol-1-il)amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (174 mg, 14%) en forma de un sólido. MS: 362 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,82 (s, 1H), 9,30 (d, 1H), 8,81 (d, 1H), 8,46 (d, 1H), 8,03 (dt, 1H), 7,59 (dd, 1H), 7,43 (dd, 1H), 7,29 (dd, 1H), 6,98 (dt, 1H), 6,35 (s, 1H), 2,79 (s, 3H), 2,38 (s, 3H). CI_{50} = 8 nM.

Ejemplo 13

(5-Fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



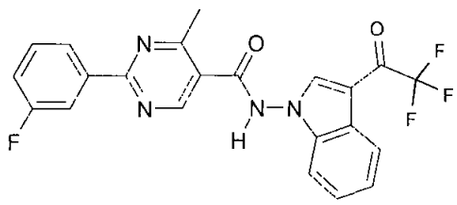
Etapa 1: Se añade nitrito de isoamilo (3,4 ml, 25,42 mmol) a una solución de 5-fluoro-3,3-dimetil-2,3-dihidro-1H-indol (3,75 g, 22,69 mmol) en DCM. La mezcla se calienta a reflujo durante una noche. La mezcla se enfría y se reparte entre DCM y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío para producir 5-fluoro-3,3-dimetil-1-nitroso-2,3-dihidro-1H-indol (4,23 g, 96%) en forma de un sólido. MS: 195 (M+H). ^{1}H RMN (300 MHz, CD_3Cl): δ 7,77 (dd, 1H), 7,08-6,98 (m, 2H), 3,94 (s, 2H), 1,39 (s, 6H).

Etapa 2: A una solución de 5-fluoro-3,3-dimetil-1-nitroso-2,3-dihidro-1H-indol (4,03 g, 20,75 mmol) en THF (70 ml) a 0°C se le añade gota a gota una solución de $LiAlH_4$ (40 ml, 40 mmol) en THF. La mezcla se deja calentar a ta y se agita durante una noche. La mezcla se inactiva con una solución saturada acuosa de Sal de Rochelle. La mezcla resultante se agita hasta que se obtiene una suspensión. La fase orgánica se separa, se lava con HCl acuoso al 10%, $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 25% en heptano para producir 5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-ilamina (3,51 g, 94%) en forma de un aceite. MS: 181 (M+H). ^{1}H RMN (300 MHz, CD_3Cl): δ 6,85-6,78 (m, 1H), 6,75-6,68 (m, 2H), 3,44 (s a, 2H), 3,14 (s, 2H), 1,28 (s, 6H).

Etapa 3: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (348 mg, 1,5 mmol), HOTT (618 mg, 1,66 mmol) y DIPEA (700 µl, 4,01 mmol) en DMF (10 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-ilamina (239 mg, 1,33 mmol). La mezcla resultante se agita a 80°C durante una noche. La mezcla se enfría y se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 15% en heptano para producir (5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (416 mg, 80%) en forma de un sólido. MS: 395 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 10,43 (s, 1H), 8,99 (s, 1H), 8,28 (d, 1H), 8,15-8,11 (m, 1H), 7,66-7,58 (m, 1H), 7,46-7,39 (m, 1H), 7,06 (dd, 1H), 6,95-6,88 (m, 1H), 6,75-6,71 (m, 1H), 3,51 (s, 2H), 2,68 (s, 3H), 1,33 (s, 6H).

Ejemplo 14

[3-(2,2,2-Trifluoro-acetil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



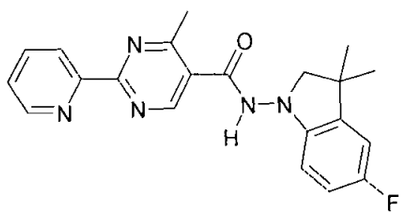
Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 1, etapa 1, pero sustituyendo 5-fluoro-2-metilindol por 3-(2,2,2-trifluoro-acetil)indol, se prepara 1-(1-amino-1H-indol-3-il)-2,2,2-trifluoro-etanona.

Etapa 2: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (360 mg, 1,55 mmol), HOTT (628 mg, 1,69 mmol) y DIPEA (740 µl, 4,24 mmol) en DMF (10 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 1-(1-amino-1H-indol-3-il)-2,2,2-trifluoro-etanona (322 mg, 1,4 mmol). La mezcla resultante se agita a 80°C durante una noche. La mezcla se enfría y se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía en columna de fase inversa HPLC eluyendo con una fase móvil de TFA al 0,1%/agua a MeCN al 100% en aumento durante 30 min para producir [3-(2,2,2-trifluoro-acetil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (71 mg, 11%) en forma de un sólido. MS: 443

(M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,56 (s, 1H), 9,32 (s, 1H), 8,90 (d, 1H), 8,35 (d, 1H), 8,30-8,27 (m, 1H), 8,22-8,17 (m, 1H), 7,75-72 (m, 1H), 7,69-7,62 (m, 1H), 7,52-7,44 (m, 3H), 2,81 (s, 3H).

Ejemplo 15

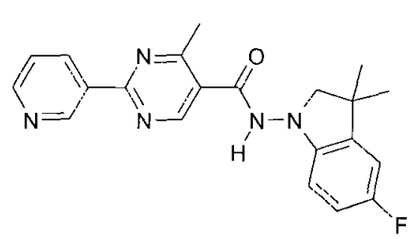
(5-Fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Una solución de ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (685 mg, 3,18 mmol), HOTT (1,29 g, 3,48 mmol) y DIPEA (1,6 ml, 9,16 mmol) en DMF (15 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-ilamina (542 mg, 3,01 mmol). La mezcla resultante se agita a 80°C durante una noche. La mezcla se enfría y se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 2% en DCM para producir (5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (585 mg, 52%) en forma de un sólido. MS: 378 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 10,46 (s, 1H), 9,02 (s, 1H), 8,78 (d, 1H), 8,42 (d, 1H), 8,00 (dt, 1H), 7,56 (dd, 1H), 7,06 (dd, 1H), 6,92 (dt, 1H), 6,76-6,72 (m, 1H), 3,32 (s, 2H), 2,70 (s, 3H), 1,33 (s, 6H).

Ejemplo 16

(5-Fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico

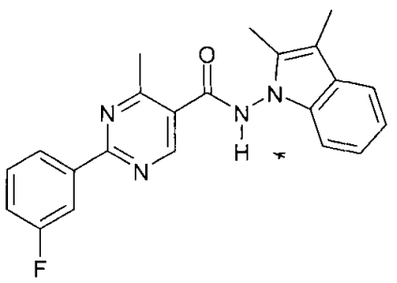


Una solución de ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico (706 mg, 3,28 mmol), HOTT (1,34 g, 3,6 mmol) y DIPEA (1,65 ml, 9,45 mmol) en DMF (15 ml) se agita a ta en

una atmósfera de N_2 durante 10 min. Se añade 5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-ilamina (560 mg, 3,11 mmol). La mezcla resultante se agita a 80ºC durante una noche. La mezcla se enfría y se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 35% en heptano para producir (5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico (617 mg, 53%) en forma de un sólido. MS: 378 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 10,44 (s, 1H), 9,55-9,54 (m, 1H), 9,01 (s, 1H), 8,77-8,75 (m, 1H), 8,72-8,68 (m, 1H), 7,60 (dd, 1H), 7,06 (dd, 1H), 6,96-6,88 (m, 1H), 6,76-6,72 (m, 1H), 3,51 (s, 2H), 2,70 (s, 3H), 1,33 (s, 6H).

Ejemplo 17

(2,3-Dimetil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

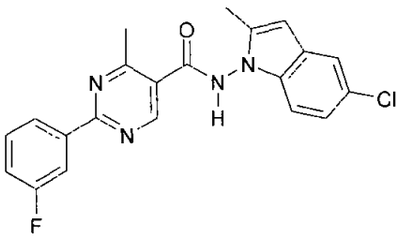


Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 1, etapa 1, pero sustituyendo 5-fluoro-2-metilindol por 2,3-dimetilindol, se prepara 2,3-dimetil-indol-1-ilamina en forma de un sólido. MS: 161 (M+H). ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,48-7,45 (m, 1H), 7,33-7,30 (m, 1H), 7,19-7,13 (m, 1H), 7,10-7,05 (m, 1 H), 4,40 (s a, 2H), 2,37 (s, 3H), 2,23 (s, 3H).

Etapa 2: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (764 mg, 3,29 mmol), HOTT (1,33 g, 3,58 mmol) y DIPEA (1,65 ml, 9,45 mmol) en DMF (15 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 2,3-dimetil-indol-1-ilamina (497 mg, 3,1 mmol). La mezcla resultante se agita a 80ºC durante una noche. La mezcla se enfría y se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 20% en heptano para producir (2,3-dimetil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina -5-carboxílico (568 mg, 49%) en forma de un sólido. MS: 375 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,68 (s, 1H), 9,24 (s, 1H), 8,33 (d, 1H), 8,20-8,15 (m, 1H), 7,69-7,61 (m, 1H), 7,50-7,43 (m, 2H), 7,37 (d, 1H), 7,17-7,05 (m, 2H), 2,78 (s, 3H), 2,30 (s, 3H), 2,24 (s, 3H).

Ejemplo 18

(5-Cloro-2-metil-indol-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

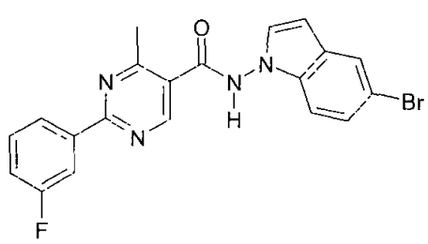


Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 1, etapa 1, pero sustituyendo 5-fluoro-2-metilindol por 5-cloro-2-metilindol, se prepara 5-cloro-2-metil-indol-1-ilamina en forma de un sólido. MS: 181 (M+H). ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,46-7,43 (m, 1H), 7,27-7,24 (m, 1H), 7,12-7,09 (m, 1H), 6,10 (s, 1 H), 4,44 (s a, 2H), 2,44-2,43 (m, 3H).

Etapa 2: Una solución de ácido 2-(3-fluro-fenil)-4-metil-pirimidina-5-carboxílico (379 mg, 1,63 mmol), HOTT (662 mg, 1,78 mmol) y DIPEA (800 µl, 4,58 mmol) en DMF (10 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-cloro-2-metil-indol-1-ilamina (274 mg, 1,52 mmol). La mezcla resultante se agita a 80°C durante una noche. La mezcla se enfría y se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se tritura en éter para producir (5-cloro-2-metil-indol-1-il)-amida de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (93 mg, 16%) en forma de un sólido. MS: 395 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,83 (s, 1H), 9,27 (s, 1H), 8,33 (d, 1H), 8,20-8,15 (m, 1H), 7,69-7,61 (m, 1H), 7,56 (d, 1H), 7,50-7,43 (m, 2H), 6,36 (s, 1H), 2,78 (s, 3H), 2,37 (s, 3H).

Ejemplo 19

(5-Bromo-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

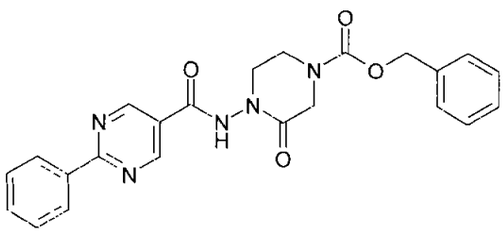


Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 1, etapa 1, pero sustituyendo 5-fluoro-2-metilindol por 5-bromoindol, se prepara 5-bromoindol-1-ilàmina en forma de un sólido. MS: 211 (M+H). ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,71-7,70 (m, 1H), 7,29-7,28 (m, 2H), 7,13 (d, 1H), 6,32-6,31 (m, 1 H), 4,73 (s a, 2H).

Etapa 2: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (596 mg, 2,57 mmol), PyAOP (2,63 mmol) y DIPEA (830 µl, 4,75 mmol) en DCM (20 ml) se agita a ta en una atmósfera de N_2 durante 10 min. Se añade 5-bromoindol-1-ilamina (500 mg, 2,37 mmol). La mezcla resultante se agita a ta durante una noche. La mezcla se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 2% en DCM para producir (5-bromo-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (246 mg, 24%) en forma de un sólido. MS: 425 (M) & 427 (M+2). ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,02 (s, 1H), 9,24 (s, 1H), 8,34 (d, 1H), 8,20-8,15 (m, 1H), 7,84 (d, 1H), 7,68-7,61 (m, 1H), 7,59 (d, 1H), 7,50-7,43 (m, 2H), 7,35 (dd, 1H), 6,57 (dd, 1H), 2,78 (s, 3H).

Ejemplo 20

Éster bencílico del ácido 3-oxo-4-[(2-fenil-pirimidina-5-carbonil)-amino]-piperazina-1-carboxílico



Etapa 1: Siguiendo los procedimientos descritos en M. A. Brook, T. H. Chan *Synthesis* **1983**, (3), 201-204, se prepara éster etílico del ácido benciloxicarbonilamino-acético (95%). MS: 238 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,24-7,41 (m, 5H), 5,20-5,37 (s a, 1H), 5,13 (s, 2H), 4,21 (c, J = 7,0 Hz, 2H), 3,96 (d a, J = 5,3 Hz, 2H), 1,27 (t, J = 7,1 Hz, 3H).

Etapa 2: Siguiendo los procedimientos descritos en P. Shenbagamurthi, H. A. Smith, J. M. Becker, F. Naider *J. Med Chem.* **1986**, *29* (5), 802-809; R. K. Olsen *J. Org. Chem.* **1970**, *35* (6), 1912-1915, se prepara éster etílico del ácido (alil-benciloxicarbonil-amino)-acético en forma de un líquido (92%): MS: 278 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,17-7,41 (m,

5H), 5,70-5,88 (m, 1H), 5,06-5,25 (m, 4H), 4,02-4,23 (m, 2H), 3,81-4,02 (m, 4H), 1,10-1,30 (m, 3H).

Etapa 3: A una solución a 0° C de AD-mix-β (2,54 g) en una mezcla de *t*-butanol (10 ml) y agua (12 ml) se le añade una solución de éster etílico del ácido (alil-benciloxicarbonil-amino)-acético (0,52 g, 1,91 mmol) en *t*-butanol (2,00 ml). La mezcla de reacción se deja calentar gradualmente a temperatura ambiente durante 2 h y se agita a ta durante 20 h. El exceso de oxidante se inactiva mediante la adición de Na_2SO_3 (2,58 g, 20,44 mmol) y la mezcla se agita vigorosamente durante 4 h. La mezcla se extrae con EtOAc (50 ml) y la fase orgánica se lava con NaCl acuoso saturado (2 x 30 ml). La solución orgánica se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice (gradiente de elución de 1:1:1 de EtOAc:DCM :heptano a 50:50 de DCM:EtOAc) para producir éster etílico del ácido [benciloxicarbonil-(2,3-dihidroxi-propil)-amino]-acético en forma de un aceite (0,276 g, 46%). MS: 312 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,20-7,40 (m, 5H), 5,05-5,18 (m, 2H), 3,95-4,25 (m, 4H), 3,80-3,95 (m, 1H), 3,20-3,80 (m, 11H), 1,11-1,35 (m, 3H). (Véase H. Takahata, H. Ouchi, M. Ichinose, H. Nemoto *Org. Lett.* **2002**, *4* (20), 3459-3462 y el material suplementario; J. Gonzalez, C. Aurigemma, L. Truesdale *Org. Synth.* **2002**, *79*, 93-102).

Etapa 4: A una solución de éster etílico del ácido [benciloxicarbonil-(2,3-dihidroxi-propil)-amino]-acético (1,98 g, 6,37 mmol) en DCM (30 ml) se le añade sílice impregnada con $NaIO_4$ (13,04 g). La suspensión se agita rápidamente durante 4,5 h y después se filtra a través de un embudo de vidrio sinterizado con porosidad gruesa. El filtrado se concentra para producir éster etílico del ácido [benciloxicarbonil-(2-oxo-etil)-amino]-acético (1,65 g, 92%). MS: 280 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 9,60-9,68 (m, 1H), 7,26-7,40 (m, 5H), 5,10-5,19 (m, 2H), 4,00-4,22 (m, 6H), 1,18-1,30 (m, 3H). (véase Y.-L. Zhong, T. K. M. Shing *J. Org. Chem.* **1997**, *62* (8), 2622-2624).

Etapa 5: Se añade N-aminoftalimida (0,55 g, 3,4 mmol) a una solución de éster etílico del ácido benciloxicarbonil-(2-oxo-etil)-amino]-acético (0,72, 2,6 mmol) en 1,4-dioxano (10 ml), y la mezcla se calienta a reflujo en una atmósfera de N_2 durante 15 h. La mezcla de reacción se enfría a ta y se filtra a través de tierra de diatomeas. El filtrado se concentra. El residuo se disuelve de nuevo en $CHCl_3$ (30 ml) y se filtra de nuevo a través de tierra de diatomeas. Este filtrado se concentra para producir éster etílico del ácido (benciloxicarbonil-{2-[(E)-1,3-dioxo-1,3-dihidro-isoindol-2-ilimino]etil}-amino)-acético (~100%). MS: 424

(M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,77-8,88 (n, 1H), 7,80-7,93 (m, 2H), 7,67-7,80 (m, 2H), 7,23-7,40 (m, 5H), 5,09-5,21 (m, 2H), 4,25-4,45 (m, 2H), 3,97-4,25 (m, 4H), 1,12-1,32 (m, 3H).

Etapa 6: Una solución de éster etílico del ácido (benciloxicarbonil-{2-[(E)-1,3-dioxo-1,3-dihidro-isoindol-2-ilimino]etil}-amino)-acético (7,7 mmol) en CH_3CN (65 ml) se trata con cianoborohidruro sódico (1,92 g, 30,5 mmol) y se añade ácido acético (6,8 ml, 118,8 mmol) con agitación en una atmósfera de N_2. Después de 5,5 h, la solución de reacción se diluye con EtOAc (150 ml) y se lava con $KHCO_3$ acuoso saturado (3 x 50 ml) y NaCl acuoso saturado (50 ml). La fase orgánica se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice (gradiente de elución de 75:25 a 50:50 de heptano:acetato de etilo) para producir éster etílico del ácido {benciloxicarbonil-[2-(1,3-dioxo-1,3-dihidro-isoindol-2-ilamino)-etil]-amino}-acético en forma de un aceite (2,66 g, 81%). MS: 426 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,79-7,91 (m, 2H), 7,69-7,79 (m, 2H), 7,17-7,39 (m, 5H), 5,04-5,21 (m, 2H), 4,87-5,04 (m, 1H), 4,04-4,23 (m, 4H), 3,48-3,59 (m, 2H), 3,18-3,38 (m, 2H), 1,10-1,30 (m, 3H).

Etapa 7: Una solución de éster etílico del ácido {benciloxicarbonil-[2-(1,3-dioxo-1,3-dihidro-isoindol-2-ilamino)-etil]-amino}-acético (0,22 g, 0,52 mmol) en éter difenílico (3 ml) se calienta a reflujo durante 2 h. El éter difenílico se retira por destilación al vacío y el residuo se purifica por cromatografía ultrarrápida sobre gel de sílice (gradiente de elución de 2:1:1 a 1:1:1 de heptano:DCM:EtOAc) para producir éster bencílico del ácido 4-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-3-oxo-piperazina-1-carboxílico en forma de un sólido (0,126 g, 64%). MS: 380 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,86-7,95 (m, 2H), 7,75-7,86 (m, 2H), 7,24-7,42 (m, 5H), 5,20 (s, 2H), 4,42 (s, 2H), 3,90-4,05 (m, 2H), 3,65-3,87 (m, 2H).

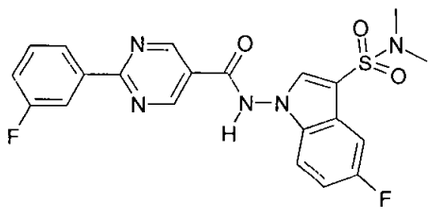
Etapa 8: A una solución de hidrocloruro de benzamidina hidrato (2 mmol) en DMF anhidra (4 ml) se le añade sal sódica de éster metílico del ácido 2-dimetoximetil-3-hidroxi-acrílico (0,46 g, 2,32 mmol) y la mezcla de reacción se calienta a 100ºC en una atmósfera de N2 durante 1 hora. La reacción se enfría a ta y se añade agua (15 ml). Después de la adición de agua, se observa la inmediata precipitación del producto. Los sólidos se recogen por filtración, se lavan con agua (2,5 ml) y se secan al vacío para producir éster metílico del ácido 2-fenil-pirimidina-5-carboxílico (0,32 g, 74%). (Véase: P. Zhichkin, D.J. Fairfax, S.A. Eisenbeis, Synthesis, 2002, 720-722).

Etapa 9: Una solución de éster metílico del ácido 2-fenil-pirimidina-5-carboxílico (3,15 g) y LiOH (0,71 g) en una mezcla de MeOH, THF y agua (1:1:1 en volumen, 120 ml) se agita a ta durante una noche. El MeOH y el THF se retiran por evaporación para dar una solución acuosa. La solución acuosa se acidifica con ácido clorhídrico al 5% para ajustar el pH entre 2,5 y 3, El precipitado se retira por filtración, se lava con agua y se seca al vacío para producir 2,94 g (~100%) de ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido. MS: 201 (M+H).

Etapa 10: Una solución de éster bencílico del ácido 4-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-3-oxo-piperazina-1-carboxílico (53 mg, 0,14 mmol) en MeOH (10 ml) se trata con hidrazina anhidra (0,3 ml, 9,56 mmol). La mezcla de reacción se agita a reflujo en una atmósfera de N_2 durante 3,5 h. La mezcla de reacción se concentra. El residuo se disuelve en una mezcla de DMF (2 ml) y DCM (2 ml) y se trata con cloruro de 2-fenil-pirimidina-5-carbonilo (32 mg, 0,15 mmol). La mezcla se agita en una atmósfera de N_2 durante 16 h y después se diluye con EtOAc (35 ml). La mezcla se lava sucesivamente con $KHCO_3$ acuoso saturado (15 ml), agua (2 x 15 ml) y NaCl acuoso saturado (15 ml), se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía ultrarrápida sobre gel de sílice (gradiente de elución de 80:20 a 0:100 de heptano:EtOAc) para producir éster bencílico del ácido 3-oxo-4-[(2-fenil-pirimidina-5-carbonil)-amino]-piperazina-1-carboxílico en forma de un aceite (111 mg, 18%). MS: 432 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 9,70-10,10 (a, 1H), 9,06 (s, 2H), 8,46 (dd, J = 7,8, 1,7 Hz, 2H), 7,44-7,60 (m, 3H), 7,25-7,40 (m, 5H), 5,18 (s, 2H), 4,36 (s, 2H), 3,93 (t, J = 5,1 Hz, 2H), 3,69-3,81 (s a, 2H). CI_{50} = 103,5 nM.

Ejemplo 21

(3-Dimetilsulfamoil-5-fluoro-indol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico



Etapa 1: Una solución de 5-fluoroindol (5,4 g) y cloruro de tolueno-4-sulfonilo (9,12 g) en tolueno (300 ml) se trata con una solución enfriada de gránulos de hidróxido sódico (23,2 g) en agua (200 ml) seguido del catalizador de hidrogenosulfato de tetrabutilamonio (400 mg). La mezcla se agita a ta durante 24 h. La fase orgánica se separa, se lava con agua y salmuera,

se seca ($MgSO_4$) y se concentra al vacío para producir 5-fluoro-1-(tolueno-4-sulfonil)-1H-indol (10,7 g, 78%). MS: 290 (M+H)

Etapa 2: Una solución de 5-fluoro-1-(tolueno-4-sulfonil)indol (5,2 g) en CH_3CN seco (80 ml) se enfría en un baño de hielo y se trata gota a gota con ácido clorosulfónico (12 ml). La mezcla de reacción se deja calentar a ta y se agita durante 24 h. La mezcla de reacción se vierte cuidadosamente sobre hielo/agua (300 ml). El precipitado se recoge por filtración y se lava con agua para producir 5-fluoro-3-clorosulfonil-1-(tolueno-4-sulfonil)-1H-indol (6,8 g, 98%) en forma de un sólido. MS: 386 (M-H).

Etapa 3: Una solución de 5-fluoro-3-clorosulfonil-1-(tolueno-4-sulfonil)indol (2,52 g) en DCM (75 ml) se añade a una solución acuosa de dimetilamina (al 40%, 20 ml) en agua (50 ml) y se agita a ta durante 20 h. La fase orgánica se separa, se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío para producir dimetilamida del ácido 5-fluoro-1-(tolueno-4-sulfonil)-1H-indolo-3-sulfónico (2,55 g, 99%) en forma de un sólido. MS: 397 (M+H).

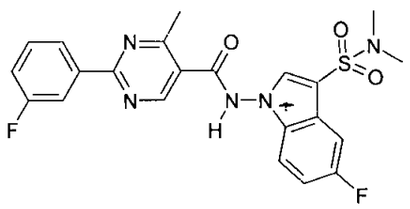
Etapa 4: Una mezcla de dimetilamida del ácido 5-fluoro-1-(tolueno-4-sulfonil)indolo-3-sulfónico (2,55 g) en MeOH (100 ml) y KOH (5 N 15 ml) se calienta a reflujo durante 1,5 horas. La mezcla de reacción se concentra al vacío. El residuo se diluye con agua (50 ml) y se acidifica a un valor de pH de ~3 con HCl acuoso 10 N. La mezcla se extrae con EtOAc. La capa orgánica se separa, se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío para producir dimetilamida del ácido 5-fluoro-1H-indolo-3-sulfónico (1,35 g, 87%) en forma de un sólido. MS: 241 (M-H).

Etapa 5: Una solución de dimetilamida del ácido 5-fluoro-1H-indolo-3-sulfónico (1,24 g) en DMF seca (50 ml) se enfría a 0°C y se trata en porciones con una dispersión al 60% en aceite de MaH (3,07 g). La mezcla se agita a 0°C durante 30 min. Se añade en porciones ácido hidroxilamina-O-sulfónico (2,9 g) y la mezcla se calienta a ta y se agita durante 5 h. La mezcla de reacción se vierte sobre hielo/agua y se extrae con EtOAc. La capa orgánica se separa, se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se tritura con éter. El sólido se recoge por filtración para producir dimetilamida del ácido 1-amino-5-fluoro-1H-indolo-3-sulfónico (0,53 g, 41%). MS: 258 (M+H).

Etapa 6: Una suspensión de ácido 2-(3-fluorofenil)-pirimidina-5-carboxílico (76 mg) en DCM seco (25 ml)/DMF seca (2 gotas) se trata con cloruro de oxalilo (0,15 ml) y se agita a ta durante 3,5 horas. La mezcla de reacción se concentra al vacío. El residuo se disuelve en tolueno (15 ml) y después se concentra al vacío. El residuo se seca en una bomba de alto vacío y después se disuelve en EtOAc (7 ml). La solución se añade a una mezcla de dimetilamida del ácido 1-amino-5-fluoro-1H-indolo-3-sulfónico (100 mg) y Na_2CO_3 (106 mg) en EtOAc (5 ml)/agua (5 ml). La mezcla se agita a ta durante 24 h. La fase orgánica se separa, se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 50% en heptano para producir (3-dimetilsulfamoil-5-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico (100 mg, 62%) en forma de un sólido. MS: 458 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,67 (s, 6H), 7,20-7,3 (m, 1H), 7,45-7,55 (m, 1H), 7,57-7,6 (dd, 1H), 7,65-7,75 (m, 2H), 8,2 (d, 1H), 8,38-8,4 (d, 2H), 9,45 (s, 2H), 12,6 (s, 1H).

Ejemplo 22

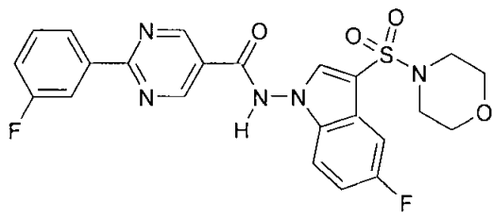
(3-Dimetilsulfamoil-5-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico



Una solución de ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico (116 mg) y HATU (190 mg) en DMF seca se trata con DIPEA (0,09 ml) y se agita a ta durante 40 min. Se añade dimetilamida del ácido 1-amino-5-fluoro-1H-indolo-3-sulfónico (192 mg) y la mezcla se agita a ta durante 24 h. La mezcla se concentra al vacío. El residuo se disuelve en EtOAc, se lava con NaOH acuoso 2 N, agua y salmuera, se seca ($MgSO_4$) y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 30% en heptano para producir (3-dimetilsulfamoil-5-fluoroindol-1-il)-amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico (85 mg, 40%) en forma de un sólido. MS: 472 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,68 (s, 6H), 2,79 (s, 3H), 7,25-7,35 (m, 1H), 7,45-7,55 (m, 1H), 7,57-7,80 (m, 3H), 8,20 (d, 1H), 8,35 (s, 1H), 8,47 (s, 2H), 9,28 (s, 1H), 12,40 (s, 1H).

Ejemplo 23

[5-Fluoro-3-(morfolina-4-sulfonil)indol-1-il]amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico



Etapa 1: Una solución de 5-fluoro-3-clorosulfonil-1-(tolueno-4-sulfonil)-1H-indol (1 g) en DCM se añade a una solución de morfolina (2,26 ml) en agua (50 ml) y se agita a ta durante 5 h. La fase orgánica se separa, se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío para producir 5-fluoro-3-(morfolina-4-sulfonil)-1-(tolueno-4-sulfonil)-1H-indol (1,3 g, ~100%). MS: 439 (M+H).

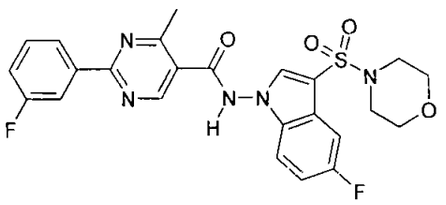
Etapa 2: Una solución de 5-fluoro-3-(morfolina-4-sulfonil)-1-(tolueno-4-sulfonil)-1H-indol (1,3 g) en MeOH (50 ml)/KOH 5 N (3 ml) se calienta a reflujo durante 1 h. La mezcla de reacción se concentra al vacío. El residuo se diluye con agua (30 ml) y se acidifica con HCl acuoso 10 N a un valor de pH de ~4. La mezcla se extrae con EtOAc. La capa orgánica se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío para producir 5-fluoro-3-(morfolina-4-sulfonil)-1H-indol (0,8 g, 95%) en forma de un sólido. MS: 285 (M+H).

Etapa 3: Siguiendo procedimientos similares a los del Ejemplo 21, etapa 5, pero sustituyendo dimetilamida del ácido 5-fluoro-1H-indolo-3-sulfónico por 5-fluoro-3-(morfolina-4-sulfonil)-1H-indol, y purificando el producto por cromatografía sobre gel de sílice eluyendo con EtOAc al 20%, se prepara 1-amino-5-fluoro-3-(morfolina-4-sulfonil)-1H-indol (16%) en forma de un sólido. MS: 300 (M+H).

Etapa 4: Siguiendo procedimientos similares a los del Ejemplo 21, etapa 6, pero sustituyendo dimetilamida del ácido 1-amino-5-fluoro-1H-indolo-3-sulfónico por 1-amino-5-fluoro-3-(morfolina-4-sulfonil)-1H-indol, se prepara [5-fluoro-3-(morfolina-4-sulfonil)indol-1-il]amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico (27%) en forma de un sólido. MS: 500 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,95 (m, 4H), 3,67 (m, 4H), 7,25-7,35 (m, 1H), 7,45-7,55 (m, 1H), 7,57-7,60 (dd, 1H), 7,62-7,72 (c, 1H), 7,75-7,80 (c, 1H), 8,20 (d, 1H), 8,35-8,40 (d, 1H), 8,41 (s, 1H), 9,45 (s, 2H), 12,6 (s, 1H).

Ejemplo 24

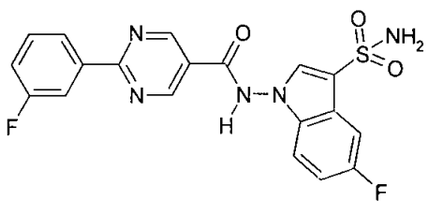
[5-Fluoro-3-(morfolina-4-sulfonil)indol-1-il]amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 22, pero sustituyendo dimetilamida del ácido 1-amino-5-fluoro-1H-indolo-3-sulfónico por 1-amino-5-fluoro-3-(morfolina-4-sulfonil)-1H-indol, se prepara [5-fluoro-3-(morfolina-4-sulfonil)indol-1-il]amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico (48%) en forma de un sólido. MS: 512 (M-H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,80 (s, 3H), 2,95 (m, 4H), 3,67 (m, 4H), 7,25-7,35 (m, 1H), 7,45-7,55 (m, 1H), 7,57-7,60 (m, 1H), 7,62-7,72 (m, 1H), 7,75-7,80 (m, 1H), 8,15-8,20 (d, 1H), 8,30-8,35 (d, 1H), 8,45 (s, 1H), 9,30 (s, 1H), 12,4 (s, 1H).

Ejemplo 25

[5-Fluoro-3-sulfamoilindol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico



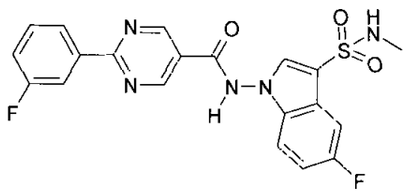
Etapa 1: Una solución de (5-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico (0,35 g) en CH_3CN seco (20 ml) se trata con ácido clorosulfónico (0,5 ml) y se agita a ta durante 24 h. La mezcla de reacción se vierte sobre hielo/agua (150 ml) y se extrae con EtOAc. La capa orgánica se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío para producir cloruro de 5-fluoro-1-{[2-(3-fluorofenil)pirimidina-5-carbonil]amino}-1H-indolo-3-sulfonilo (0,43 g, 95%). MS: 449 (M+H).

Etapa 2: Una solución de cloruro de 5-fluoro-1-{[2-(3-fluorofenil)pirimidina-5-carbonil]amino}-1H-indolo-3-sulfonilo (0,14 g) en DCM (20 ml) se trata con una solución acuosa de amoniaco (28%-5 ml) en agua (15 ml) y se agita a ta durante 24 h. La mezcla de reacción se acidifica con HCl acuoso 10 N a un valor de pH de ~3 y se extrae con DCM. La capa orgánica se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío.

El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 50% en heptano para producir [5-fluoro-3-sulfamoilindol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico (10 mg, 8%) en forma de un sólido. MS: 430 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 7,20-7,30 (m, 1H), 7,40-7,50 (m, 2H), 7,60-7,72 (m, 2H), 8,10 (s, 1H), 8,19-8,22 (d, 1H), 8,33-8,37 (d, 1H), 9,44 (s, 1H), 12,45 (s, 1H).

Ejemplo 26

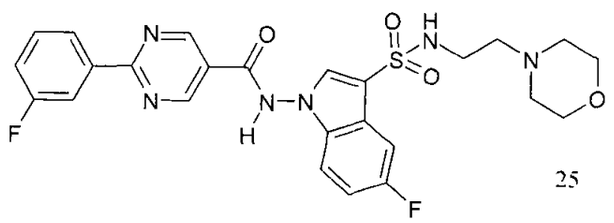
[5-Fluoro-3-metilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 25, pero sustituyendo la solución acuosa de amoniaco por metilamina acuosa al 40%, se prepara [5-fluoro-3-metilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico (60%) en forma de un sólido. MS: 444 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,45 (d, 3H), 7,20-7,30 (m, 1H), 7,40-7,50 (m, 2H), 7,60-7,70 (m, 3H), 8,19-8,22 (d, 1H), 8,24 (s, 1H), 8,34-8,37 (d, 1H), 9,44 (s, 1H), 12,50 (s, 1H).

Ejemplo 27

[5-Fluoro-3-(2-morfolin-4-iletilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico

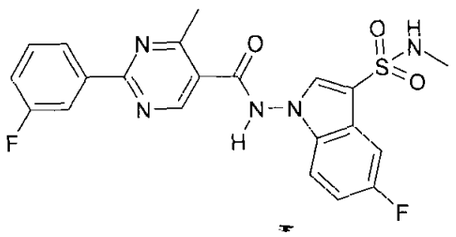


25

Siguiendo procedimientos similares a los del Ejemplo 25, pero sustituyendo la solución acuosa de amoniaco por una solución acuosa de 2-(morfolin-4-il)etilamina, se prepara [5-fluoro-3-(2-morfolin-4-iletilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico (35%). MS: 543 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,20-2,38 (m, 6H), 2,89-2,95 (c, 2H), 3,40-3,50 (s, 4H), 7,20-7,30 (m, 1H), 7,42-7,55 (m, 2H), 7,63-7,70 (m, 3H), 8,19-8,22 (d, 1H), 8,26 (s, 1H), 8,34-8,37 (d, 1H), 9,44 (s, 2H), 12,40-12,60 (s, 1H).

Ejemplo 28

[5-Fluoro-3-metilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico



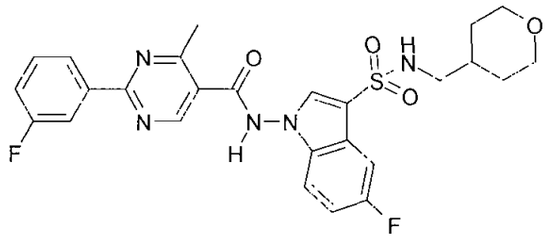
Etapa 1: Una solución de (5-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico (1 g, 2,75 mmol) en CH_3CN seco se enfría a 0ºC, se trata gota a gota con ácido clorosulfónico (0,55 ml) y se agita durante 2 horas.El sólido precipitado se retira por filtración y se lava con éter para producir ácido 5-fluoro-1-{[2-(3-fluorofenil)-4-metilpirimidina-5-carbonil]amino}-1H-indolo-3-sulfónico (1,06 g, 87%) en forma de un sólido blanquecino. MS: 443 (MH-).

Etapa 2: A una suspensión de ácido 5-fluoro-1-{[2-(3-fluorofenil)-4-metilpirimidina-5-carbonil]amino}-1H-indolo-3-sulfónico (1,06 g) en DCM (60 ml) a 0ºC se le añade DMF seca (10 gotas). Se añade gota a gota cloruro de oxalilo (1,05 ml) y la mezcla se agita a 0ºC durante 3 h. La mezcla se filtra y el sólido recogido se lava con éter para producir cloruro de 5-fluoro-1-{[2-(3-fluorofenil)-4-metilpirimidina-5-carbonil]amino}-1H-indolo-3-sulfonilo (0,94 g). MS: 461 (M-H)

Etapa 3: Siguiendo procedimientos similares a los del Ejemplo 25, etapa 2, pero sustituyendo la solución acuosa de amoniaco por metilamina acuosa al 40%, y sustituyendo cloruro de 5-fluoro-1-{[2-(3-fluorofenil)pirimidina-5-carbonil]amino}-1H-indolo-3-sulfonilo por cloruro de 5-fluoro-1-{[2-(3-fluorofenil)-4-metilpirimidina-5-carbonil]amino}-1H-indolo-3-sulfonilo, se prepara [5-fluoro-3-metilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico (40 mg, 35%) en forma de un sólido. MS: 456 (M-H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,45 (d, 3H), 2,80 (s, 3H), 7,20-7,30 (m, 1H), 7,40-7,50 (m, 2H), 7,60-7,70 (m, 3H), 8,17-8,20 (d, 1H), 8,30-8,35 (d, 2H), 9,28 (s, 1H), 12,30 (s, 1H).

Ejemplo 29

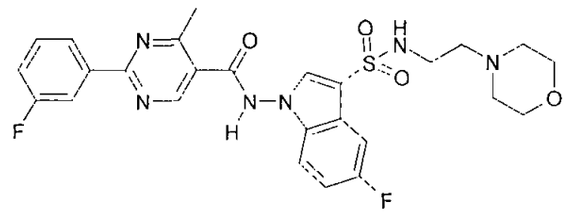
{5-Fluoro-[(3-tetrahidropiran-4-ilmetil)sulfamoil]indol-1-il}amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 25, etapa 2, pero sustituyendo la solución acuosa de amoniaco por una solución acuosa de 4-aminometiltetrahidropirano, y sustituyendo cloruro de 5-fluoro-1-{[2-(3-fluorofenil)pirimidina-5-carbonil]amino}-1H-indolo-3-sulfonilo por cloruro de 5-fluoro-1-{[2-(3-fluorofenil)-4-metilpirimidina-5-carbonil]amino}-1H-indolo-3-sulfonilo, se prepara {5-fluoro-[(3-tetrahidropiran-4-ilmetil)sulfamoil]indol-1-il}amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico en forma de un sólido. MS: 542 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,00-1,15, (m, 2H), 1,50-1,70, (m, 3H), 2,60-2,70, (t, 2H), 2,80, (s, 1H), 3,1-3,2, (t, 2H), 3,70-3,80, (dd, 2H), 7,20-7,30, (m, 1H), 7,40-7,50, (m, 1H), 7,60-7,70, (m, 4H), 8,16-8,20, (d, 1H), 8,28-8,34 (d, 2H), 9,28, (s, 1H), 12,25, (s, 1H).

Ejemplo 30

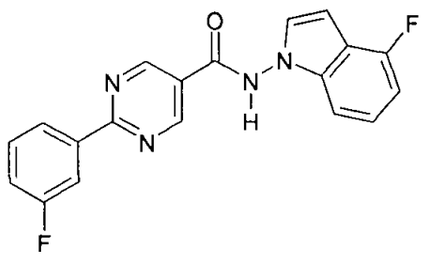
[5-Fluoro-3-(2-morfolin-4-iletilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 25, etapa 2, pero sustituyendo la solución acuosa de amoniaco por una solución acuosa de 2-(morfolin-4-il) etilamina, y sustituyendo cloruro de 5-fluoro-1-{[2-(3-fluorofenil)pirimidina-5-carbonil]amino}-1H-indolo-3-sulfonilo por cloruro de 5-fluoro-1-{[2-(3-fluorofenil)-4-metilpirimidina-5-carbonil]amino}-1H-indolo-3-sulfonilo, se prepara [5-fluoro-3-(2-morfolin-4-iletilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico (58%) MS: 557 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,20-2,30 (s, 4H), 2,30-2,40 (t, 2H), 2,80 (s, 3H), 2,89-2,95 (c, 2H), 3,40-3,50 (s, 4H), 7,20-7,30 (m, 1H), 7,42-7,55 (m, 2H), 7,63-7,70 (m, 3H), 8,17-8,20 (d, 1H), 8,32-8,35 (d, 2H), 9,28 (s, 2H), 12,25-12,30 (s, 1H).

Ejemplo 31

(4-Fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico

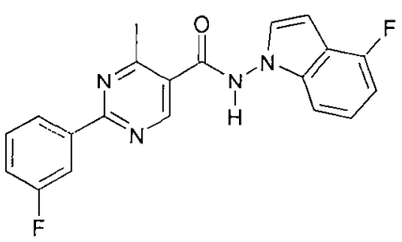


Etapa 1: El producto bruto de 1-amino-4-fluoroindol se prepara de acuerdo con los procedimientos descritos en J.Hymes et al., J.O.C., (2004), 69, 1368-1371. Después, el producto bruto se purifica por cromatografía sobre gel de sílice eluyendo con DCM al 30% en heptano para producir 1-amino-4-fluoroindol (43%). MS: 151 (M+H).

Etapa 2: Una solución de ácido 2-(3-fluorofenil)-pirimidina-5-carboxílico (0,33 g), HATU (0,67 g) e hidroxiazabenzotriazol (0,26 g) en DMF seca (15 ml) se agita a ta durante 30 min en una atmósfera de N_2. Se añade una solución de 1-amino-4-fluoroindol (0,24 g) en DMF seca (5 ml) seguido de la adición de DIPEA (0,39 ml). La mezcla se agita a 80°C durante 24 h, se enfría a ta y después se concentra al vacío. El residuo se disuelve en EtOAc, se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con DCM al 60%/heptano para producir (4-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico (0,24 g, 53%) en forma de un sólido. MS: 351 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 6,64 (d, 1H), 6,89-6,92 (c, 1H), 7,15-7,22 (m, 1H), 7,31-7,33 (d, 1H), 7,46-7,52 (m, 1H), 7,56 (d, 1H), 7,63-7,70 (c, 1H), 8,18-8,23 (d, 1H), 8,34-8,37 (d, 1H), 9,45 (s, 2H), 12,30 (s, 1H). CI_{50} = 11 nM.

Ejemplo 32

(4-Fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico

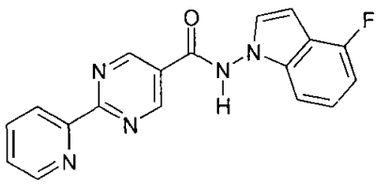


Siguiendo procedimientos similares a los del Ejemplo 31, etapa 2, pero sustituyendo ácido 2-(3-fluorofenil)-pirimidina-5-carboxílico por ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico, se prepara (4-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico (63%) en forma de un sólido. MS: 365 (M-H); ^{1}H RMN (300

MHz, DMSO-d_6): δ 2.75 (σ, 3H), 6,61 (d, 1H), 6,86-6,92 (c, 1H), 7,15-7,22 (m, 1H), 7,30-7,32 (d, 1H), 7,40-7,46 (m, 1H), 7,56-7,65 (m, 2H), 8,13-8,16 (d, 1H), 8,28-8,31 (d, 1H), 9,21 (s, 1H), 12,05 (s, 1H).

Ejemplo 33

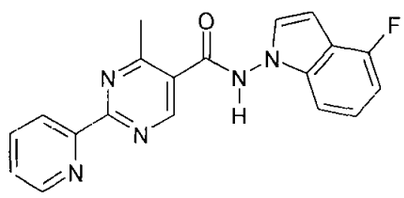
(4-Fluoroindol-1-il)amida del ácido 2-(piridin-2-il)-pirimidina-5-carboxílico



Una suspensión de cloruro de 2-(piridina-2-il)-pirimidina-5-carbonilo (0,44 g) en EtOAc (20 ml) se añade en porciones a una mezcla de 1-amino-4-fluoroindol (0,30 g) y K_2CO_3 (0,276 g) en EtOAc (10 ml)/agua (20 ml) y la mezcla resultante se agita a ta durante 24 h. La fase acuosa se separa y se extrae dos veces con EtOAc. La capa orgánica combinada se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc para producir (4-fluoroindol-1-il)amida del ácido 2-(piridin-2-il)pirimidina-5-carboxílico (0.115 g, 17%) en forma de un sólido. MS: 334 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 6,65 (d, 1H), 6,89-6,95 (c, 1H), 7,16-7,23 (m, 1H), 7,32-7,35 (d, 1H), 7,57 (d, 1H), 7,57-7,64 (m, 1H), 8,02-8,08 (t, 1H), 8,50-8,52 (d, 1H), 8,82-8,83 (d, 1H), 9,49 (s, 2H), 12,30 (s, 1H).

Ejemplo 34

(4-Fluoroindol-1-il)amida del ácido 2-(piridin-2-il)-4-metilpirimidina-5-carboxílico

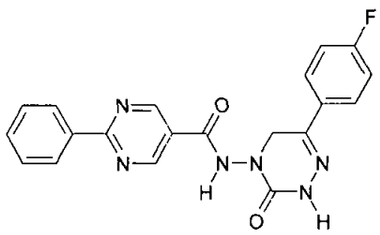


Una solución de ácido 2-(piridina-2-il)-4-metilpirimidina-5-carboxílico (0,11 g) y HATU (0,19 g) en DMF seca (7 ml) se trata con DIPEA (0,09 ml) y se agita a ta en una atmósfera de N_2 durante 30 min. Se añade 1-amino-4-fluoroindol (0,112 g) y la mezcla se agita a ta durante 24 h. La mezcla se concentra al vacío. El residuo se disuelve en EtOAc, se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 75% para producir (4-fluoroindol-1-il)amida del ácido 2-(piridin-2-il)-4-metilpirimidina-5-carboxílico (0,085 g, 50%). MS:

348 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,82 (s, 3H), 6,65 (d, 1H), 6,93-6,97 (c, 1H), 7,19-7,26 (m, 1H), 7,35-7,38 (d, 1H), 7,62 (d, 1H), 7,74-7,78 (m, 1H), 8,20-8,25 (t, 1H), 8,58-8,61 (d, 1H), 8,85-8,86 (d, 1H), 9,33 (s, 1H), 12,15 (s, 1H).

Ejemplo 35

[6-(4-Fluoro-fenil)-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico



Etapa 1: Siguiendo los procedimientos descritos en F. Chau, J.-C. Malanda, y R. Milcent *J. Heterocyclic Chem.* **1997**, *34*, 1603-1606, se prepara 5-metil-3H-1,3,4-oxadiazol-2-ona (24%). MS: 101 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 9,76 (s a, 1H), 2,28 (s, 3H).

Etapa 2: A una solución de 5-metil-3H-1,3,4-oxadiazol-2-ona (2,77 g, 27,7 mmol) en MeOH (25 ml) se le añade una solución al 25% en peso de NaOMe en metanol (6,4 ml, 27,9 mmol) y la mezcla se agita a ta durante 10 min. La mezcla se concentra al vacío y el residuo se añade a una solución de 2-cloro-4'-fluoroacetofenona (4,71 g, 27,3 mmol) y bromuro de tetrabutilamonio (0,174 g, 0,54 mmol) en $CHCl_3$ (16 ml). La mezcla se calienta a reflujo durante 2,5 h en una atmósfera de N_2. Después, la mezcla de reacción se deja enfriar y se agita durante una noche a temperatura ambiente. La suspensión resultante se filtra a través de papel de filtro cualitativo y el filtrado se concentra para obtener un líquido. Este líquido se filtra adicionalmente a través de una capa de gel de sílice, eluyendo con 1:1 de EtOAc/DCM. El filtrado se concentra al vacío para producir 3-[2-(4-fluoro-fenil)-2-oxo-etil]-5-metil-3H-1,3,4-oxadiazol-2-ona (~†00%). MS: 237 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,90-8,10 (m, 2H), 7,10-7,22 (m, 2H), 5,08 (s, 2H), 2,29 (s, 3H).

Etapa 3: A una solución de 3-[2-(4-fluoro-fenil)-2-oxo-etil]-5-metil-3H-1,3,4-oxadiazol-2-ona (2,3 g, 9,7 mmol) en una mezcla de 2-propanol (12 ml) y agua (0,3 ml) se le añade hidrazina monohidrato (0,71 ml, 14,6 mmol). La mezcla de reacción se calienta a reflujo en una atmósfera de N_2 durante 14,5 h y después se añade una solución de ácido oxálico (0,3 g, 3,3 mmol) en 2-propanol (6 ml). El precipitado resultante se retira por filtración. El filtrado se concentra hasta alcanzar un volumen de ~35 ml y después se enfría para producir N-[6-(4-

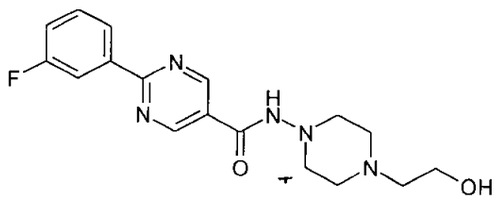
fluoro-fenil)-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il]-acetamida en forma de un cristal que se recoge por filtración (0,83 g, 34%). MS: 251 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6) δ 10,37 (s, 1H), 10,16 (s, 1H), 7,65-7,79 (m, 2H), 7,16-7,27 (m, 2H), 4,57 (s, 2H), 1,90 (s, 3H).

Etapa 4: A una suspensión de N-[6-(4-fluoro-fenil)-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il]-acetamida (0,48 g, 1,9 mmol) en MeOH (5 ml) se le añade HCl acuoso al 37%. La mezcla se calienta a reflujo durante 3 h y después se enfría a ta. La mezcla se basifica con NaOH acuoso 1 M a un valor de pH de ~12. El precipitado resultante se recoge por filtración y se seca para producir 4-amino-6-(4-fluoro-fenil)-4,5-dihidro-2H-1,2,4-triazin-3-ona (0,35 g, 88%). MS: 209 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6) δ 10,17 (s, 1H), 7,67-7,75 (m, 2H), 7,18-7,29 (m, 2H), 4,75 (s, 2H), 4,45 (s, 2H).

Etapa 5: A una suspensión de 4-amino-6-(4-fluoro-fenil)-4,5-dihidro-2H-1,2,4-triazin-3-ona (0,26 g, 1,23 mmol), ácido 2-fenil-pirimidina-5-carboxílico (0,25 g, 1,23 mmol) y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0,37 g, 1,94 mmol) en DMF (12 ml) se le añade Et_3N (0,2 ml, 1,435 mmol) en una atmósfera de N_2 y la mezcla de reacción se agita a ta durante 49 h. La mezcla se diluye con EtOAc (120 ml) y se lava sucesivamente con NH_4Cl acuoso saturado (2 x 50 ml), agua (2 x 50 ml) y NaCl acuoso saturado (50 ml). La fase orgánica se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se tritura con EtOH (30 ml) para producir [6-(4-fluoro-fenil)-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico (0,12 g, 25%). MS: 391 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6) δ 11,25 (s, 1H), 10,58 (s, 1H), 9,31 (s, 2H), 8,47 (dd, J = 7,7, 1,8 Hz, 2 H), 7,70-7,86 (m, 2 H), 7,49-7,67 (m, 3H), 7,18-7,34 (m, 2H), 4,77.

Ejemplo 36

[4-(2-Hidroxi-etil)-piperazin-1-il]-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico

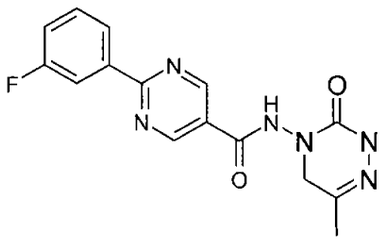


A una solución de ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (0,28 g, 1,4 mmol) en DCM anhidro (10 ml) a 0°C se le añade el cloruro de oxalilo (0,18 ml, 1,4 mmol) seguido de la adición de DMF (0,11 ml). La mezcla se agita a 0°C durante 30 min y después se deja

calentar a ta y se agita durante 30 min. La mezcla se concentra al vacío. El residuo se disuelve en DCM anhidro (10 ml). Se añade 2-(4-amino-piperazin-1-il)-etanol (0,145 g, 1 mmol) a ta seguido de la adición de NMP (0,19 ml, 2 mmol). La mezcla se agita a ta durante 2 h y la mezcla después se concentra al vacío. El residuo se tritura en Et_2O y el sólido resultante se recoge por filtración para producir [4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (0,16 g). MS: 346 (M+H).

Ejemplo 37

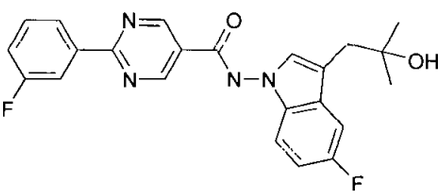
(6-Metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



A una solución de ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (0,317 g, 1,45 mmol) en DMF anhidra (5 ml) se le añade 4-amino-6-metil-4,5-dihidro-2H-[1,2,4]triazin-3-ona (0,206 g, 1,45 mmol) seguido de la adición de DMTMM (0,421 g, 1,52 mmol). La mezcla se agita a ta durante una noche. La mezcla se reparte entre una solución acuosa saturada de $NaHCO_3$ y EtOAc. La fase orgánica se separa, se seca ($MgSO_4$), se filtra y se concentra al vacío para producir (6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (0,306 g) en forma de un sólido. MS: 329 (M+H).

Ejemplo 38

[5-Fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



Etapa 1: Una solución de ácido (5-fluoro-1H-indol-3-il)-acético (1 g, 5,2 mmol) en MeOH (20 ml) se trata con ácido sulfúrico (20 µl) y se agita a ta durante 1 h. Esta mezcla se trata con $NaHCO_3$ acuoso al 10% (200 µl) y después se concentra al vacío para producir éster metílico del ácido (5-fluoro-1H-indol-3-il)-acético, que se usa en la siguiente etapa sin

purificación adicional. MS: 208 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 3,68 (s, 3H), 3,72 (s, 2H), 6,86 (m, 1H), 7,16 (m, 1H), 7,21 (s, 1H), 7,28 (m, 1H).

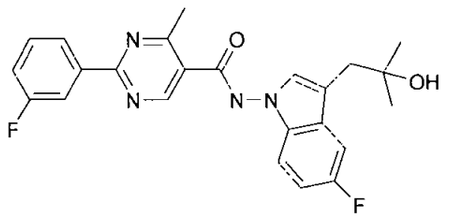
Etapa 2: El éster metílico del ácido (5-fluoro-1H-indol-3-il)-acético anterior se disuelve en THF (40 ml), se enfría a 0°C y se trata con MeMgBr (18,5 ml, 26 mmol, 1,4 M en PhMe/THF (3:1)). La mezcla se agita a ta durante 12 h. Se añade más cantidad de MeMgBr (5 ml, 7 mmol) y la mezcla se agita a ta durante 6 h. La mezcla se vierte sobre hielo/agua, se extrae con EtOAc (100 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 20% - 70% en heptano para producir 1-(5-fluoro-1H-indol-3-il)-2-metil-propan-2-ol (0,65 g, 60%). MS: 208 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,28 (s, 6H), 2,87 (s, 2H), 6,94 (m, 1H), 7,14 (m, 1H), 7,26-7,30 (m, 2H).

Etapa 3: Una solución de 1-(5-fluoro-1H-indol-3-il)-2-metil-propan-2-ol (207 mg, 1 mmol) en DMF (10 ml) se enfría a 0°C, se trata con NaH (600 mg, 15 mmol, al 60% en aceite mineral) y se agita durante 30 min. Se añade en porciones H_2NOSO_3H (565 mg, 5 mmol) y la mezcla se calienta a ta durante 2 h. La mezcla se diluye con EtOAc (100 ml), se inactiva con agua, se extrae con EtOAc, se seca (Na_2SO_4), se filtra y se concentra al vacío para producir 1-(1-amino-5-fluoroindol-3-il)-2-metil-propan-2-ol, que se usa en la siguiente etapa sin purificación adicional.

Etapa 4: Una solución de ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (175 mg, 0,8 mmol) en DCM (5 ml) se trata con DMF (20 µl) y ClCOCOCl (348 µl, 4 mmol) y se agita a ta durante 3 h. Se añade tolueno (10 ml) y la mezcla se concentra al vacío. El residuo se añade a una solución del 1-(1-amino-5-fluoroindol-3-il)-2-metil-propan-2-ol anterior y Na_2CO_3 (1 g) en EtOAc/H_2O (20 ml, 1:1). La mezcla se agita a ta durante 12 h. Después, la mezcla se diluye con Na_2CO_3 acuoso saturado y se extrae con EtOAc. La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 30% - 50% en heptano para producir [5-fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (160 mg, 50%). MS: 423 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,14 (s, 6H), 2,77 (s, 2H), 7,03 (m, 1H), 7,33 (s, 1H), 7,35-7,55 (m, 3H), 7,65 (m, 1H), 8,21 (m, 1H), 8,36 (m, 1H), 9,43 (s, 2H).

Ejemplo 39

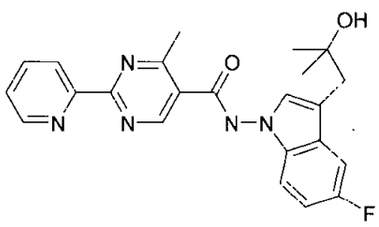
[5-Fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (250 mg, 1,07 mmol) en DCM (10 ml) se enfría a 0°C, se trata con DMF (20 µl) y ClCOCOCl (280 µl, 3,21 mmol) y se agita a ta durante 20 min. Se añade tolueno (10 ml) y la mezcla se concentra al vacío. El residuo se disuelve en piridina (10 ml) y se trata con DMAP (5 mg) y 1-(1-amino-5-fluoroindol-3-il)-2-metil-propan-2-ol (0,72 mmol). La mezcla se agita a ta durante 12 h. Después, la mezcla se diluye con Na_2CO_3 acuoso saturado y se extrae con EtOAc. La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 20% - 60% en heptano para producir [5-fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (218 mg, 70%). MS: 437 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,14 (s, 6H), 2,77 (s, 2H), 3,29 (s, 3H), 7,03 (m, 1H), 7,37 (s, 1H), 7,35-7,55 (m, 3H), 7,65 (m, 1H), 8,19 (m, 1H), 8,34 (m, 1H), 9,22 (s, 1H).

Ejemplo 40

[5-Fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico

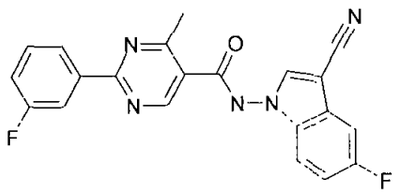


Una solución de ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (748 mg, 3,48 mmol) en DMF (30 ml) se trata con HATU (1,3 g, 3,48 mmol) y DIPEA (1,2 ml, 6,96 mmol) y la mezcla se agita a ta durante 30 min. Se añade 1-(1-amino-5-fluoroindol-3-il)-2-metil-propan-2-ol (2,9 mmol) y la mezcla se agita a 80°C durante 12 h. La mezcla se diluye con EtOAc, se lava con NH_4Cl acuoso saturado y Na_2CO_3 acuoso saturado, se seca (Na_2SO_4), se filtra y se concentra al vacío para producir [5-fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del

ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (990 mg, 81%). MS: 420 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 1,13 (s, 6H), 2,75 (s, 2H), 2,85 (s, 3H), 6,84 (m, 1H), 7,24 (m, 1H), 7,37 (m, 1H), 7,53 (m, 1H), 7,95 (s, 1H), 7,98 (m, 1H), 8,44 (m, 1H), 8,76 (m, 1H), 9,15 (s, 1H).

Ejemplo 41

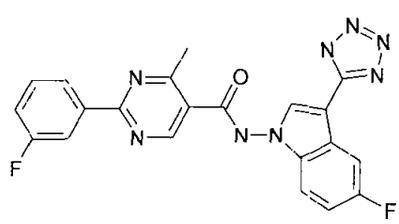
(3-ciano-5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Una solución de (5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (300 mg, 0,82 mmol) en THF (8 ml) se enfría a 0°C, se trata con isocianato de clorosulfonilo (86 µl, 0,99 mmol) y la mezcla se agita a ta durante 1 h. La mezcla se trata con Et_3N (138 µl, 0,99 mmol) y se agita durante 1 h. La mezcla se diluye con salmuera y se extrae con EtOAc. La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 25% - 35% en heptano para producir (3-ciano-5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (120 mg, 38%). MS: 390 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,78 (s, 3H), 7,32 (m, 1H), 7,46 (m, 1H), 7,55 (m, 1H), 7,66 (m, 1H), 7,77 (m, 1H), 8,20 (m, 1H), 8,35 (m, 1H), 8,65 (s, 1H), 9,28 (s, 1H).

Ejemplo 42

[5-Fluoro-3-(1H-tetrazol-5-il)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

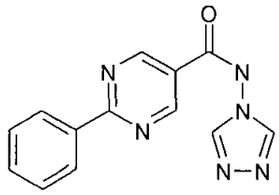


Una solución de (3-ciano-5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (120 mg, 0,31 mmol), $TMSN_3$ (62 µl, 0,465 mmol) y TBAF (0,155 µl, 0,155 mmol, 1 M en THF) en tolueno (3 ml) se calienta a 80°C durante 18 h. La mezcla se enfría, se diluye con EtOAc y se lava con HCl 1 M. La capa orgánica se extrae con

Na_2CO_3. La capa acuosa se acidifica a un valor de pH de ~3 con HCl acuoso 3 N y se extrae con EtOAc. La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío para producir [5-fluoro-3-(1H-tetrazol-5-il)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (100 mg, 75%). MS: 433 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,81 (s, 3H), 7,28 (m, 1H), 7,47 (m, 1H), 7,67 (m, 1H), 7,73 (m, 1H), 8,01 (m, 1H), 8,21 (m, 1H), 8,33 (m, 1H), 8,36 (s, 1H), 9,33 (s, 1H). CI_{50} = 5 nM.

Ejemplo 43

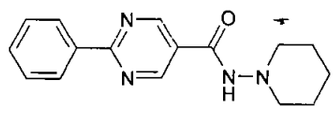
[1,2,4]Triazol-4-ilamida del ácido 2-fenil-pirimidina-5-carboxílico



A una solución de ácido 2-fenil-pirimidina-5-carboxílico (300 mg, 1,5 mmol) en DCM (10 ml) se le añaden 1-[3-(dimetilamino)propil-3-etilcarbodiimida (316 mg, 1,65 mmol) y N-hidroxibenzotriazol (223 mg, 1,65 mmol) a ta y la mezcla se agita durante 10 min. Se añade 4-amino-4H-1,2,4-triazol (252 mg, 3 mmol) y la mezcla se agita a ta durante 3 días. El precipitado resultante se filtra, se lava con DCM y agua y se seca en una estufa de vacío a 40°C durante una noche para producir [1,2,4]triazol-4-ilamida del ácido 2-fenil-pirimidina-5-carboxílico (270 mg) en forma de un sólido. MS: 267 (M+H); ^{1}H RMN (300 MHz, DMSO): δ = 7,59 (m, 3H), 8,50 (d, 2H), 8,84 (s, 2H), 9,36 (s, 2H). CI_{50} = 262,5 nM.

Ejemplo 44

Piperidin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico



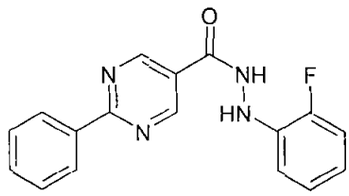
Método A: A una solución de ácido 2-fenil-pirimidina-5-carboxílico (150 mg, 075 mmol) en DCM (10 ml) se le añaden 1-[3-(dimetilamino)propil-3-etilcarbodiimida (158 mg, 0,83 mmol) y N-hidroxibenzotriazol (112 mg, 0,83 mmol) a ta y la mezcla se agita durante 10 min. Se añade 1-aminopiperidina (150 mg, 1,5 mmol). La mezcla se agita a ta durante una noche. La mezcla se lava con HCl acuoso 2 N (5 ml), $NaHCO_3$ acuoso saturado (5 ml) y agua (5 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10% en heptano para producir

piperidin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico (125 mg) en forma de un sólido. MS: 290 (M+H).

Método B: Siguiendo procedimientos similares a los del Ejemplo 127 pero sustituyendo éster metílico del ácido 3-[3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por piperidin-1-ilamina, se prepara piperidin-1-il-amida del ácido 2-fenil-pirimidina-5-carboxílico (72%) en forma de un sólido. MS: 283 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,35-1,98 (m, 6H), 2,20-3,60 (m, 4H), 6,60-7,17 (d, N-H), 7,52 (s, 3H), 8,52 (s, 2H), 9,07-9,39 (d, 2H).

Ejemplo 45

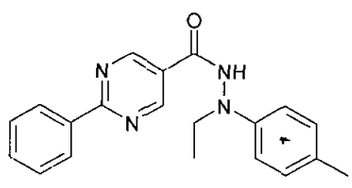
N'-(2-Fluoro-fenil)-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 44, pero sustituyendo 1-aminopiperidina por (2-fluoro-fenil)-hidrazina, se prepara N'-(2-fluoro-fenil)-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido. MS: 309 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 6,68 (ancho, 1H), 6,87 (m, 1H), 7,04 (m, 3H), 7,51 (m, 3H), 8,51 (m, 2H), 9,36 (s, 2H), 10,65 (ancho, 1H). CI_{50} = 12 nM.

Ejemplo 46

N'-Etil-N'-tolil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico

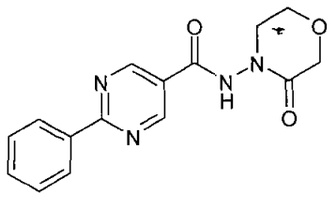


Siguiendo procedimientos similares a los del Ejemplo 44, pero sustituyendo 1-aminopiperidina por N-etil-N-para-tolil-hidrazina, se prepara N'-etil-N'-tolil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido. MS: 333 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ = 0,87 (t, 1H), 1,11 (t, 2H), 1,28 (t, 3H), 2,28 (d, 3H), 3,46 (c, 1H),

3,65 (c, 1H), 6,84 (d, 1H), 6,94 (d, 1H), 7,10 (t, 2H), 7,52 (m, 3H), 8,47 (m, 2H), 9,12 (s, 1H0, 9,23 (s, 1H).

Ejemplo 47

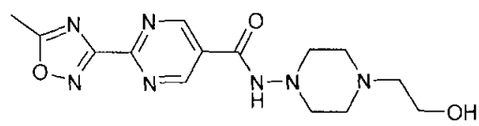
(3-Oxo-morfolin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 44, pero sustituyendo 1-aminopiperidina por 4-amino-morfolin-3-ona, se prepara (3-oxo-morfolin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido. MS: 299 (M+H); ^{1}H RMN (300 MHz, DMSO): δ = 3,66 (m, 2H), 4,00 (m, 2H), 4,26 (s, 2H), 7,60 (m, 3H), 8,47 (m, 2H), 9,29 (s, 2H), 11,27 (s, 1H). CI_{50} = 55 nM.

Ejemplo 48

[4-(2-Hidroxi-etil)-piperazin-1-il]-amida del ácido 2-(5-metil-[1,2,4]oxadiazol-3-il)-pirimidina-5-carboxílico



Etapa 1: A una solución del éster metílico del ácido 2-metilsulfanil-pirimidina-5-carboxílico 1 (1 g, 5,43 mmol) en DCM (60 ml) se le añade en porciones MCPBA (2,81 g, 16,29 mmol) a ta. La solución resultante se agita a ta durante una noche. Se añade una solución de $Na_2S_2O_3$ (1,6 g) en agua (60 ml). La mezcla se agita a ta durante 20 min. La capa se separa y la capa de agua se extrae con DCM (2 x 20 ml). La capa de DCM combinada se lava con $NaHCO_3$ saturado (3 x 20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío para producir éster metílico del ácido 2-metanosulfonil-pirimidina-5-carboxílico en forma de un sólido (1,05 g, 90%). MS: 217 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,41 (s, 3H), 4,06 (s, 3H), 9,44 (s, 2H).

Etapa 2: A una solución del éster metílico del ácido 2-metanosulfonil-pirimidina-5-carboxílico 2 (2,5 g, 11,56 mmol) en DCM (30 ml) se le añade lentamente una solución de cianuro de tetrabutilamonio (3,1 g, 11,56 mmol) en agua (30 ml) a ta. La mezcla se agita

durante 80 min. La mezcla se lava con agua (2 x 20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía en columna eluyendo con EtOAc al 5-60% en heptano para producir éster metílico del ácido 2-ciano-pirimidina-5-carboxílico (1,16 g, 61%) en forma de un sólido. MS: 164 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,05 (s, 3H), 9,37 (s, 2H).

Etapa 3: A una solución del éster metílico del ácido 2-ciano-pirimidina-5-carboxílico 3 (1 g, 6,13 mmol) en MeOH (20 ml) a ta se le añaden clorhidrato de hidroxilamina (0,64 g, 9,2 mmol) y acetato sódico (0,76 g, 9,2 mmol). La mezcla resultante se calienta a reflujo durante 2 horas. La mezcla se enfría a ta y se concentra al vacío. Al residuo se le añade agua (30 ml) y el sólido se filtra y se lava dos veces con agua. El sólido se seca en una estufa de vacío durante una noche para producir éster metílico del ácido 2-(N-hidroxicarbamimidoil)-pirimidina-5-carboxílico (1,09 g, 91%) en forma de un sólido. MS: 197 (M+H).

Etapa 4: A una solución de éster metílico del ácido 2-(N-hidroxicarbamimidoil)-pirimidina-5-carboxílico (900 mg, 4,59 mmol) en piridina (15 ml) se le añade gota a gota cloruro de acetilo (432 mg, 5,5 mmol). La solución resultante se agita a ta durante 1 hora y se calienta a reflujo durante 3 h. La solución se enfría a ta y se concentra al vacío. Al residuo se le añade agua (30 ml) y la mezcla se extrae con EtOAc (3 x 20 ml). La capa orgánica combinada se lava con $NaHCO_3$ saturado, se seca (Na_2SO_4), se filtra y se concentra al vacío para producir éster metílico del ácido 2-(5-metil-[1,2,3]oxadiazo-3-il)-pirimidina-5-carboxílico (900 mg, 89%) en forma de un sólido. MS: 221 (M+H).

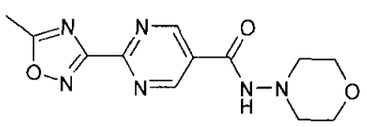
Etapa 5: A una solución de éster metílico del ácido 2-(5-metil-[1,2,3]oxadiazo-3-il)-pirimidina-5-carboxílico (900 mg) en MeOH (20 ml) se le añade una solución de LiOH (100 mg) en agua (20 ml) a 0ºC. El baño de hielo se retira y la mezcla se agita durante 10 min más. El disolvente se evapora y se añade agua (20 ml). La solución de agua se lava con éter (2 x 20 ml) y se acidifica con HCl 2 N a un valor de pH de ~3. El precipitado resultante se filtra, se lava con agua y se seca en una estufa de vacío durante una noche para producir ácido 2-(5-metil-[1,2,4]oxadiazol-3-il)-pirimidina-5-carboxílico (350 mg, 37%) en forma de un sólido. MS: 207 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,73 (s, 3H), 9,39 (s, 2H).

Etapa 6: Siguiendo procedimientos similares a los del Ejemplo 44, pero sustituyendo ácido 2-fenil-pirimidina-5-carboxílico por ácido 2-(5-metil-[1,2,4]oxadiazol-3-il)-pirimidina-5-carboxílico, y sustituyendo 1-aminopiperidina por 2-(4-amino-piperazin-1-il)-etanol, se

prepara [4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-(5-metil-[1,2,4]oxadiazol-3-il)-pirimidina-5-carboxílico en forma de un sólido. MS: 334 (M+H). CI_{50} = 461 nM.

Ejemplo 49

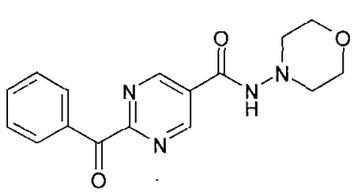
Morfolin-4-ilamida del ácido 2-(5-metil-[1,2,4]oxadiazol-3-il)-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 44, pero sustituyendo ácido 2-fenil-pirimidina-5-carboxílico por ácido 2-(5-metil-[1,2,4]oxadiazol-3-il)-pirimidina-5-carboxílico, y sustituyendo 1-aminopiperidina por morfolina-4-ilamina, se prepara morfolin-4-ilamida del ácido 2-(5-metil-[1,2,4]oxadiazol-3-il)-pirimidina-5-carboxílico en forma de un sólido. MS: 291 (M+H).

Ejemplo 50

Morfolin-4-ilamida del ácido 2-benzoil-pirimidina-5-carboxílico



Etapa 1: Se disuelve 5-bromo-2-cloropirimidina (7,51 g, 38,83 mmol) en DMSO (20 ml) y se añade a una mezcla de NaCN (1,9 g, 38,83 mmol) y 1,4-diazabiciclo[2,2,2]octano (0,87 g, 7,77 mmol) en DMSO (10 ml) y agua (20 ml). La mezcla se agita a ta durante una noche y después se añade agua (100 ml). La mezcla se extrae con éter (3 x 100 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío para producir 5-bromo-pirimidina-2-carbonitrilo (6,28 g, 88%) en forma de un sólido. MS: 184 (M+H).

Etapa 2: Se disuelve 5-bromo-pirimidina-2-carbonitrilo (2,5 g, 13,59 mmol) en éter (30 ml) y se añade gota a gota PhMgBr (solución en éter 3, 13,59 mmol, 4,53 ml) a ta. La mezcla se calienta a reflujo durante 3 h en una atmósfera de N_2 y después se enfría a ta. Se añade THF (30 ml) seguido de la adición de HCl acuoso 2 N (10 ml). La solución resultante se agita a ta durante 30 min y se añade agua (30 ml). La capa acuosa se extrae con EtOAc (3 x 20 ml). La capa orgánica combinada se lava con $NaHCO_3$ acuoso saturado (15 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice

eluyendo con EtOAc al 70% en heptano para producir (5-bromo-pirimidina-2-il)-fenil-metanona (3,01 g, 84%) en forma de un sólido. MS: 264 (M+H).

Etapa 3: Se disuelve (5-bromo-pirimidina-2-il)-fenil-metanona (1,6 g, 6,08 mmol) en dimetilacetamida (20 ml) y se añade hexacianoferrato potásico (II) trihidrato (0,57 g, 1,34 mmol), seguido de Na_2CO_3 (0,64 g, 6,08 mmol) y acetato de paladio (II) (68 mg, 0,3 mmol). La mezcla se calienta a 150°C en una atmósfera de N_2 durante 3 h y después se enfría a ta. Se añade EtOAc (30 ml) y la mezcla se filtra. El filtrado se lava con agua (2 x 15 ml) y NH_4OH acuoso al 5% (15 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 70% en heptano para producir 2-benzoil-pirimidina-5-carbonitrilo (0,53 g, 42%) en forma de un sólido. MS: 210 (M+H).

Etapa 4: Se suspende 2-benzoil-pirimidina-5-carbonitrilo (500 mg, 2,39 mmol) en MeOH (5 ml) y se añade en una porción una solución de KOH (148 mg, 2,63 mmol) en agua (5 ml) a 0°C. La mezcla se agita a 0°C durante 25 min y después se acidifica con HCl acuoso 2 N a un valor de pH de ~3. El MeOH se evapora al vacío y el residuo se extrae con DCM (2x 5 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío para producir éster metílico del ácido 2-benzoil-pirimidina-5-carboxílico (500 mg, 86%) en forma de un aceite. MS: 243 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,05 (s, 3H), 7,50 (m, 2H), 7,65 (m, 1H), 8,01 (m, 2H), 9,46 (s, 2H).

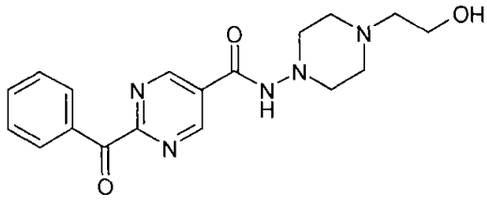
Etapa 5: Se disuelve éster metílico del ácido 2-benzoil-pirimidina-5-carboxílico (420 mg, 1,73 mmol) en THF (5 ml) y se añade en una porción una solución de LiOH (46 mg, 1,91 mmol) en agua (5 ml) a 0°C. La mezcla se agita a 0°C durante 60 min. El THF se evapora al vacío y el residuo se diluye con agua (5 ml) y se lava con éter (10 ml). La capa acuosa se acidifica con HCl acuoso 2 N a un valor de pH de ~3. El precipitado resultante se recoge por filtración, se lava tres veces con agua y se seca en una estufa de vacío durante una noche para producir ácido 2-benzoil-pirimidina-5-carboxílico (260 mg, 66%). MS: 229 (M+H); ^{1}H RMN (300 MHz, DMSO): δ 7,60 (m, 3H), 7,73 (m, 1H), 7,85 (m, 2H), 9,4 (s, 1H).

Etapa 6: Se disuelve ácido 2-benzoil-pirimidina-5-carboxílico (50 mg, 0,22 mmol) en DCM anhidro (5 ml) y se añade una solución 2 M de cloruro de oxalilo (0,26 mmol, 0,13 ml) en DCM a ta seguido de una gota de DMF. La mezcla se agita a ta durante 2 h y después se concentra al vacío. El residuo se disuelve en DCM (5 ml) y se añade morfolina-4-ilamina

(0,24 mmol, 25 mg), seguido de DIPEA (0,44 mmol, 57 mg). La mezcla de reacción se agita a ta durante una noche y después se concentra al vacío. El residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con MeOH al 10% en DCM para producir morfolin-4-ilamida del ácido 2-benzoil-pirimidina-5-carboxílico (42 mg) en forma de un sólido. MS: 313 (M+H). CI_{50} = 342 nM.

Ejemplo 51

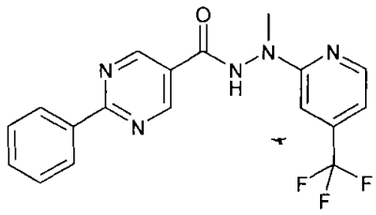
[4-(2-Hidroxi-etil)-piperazin-1-il]-amida del ácido 2-benzoil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 49, etapa 6, pero sustituyendo morfolina-4-ilamina por 2-(4-amino-piperazin-1-il)-etanol, se prepara [4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-benzoil-pirimidina-5-carboxílico en forma de un sólido. MS: 356 (M+H). CI_{50} = 665 nM.

Ejemplo 52

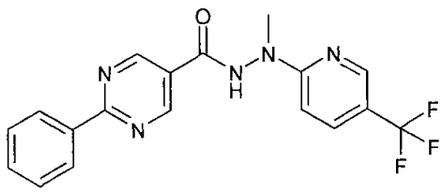
N'-Metil-N'-[5-trifluorometil-piridin-2-il]-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico



A una solución de ácido 2-fenil-pirimidina-5-carboxílico (100 mg, 0,52 mmol), 1-hidroxibenzotriazol (77 mg, 0,57 mmol), 1-[3-(dimetilamino)propil-3-etilcarbodiimida (111 mg, 0,57 mmol) y DIPEA (0,57 mmol) en DCM (5 ml) se le añade N-metil-N-(5-trifluorometil-piridin-2-il)-hidrazina (109 mg, 0,57 mmol). La mezcla de reacción se agita a ta durante 18 horas y después se concentra. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10-75% en heptano para producir N'-metil-N'-[5-trifluorometil-piridin-2-il]-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido (189 mg). MS: 374 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,54 (s, 3H), 6,82 (d, 1H), 7,53-7,59 (m, 3H), 7,74 (d, 1H), 8,45 (d, 2H), 8,53 (d, 2H), 9,25 (s, 2H). CI_{50} = 100 nM.

Ejemplo 53

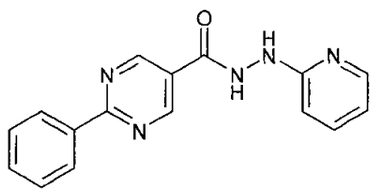
N'-Metil-N'-[4-trifluorometil-piridin-2-il]-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 52, pero sustituyendo N-metil-N-(5-trifluorometil-piridin-2-il)-hidrazina por N-metil-N-(4-trifluorometil-piridin-2-il)-hidrazina (109 mg, 0,57 mmol), se prepara N'-metil-N'-[4-trifluorometil-piridin-2-il]-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido. MS: 374 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,54 (s, 3H), 6,95 (m, 2H), 7,50-7,68 (m, 3H), 8,35 (d, 1H), 8,4 (s, 1H), 8,52 (d, 2H), 9,26 (s, 2H).

Ejemplo 54

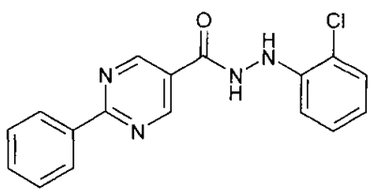
N'-Piridin-2-il-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 52, pero sustituyendo N-metil-N-(5-trifluorometil-piridin-2-il)-hidrazina por 2-hidrazinopiridina (54 mg, 0,52 mmol), se prepara N'-piridin-2-il-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido (56 mg). MS: 292 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 6,72-6,8 (m, 2H), 7,53-7,62 (m, 4H), 8,09 (m, 2H), 8,48 (d, 2H), 8,62 (s, 1H), 9,34 (s, 2H).

Ejemplo 55

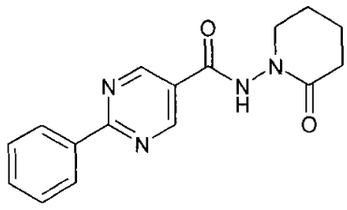
N'-(2-Cloro-fenil)-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 52, pero sustituyendo N-metil-N-(5-trifluorometil-piridin-2-il)-hidrazina por hidrocloruro de 2-clorofenilhidrazina (93 mg, 0,52 mmol), y usando 1,14 mmol de DIPEA, se prepara N'-(2-cloro-fenil)-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido (65 mg). MS: 325 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 6,65-6,75 (m, 2H), 6,90-7,05 (m, 2H), 7,25 (t, 1H), 7,39 (d, 1H), 7,58 (m, 3H), 8 (s, 1H), 8,55 (d, 2H), 9,25 (s, 2H).

Ejemplo 56

N'-(2-Oxo-piperidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico

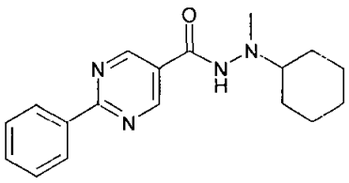


Etapa 1: Una mezcla de 5-bromovalerato de metilo (3 g, 15,4 mmol) e hidrazina hidrato (55%, 15,4 mmol) en MeOH (50 ml) se agita a ta durante 18 h. Se añade una solución de NaOMe (15,4 mmol) en MeOH (10 ml) y la mezcla de reacción se agita a ta durante 18 h. La mezcla de reacción se concentra al vacío. El residuo se tritura con MeOH frío y después se filtra. El filtrado se concentra al vacío. El residuo se pone en una columna SCX (10 g) y la columna se lava con MeOH (3 x 20 ml). El producto se eluye con amoniaco 7 M en MeOH para producir 1-amino-piperidin-2-ona en forma de un aceite. MS: 137 (M+Na).

Etapa 2: A una solución de ácido 2-fenil-pirimidina-5-carboxílico (100 mg, 0,52 mmol), 1-hidroxibenzotriazol (77 mg, 0,57 mmol), 1-[3-(dimetilamino)propil-3-etilcarbodiimida (111 mg, 0,57 mmol) y DIPEA (0,57 mmol) en DCM (5 ml) se le añade 1-amino-piperidin-2-ona (64 mg, 0,57 mmol) y la mezcla se agita a ta durante 18 h. Se añade DCM (15 ml) y la mezcla se lava con HCl acuoso 0,5 N (25 ml) y salmuera, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 50-100% en heptano para producir N'-(2-oxo-piperidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (20 mg) en forma de un sólido. MS: 297 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,96-2,10 (m, 4H), 2,60 (t, 2H), 3,77 (t, 2H), 7,51-7,56 (m, 3H), 8,51 (d, 2H), 9,02 (s a, 1H), 9,46 (s, 2H). CI_{50} = 55 nM.

Ejemplo 57

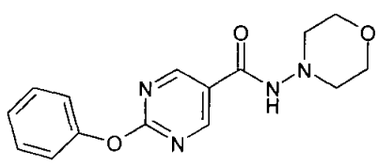
N'-Ciclohexil-N'-metil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 52, pero sustituyendo N-metil-N-(5-trifluorometil-piridin-2-il)-hidrazina por hidrocloruro de N-metil-N-ciclohexil-hidrazina (72 mg, 0,44 mmol), y usando 0,88 mmol de DIPEA, se prepara N'-ciclohexil-N'-metil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido (40 mg). MS: 311 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 0,9-1,35 (m, 5H), 1,60-1,95 (m, 6H), 3,25 (s, 3H) 7,53-7,62 (m, 3H), 8,09 (m, 2H), 9,09 (s, 2H). CI_{50} = 146,5 nM.

Ejemplo 58

N'-Morfolin-4-il-amida del ácido 2-fenoxi-pirimidina-5-carboxílico



Etapa 1: A una solución del éster metílico del ácido 2-metilsulfanil-pirimidina-5-carboxílico (1 g, 5,43 mmol) en DCM (60 ml) se le añade en porciones MCPBA (2,81 g, 16,29 mmol) a ta. La solución resultante se agita a ta durante una noche. Se añade una solución de $Na_2S_2O_3$ (1,6 g) en agua (60 ml). La mezcla se agita a ta durante 20 min. La capa orgánica y la capa acuosa se separan, y la capa acuosa se extrae con DCM (2 x 20 ml). La capa orgánica combinada se lava con $NaHCO_3$ acuoso saturado (3 x 20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío para producir éster metílico del ácido 2-metanosulfonil-pirimidina-5-carboxílico (1,05 g, 90%) en forma de un sólido. MS: 217 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,41 (s, 3H), 4,06 (s, 3H), 9,44 (s, 2H).

Etapa 2: A una solución de éster metílico del ácido 2-metanosulfonil-pirimidina-5-carboxílico (0,8 g, 3,7 mmol) en NMP (3 ml) se le añade fenóxido sódico trihidrato (0,68 g, 4 mmol). La mezcla se calienta a 100°C en un Microondas Biotage durante 60 seg. La reacción se vierte en agua y el precipitado se recoge por filtración y se seca para producir éster metílico del ácido 2-fenoxi-pirimidina-5-carboxílico (0,56 g, 66%) en forma de un

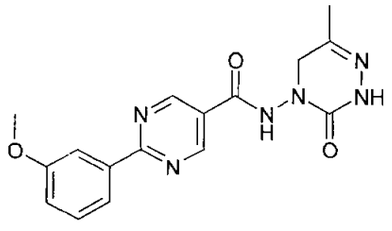
sólido. MS: 231 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,75 (s, 3H), 7,19-7,33 (m, 3H), 7,46 (t, 2H) 9,10 (s, 2H).

Etapa 3: A una solución de éster metílico del ácido 2-fenoxi-pirimidina-5-carboxílico (0,5 g, 2,17 mmol) en THF (10 ml) y agua (5 ml) se le añade LiOH (105 mg, 4,35 mmol). La reacción se agita a 0°C durante 1 h. El THF se evapora y el residuo acuoso se lava con éter y se acidifica con HCl acuoso 2 M. El precipitado resultante se filtra y se seca para producir ácido 2-fenoxi-pirimidina-5-carboxílico (0,34 g, 73%) en forma de un sólido. MS: 217 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,20-7,35 (m, 3H), 7,47 (t, 2H) 9,16 (s, 2H).

Etapa 4: A una solución de ácido 2-fenoxi-pirimidina-5-carboxílico (60 mg, 0,28 mmol) en DCM (5 ml) se le añaden cloruro de oxalilo (2M en DCM (0,15 ml, 0,29 mmol) y 1 gota de DMF. La reacción se agita a ta durante 1 h y después se concentra al vacío. El residuo se disuelve en DCM (3 ml) y se añaden DIPEA (53 µl, 0,3 mmol) y 4-amino-morfolina (30 µl, 0,3 mmol). La reacción se agita a ta durante 18 h y después se añaden agua y DCM. La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 20-100% en heptano para producir N'-morfolin-4-il-amida del ácido 2-feniloxi-pirimidina-5-carboxílico (20 mg) en forma de un sólido. MS: 301 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,85-3,05 (m, 4H), 3,75-3,95 (m, 4H), 7,18-7,35 (m, 3H), 7,45 (t, 2H), 8,95 (s, 2H). CI_{50} = 227 nM.

Ejemplo 59

(6-Metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico



Etapa 1: Se ponen en un tubo de vidrio éster metílico del ácido 2-metilsulfanil-pirimidina-5-carboxílico (323 mg, 1,75 mmol), tiofeno-2-carboxilato de cobre (I) (501 mg, 2,63 mmol), tetraquis(trifenilfosfina)paladio (0) (202 mg, 0,175 mmol) y ácido 3-metoxifenilborónico (400 mg, 2,63 mmol), se evacúa, se rellena con N_2, se añade THF anhidro (6 ml) y se calienta durante una noche a 85°C después de cerrarlo con un tapón. La reacción se enfría a ta, se diluye con EtOAc y se añade hidróxido de amonio. La capa orgánica se separa, se seca

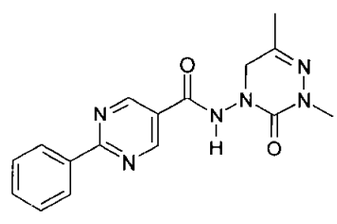
($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía ultrarrápida sobre gel de sílice para producir éster metílico del ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico (152 mg) en forma de un polvo. MS: 245 (M+H); ^{1}H RMN ($CDCl_3$): δ 4,00 (s, 3H), 4,82 (d, 2H), 7,55 (m, 2H), 8,46 (m, 1H), 8,53 (s, 1H), 9,33 (s, 2H).

Etapa 2: Una mezcla de éster metílico del ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico (145 mg, 0,59 mmol), hidróxido de litio monohidrato (49,5 mg, 1,18 mmol), MeOH (1,5 ml), agua (1,5 ml) y THF (1,5 ml) se agita a ta durante 3,5 h. La mezcla de reacción se concentra y se añaden agua (1 ml) y HCl acuoso 1 N (1,2 ml). El producto precipitado se filtra y se seca para producir ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico (140 mg). MS: 231 (M+H); ^{1}H RMN (DMSO-d6): δ 4,62 (s, 3H), 7,54 (m, 2H), 8,14 (s, 1H), 8,34 (m, 1H), 8,46 (s, 1H), 9,30 (s, 2H).

Etapa 3: Una mezcla de ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico (135 mg, 0,58 mmol), 4-amino-6-metil-4,5-dihidro-2H-[1,2,4]triazin-3-ona (76 mg, 0,58 mmol), DMTMM (171 mg, 0,6 mmol) y DMF (3 ml) se agita a ta durante 2 días. Se añade agua (3 ml) y el producto precipitado se filtra, se lava con agua y se seca para producir (6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico (127 mg). MS: 341 (M+H); ^{1}H RMN (DMSO-d_6): δ 1,91 (s, 3H), 4,23 (s, 3H), 4,62 (s, 2H), 7,53 (m, 2H), 8,34 (m, 1H), 8,46 (s, 1H), 9,27 (s, 2H), 9,97 (s, 1H), 11,08 (s, 1H). CI_{50} = 174,5 nM.

Ejemplo 60

(2,6-Dimetil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Etapa 1: A una solución de 5-metil-3H-1,3,4-oxadiazol-2-ona (5,509 g, 55,0 mmol) en MeOH (40 ml) se le añade una solución al 25% en peso de NaOMe en metanol (12,7 ml, 58,8 mmol). La mezcla se agita a ta durante 15 min y después se concentra al vacío. El residuo se añade a una solución de bromuro de tetrabutilamonio (0,358 g, 1,08 mmol) y cloro-acetona (4,6 ml, 54,9 mmol) en $CHCl_3$ (33 ml) y la mezcla se calienta a reflujo durante

5 h en una atmósfera de N_2. La mezcla se enfría a ta y se agita durante una noche. La suspensión resultante se filtra y el filtrado se concentra al vacío. El residuo se purifica sobre una capa de gel de sílice, eluyendo con 2:1:1 de heptano:EtOAc:DCM para producir 5-metil-3-(2-oxo-propil)-3H-1,3,4-oxadiazol-2-ona (7,32 g, 86%) en forma de un sólido cristalino. MS: 157 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 4,46 (s, 2H), 2,27 (s, 3H), 2,21 (s, 3H).

Etapa 2: A una solución de 5-metil-3-(2-oxo-propil)-3H-1,3,4-oxadiazol-2-ona (1,518 g, 9,72 mmol) en una mezcla de 2-propanol (8,8 ml) y agua (0,22 ml) se le añade metil hidrazina (0,79 ml, 14,6 mmol). La mezcla de reacción se calienta a reflujo en una atmósfera de N_2 durante 4 h y después se añade una solución de ácido oxálico (0,273 g, 2,92 mmol) en 2-propanol (4 ml). El precipitado resultante se retira por filtración. El filtrado se concentra al vacío y el residuo se disuelve en 2-propanol (25 ml). La solución se enfría y se añade Et_2O. El precipitado se recoge por filtración y se seca para producir N-(2,6-dimetil-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il)-acetamida (0,96 g, 54%) en forma de un sólido cristalino. MS: 185 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,28 (s, 1H), 4,18 (s, 2H), 3,28 (s, 3H), 2,02 (s, 3H), 1,95 (s, 2H).

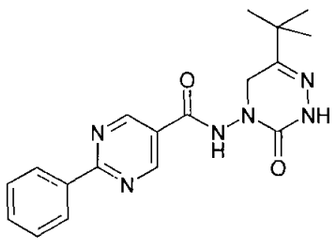
Etapa 3: A una suspensión de N-(2,6-dimetil-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il)-acetamida (0,34 g, 1,846 mmol) en MeOH (3 ml) se le añade HCl concentrado (0,25 ml, 2,9 mmol). La mezcla se calienta a reflujo durante 3 h. Después, la mezcla se enfría a 0°C, se ajusta a un valor de pH de ~12 con NaOH acuoso 1 M (2,9 ml) y se concentra al vacío. Al residuo se le añade CH_3CN con agitación y la mezcla se filtra. El filtrado se concentra al vacío. Al residuo se le añade CH_3CN con agitación y la mezcla se filtra. El filtrado se concentra al vacío para producir 4-amino-2,6-dimetil-4,5-dihidro-2H-1,2,4-triazin-3-ona (~100%). MS: 143 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6) δ 4,6-3,6 (pico ancho, 2H), 4,02 (s, 2H), 3,29 (s, 3H), 1,95 (s, 3H).

Etapa 4: A una solución de 4-amino-2,6-dimetil-4,5-dihidro-2H-1,2,4-triazin-3-ona (0,219 g, 1,58 mmol) y ácido 2-fenil-pirimidina-5-carboxílico (0,317 g, 1,58 mmol) en DMF seca (10 ml) en una atmósfera de N_2 se le añade DMTMM (0,46 g, 1,66 mmol). La mezcla se agita a ta durante 22 h, después se diluye con EtOAc (70 ml) y se lava sucesivamente con una solución acuosa saturada de $NaHCO_3$ (2 x 10 ml) y salmuera (10 ml). La fase orgánica se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con un gradiente de heptano:EtOAc para producir (2,6-dimetil-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico en

forma de un sólido (0,28 g, 55%). MS: 325 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6) δ 9,24 (s, 2H), 8,45 (dd, J = 7,7, 2,0 Hz, 2 H), 7,52-7,62 (m, 3H), 4,25 (s, 2H), 3,18 (s, 3H), 1,95 (s, 3H).

Ejemplo 61

(6-terc-Butil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Etapa 1: A una solución de 5-metil-3H-1,3,4-oxadiazol-2-ona (1,01 g, 10,09 mmol) en MeOH (8 ml) se le añade una solución al 25% en peso de NaOMe en metanol (2,32 ml, 10,8 mmol). La mezcla se agita a ta durante 15 min y después se concentra al vacío. El residuo se añade a una solución de bromuro de tetrabutilamonio (0,07 g, 0,22 mmol) y 1-cloropinacolona (1,35 ml, 10,07 mmol) en $CHCl_3$ (7 ml), y la mezcla se calienta a reflujo durante 5 h en una atmósfera de N_2. La mezcla se enfría a ta y se agita durante el fin de semana a ta. La suspensión resultante se filtra y el filtrado se concentra al vacío para producir 3-(3,3-dimetil-2-oxo-butil)-3H-1,3,4-oxadiazol-2-ona (1,876 g, 94%) en forma de un aceite. MS: 199 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 4,62 (s, 2H), 2,26 (s, 3H), 1,23 (s, 9H).

Etapa 2: A una solución de 3-(3,3-dimetil-2-oxo-butil)-3H-1,3,4-oxadiazol-2-ona (0,91 g, 4,59 mmol) en una mezcla de 2-propanol (4 ml) y agua (0,1 ml) se le añade hidrazina monohidrato (0,34 ml, 6,89 mmol). La mezcla de reacción se calienta a reflujo en una atmósfera de nitrógeno durante 5 h y después a la solución caliente se le añade una solución de ácido oxálico (0,13 g, 1,38 mmol) en 2-propanol (5 ml). El precipitado resultante se retira mientras permanece caliente por filtración. El filtrado se concentra al vacío y el residuo se purifica sobre una capa de gel de sílice, eluyendo con un gradiente de heptano:EtOAc para producir N-(6-terc-butil-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il)-acetamida (0,546 g, 56%) en forma de un sólido. MS: 213 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,29 (s, 1H), 7,64 (s, 1H), 4,22 (s, 2H), 2,04 (s, 3H), 1,15 (s, 9H).

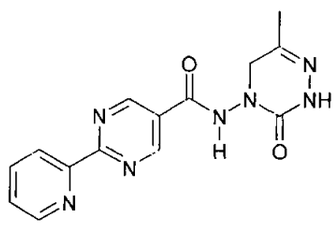
Etapa 3: A una suspensión de N-(6-terc-butil-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il)-

acetamida (0,51 g, 2,40 mmol) en MeOH (5 ml) se le añade HCl concentrado (0,33 ml, 3,84 mmol). La mezcla se calienta a reflujo durante 3 h. Después, la mezcla se enfría a 0°C, se basifica con NaOH acuoso 1 M (2,9 ml) a un valor de pH de ~12 y se concentra al vacío. Al residuo se le añade EtOH con agitación y la mezcla se filtra. El filtrado se concentra al vacío. Al residuo se le añade CH_3CN con agitación y la mezcla se filtra. El filtrado se concentra al vacío para producir 4-amino-6-terc-butil-4,5-dihidro-2H-1,2,4-triazin-3-ona (0,354 g, 84%) en forma de un sólido. MS: 171 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6) δ 7,49 (s a, 1H), 4,22 (s a, 2H), 4,06 (s, 2H), 1,15 (s, 9H).

Etapa 4: Siguiendo un procedimiento similar al del Ejemplo 60, etapa 4, pero sustituyendo 4-amino-2,6-dimetil-4,5-dihidro-2H-1,2,4-triazin-3-ona por 4-amino-6-terc-butil-4,5-dihidro-2H-1,2,4-triazin-3-ona, se prepara (6-terc-butil-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (74%) en forma de un sólido. MS: 353 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6) δ 11,09 (s, 1H), 10,03 (s, 1H), 9,27 (s, 2H), 8,45 (dd, J = 7,7, 2,0 Hz, 2 H), 7,52-7,60 (m, 3H), 4,29 (s, 2H), 1,13 (s, 9H).

Ejemplo 62

(6-Metil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico



Etapa 1: A una solución de 5-metil-3-(2-oxo-propil)-3H-1,3,4-oxadiazol-2-ona (2,052 g, 13,14 mmol) en una mezcla de 2-propanol (12 ml) y agua (0,3 ml) se le añade hidrazina monohidrato (0,96 ml, 19,8 mmol). La mezcla se agita a ta en una atmósfera de N_2 durante 15 h y después se calienta a reflujo durante 7 h. A la solución de reacción caliente se le añade una solución de ácido oxálico (0,363 g, 4,032 mmol) en 2-propanol (6 ml). El precipitado resultante se retira por filtración a través de un embudo de vidrio sinterizado con porosidad gruesa y el filtrado se concentra al vacío hasta alcanzar un volumen total de aproximadamente 10 ml. La solución concentrada se enfría a -12°C y los cristales resultantes se recogen por filtración y se secan para producir N-(6-metil-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il)-acetamida (1,562 g, 70%). MS: 171 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,10

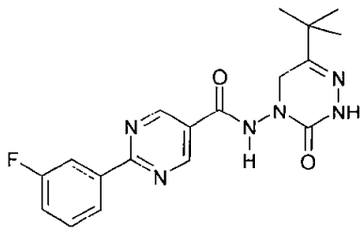
(s a, 1H), 7,57 (s a, 1H), 4,20 (s, 2H), 2,04 (s, 3H), 1,95 (s, 3H); ^{1}H RMN (300 MHz, DMSO-d_6) δ 9,98 (s, 1), 9,74 (s, 1), 4,04 (s, 2), 1,84 (s, 6).

Etapa 2: Siguiendo un procedimiento similar al del Ejemplo 35, etapa 4, pero sustituyendo N-[6-(4-fluoro-fenil)-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il]-acetamida por N-(6-metil-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il)-acetamida, se prepara 4-amino-6-metil-4,5-dihidro-2H-1,2,4-triazin-3-ona (92%) en forma de un sólido. MS: 129 (M+H); ^{1}H RMN (300 MHz, CD_3CN) δ 8,25 (s a, 1H), 4,26 (s a, 2H), 3,96 (s, 2H), 1,85 (s, 3H).

Etapa 3: A una solución de ácido 2-piridin-2-il-pirimidina-5-carboxílico (0,152 g, 0,75 mmol), en DCM seco (3 ml) y DMF (0,9 µl) en un matraz seco en una atmósfera de N_2 se le añade cloruro de oxalilo (74 µl, 0,86 mmol). La mezcla de reacción se agita a ta durante 1 h. El disolvente se evapora, se añade tolueno y se evapora tres veces. El residuo se disuelve en DCM seco (3 ml) y se añade una solución de 4-amino-6-metil-4,5-dihidro-2H-1,2,4-triazin-3-ona (0,77 g, 0,6 mmol) en DCM (5 ml) seguido de la adición de DIPEA (0,14 ml, 0,79 mmol). La mezcla se agita a ta durante una noche y después se concentra al vacío. El residuo se diluye con agua y se ajusta a un valor de pH de ~8,5 con una solución acuosa saturada de $NaHCO_3$. El precipitado resultante se filtra para producir (6-metil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico (0,043 g, 23%). MS: 312 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6) δ 11,11 (s, 1H), 9,95 (s, 1H), 9,31 (s, 2H), 8,78 (d, 1H), 8,45 (d, 1H), 8,01 (t, 1H), 7,58 (dd, 1H), 4,22 (2, 2H), 1,91 (s, 3H).

Ejemplo 63

(6-terc-Butil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico

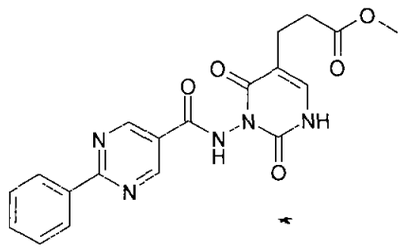


Siguiendo un procedimiento similar al del Ejemplo 62, etapa 3, pero sustituyendo cloruro de 2-piridin-2-il-pirimidina-5-carbonilo por cloruro de 2-(3-fluoro-fenil)-pirimidina-5-carbonilo, sustituyendo 4-amino-6-metil-4,5-dihidro-2H-1,2,4-triazin-3-ona por 4-amino-6-terc-butil-4,5-dihidro-2H-1,2,4-triazin-3-ona, y sustituyendo DIPEA por Et_3N, se prepara (6-terc-butil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-(3-fluoro-fenil)-

pirimidina-5-carboxílico (0,067 g, 61%). MS: 371 (M+H); ^{1}H RMN (300 MHz, CD_3OD) δ 9,26 (s, 2H), 8,35 (d, J = 8,1 Hz, 1H), 8,21 (d, J = 10,3 Hz), 7,55 (c, J = 10,3 Hz, 1 H), 7,30 (t, J = 8,2 Hz, 1H), 4,37 (s, 2H), 1,19 (s, 9H).

Ejemplo 64

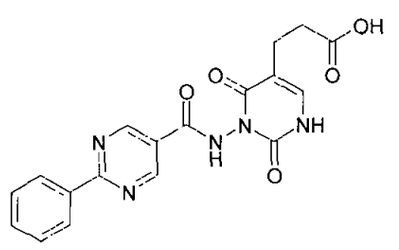
Éster metílico del ácido 3-{2,4-dioxo-3-[(2-fenil-pirimidina-5-carbonil)-amino]-1,2,3,4-tetrahidro-pirimidin-5-il}-propiónico



Una mezcla de ácido 2-fenil-pirimidina-5-carboxílico (1,17 mmol), 1-hidroxibenzotriazol (1,99 mmol) y PS-DCC (1,21 mmol/g, 2,34 mmol) en DMF (8 ml) se agita a ta durante 60 min. Se añade éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico (1,17 mmol) y la mezcla se agita a ta durante 2-4 días. Se añade trisamina soportada con polímero (PS-trisamina) (4,08 mmol/g, 3,51 mmol) y la mezcla continua en agitación a ta durante 18 horas. El sólido se filtra y se lava con MeOH. El filtrado se concentra. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10-60% en hexanos para producir éster metílico del ácido 3-{2,4-dioxo-3-[(2-fenil-pirimidina-5-carbonil)-amino]-1,2,3,4-tetrahidro-pirimidin-5-il-propiónico (115 mg, 25%) en forma de un sólido. MS: 397 (M+H) 397; ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,57-2,76 (m, 2H), 2,80-3,00 (m, 2H), 3,64 (s, 3H), 5,30 (a, N-H), 7,37-7,55 (m, 3H), 8,35 (d, 2H), 9,26 (s, 2H).

Ejemplo 65

Ácido 3-{2,4-dioxo-3-[(2-fenil-pirimidina-5-carbonil)-amino]-1,2,3,4-tetrahidro-pirimidin-5-il}-propiónico

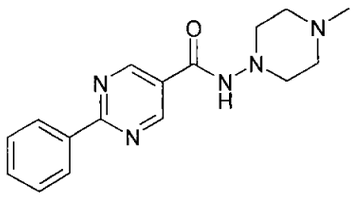


Se hidroliza éster metílico del ácido 3-{2,4-dioxo-3-[(2-fenil-pirimidina-5-carbonil)-amino]-1,2,3,4-tetrahidro-pirimidin-5-il}-propiónico (0,22 mol) con LiOH (0,88 mol) en

MeOH/agua/THF (1:1:1) a ta durante una noche. El MeOH y el THF se evaporan al vacío. El residuo se acidifica con HCl acuoso al 5%. El precipitado resultante se recoge y se seca para producir ácido 3-{2,4-dioxo-3-[(2-fenil-pirimidina-5-carbonil)-amino]-1,2,3,4-tetrahidro-pirimidin-5-il}-propiónico (40 mg, 48%). MS: 383 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,68-2,77 (m, 2H), 2,98-2,90 (m, 2H), 5,49 (s, N-H), 7,48-7,60 (m, 3H), 8,41-8,56 (m, 2H), 9,32 (s, 2H).

Ejemplo 66

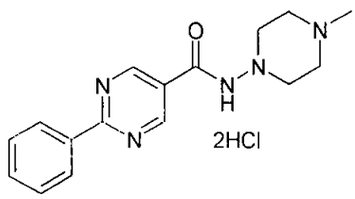
(4-Metil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 4-metil-piperazin-1-ilamina, se prepara (4-metil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico.

Ejemplo 67

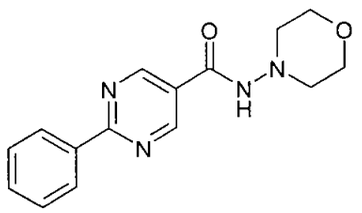
Dihidrocloruro de (4-metil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Se disuelve (4-metil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico en una solución de HCl y metanol y el metanol se evapora a sequedad para producir dihidrocloruro (4-metil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido. MS: 298 (M+H).

Ejemplo 68

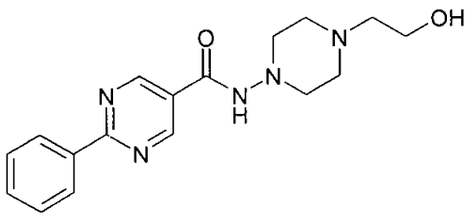
Morfolin-4-ilamida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 4-aminomorfolina, se prepara morfolin-4-ilamida del ácido 2-fenil-pirimidina-5-carboxílico (71%) en forma de un sólido. MS: 285 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,90-3,00 (m, 2H), 3,80-3,85 (m, 2H), 7,44-7,58 (m, 3H), 8,45-8,53 (m, 2H), 9,18 (s, 2H).

Ejemplo 69

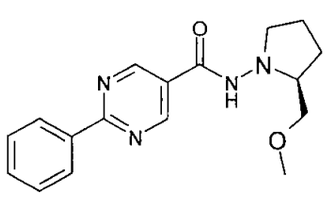
[4-(2-Hidroxi-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 2-(4-amino-piperazin-1-il)-etanol, se prepara [4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico (25%) en forma de un sólido. MS: 328 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,65 (t, 2H), 2,80 (a, 2H), 3,04 (a, 2H), 3,73 (t, 2H), 7,24-7,34 (m, H), 7,47-7,57 (m, 3H), 7,62-7,73 (m, H), 8,43-8,52 (m, 2H), 9,18 (s, 2H).

Ejemplo 70

((S)-2-Metoximetil)-pirrolidin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico

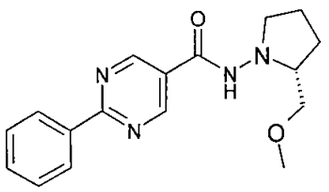


Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por (S)-2-metoximetil-pirrolidin-1-ilamina, se prepara ((S)-2-metoximetil)-pirrolidin-1-il]-amida del

ácido 2-fenil-pirimidina-5-carboxílico (63%) en forma de un sólido. MS: 313 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,57-2,15 (m, 4H), 2,70-3,70 (m, 8H), 6,93 (a, 0,4N-H), 7,81 (a, 0,6N-H), 7,50 (m, 3H), 8,48 (m, 2H), 9,10-9,38 (d, 2H).

Ejemplo 71

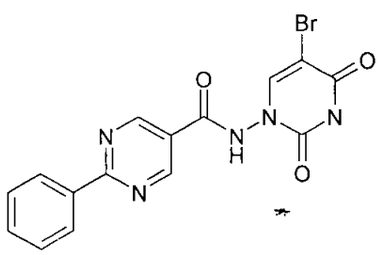
((R)-2-Metoximetil)-pirrolidin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por (R)-2-metoximetil-pirrolidin-1-ilamina, se prepara ((R)-2-metoximetil)-pirrolidin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico (66%) en forma de un sólido. MS: 313 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,57-2,15 (m, 4H), 2,71-3,63 (m, 8H), 6,93 (a, 0,4N-H), 7,71 (a, 0,6N-H), 7,50 (m, 3H), 8,50 (m, 2H), 9,10-9,38 (d, 2H).

Ejemplo 72

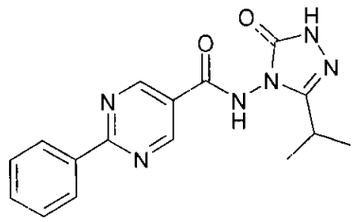
(5-Bromo-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 5-bromo-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilamina, se prepara (5-bromo-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (34%) en forma de un sólido. MS: 389 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 7,49-7,62 (m, 3H), 7,98 (a, 3H), 8,23 (s, H), 8,54 (d, 2H), 9,29 (s, 2H). CI_{50} = 107,5 nM.

Ejemplo 73

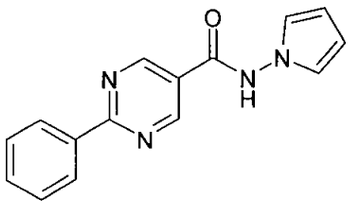
(3-Isopropil-5-oxo-1,5-dihidro-[1,2,4]triazol-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 3-isopropil-5-oxo-1,5-dihidro(1,2,4)-triazol-4-ilamina, se prepara (3-isopropil-5-oxo-1,5-dihidro-[1,2,4]triazol-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (25%) en forma de un sólido. MS: 325 (M+H).

Ejemplo 74

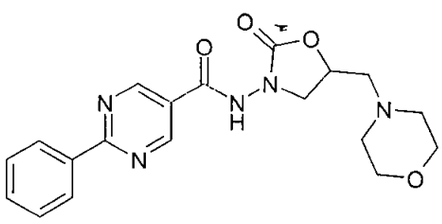
Pirrol-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por pirrol-1-ilamina, se prepara pirrol-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico (62%) en forma de un sólido. MS: 265 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 6,25 (d, 2H), 6,76 (d, 2H), 7,48-7,63 (m, 3H), 8,52 (d, 2H), 8,95-9,60 (a, 2H).

Ejemplo 75

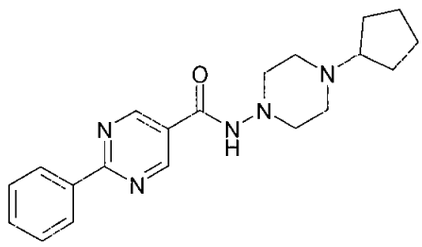
(5-Morfolin-4-ilmetil-2-oxo-oxazolidin-3-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 5-morfolin-4-ilmetil-2-oxo-oxazolidin-3-ilamina, se prepara (5-morfolin-4-ilmetil-2-oxo-oxazolidin-3-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (51%) en forma de un sólido. MS: 384 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,50-2,95 (m, 6H), 3,64-3,85 (m, 5H), 3,98 (t, H), 4,88 (m, H), 7,48-7,60 (m, 3H), 8,49 (d, 2H), 9,16 (s, 2H), 9,37 (a, N-H). CI_{50} = 20 nM.

Ejemplo 76

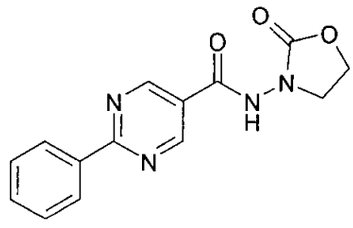
(4-Ciclopentil-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 4-ciclopentil-piperazin-1-ilamina, se prepara (4-ciclopentil-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico (67%) en forma de un sólido. MS: 352 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,25-2,00 (m, 8H), 2,00-3,35 (m, 9H), 6,70-7,40 (m, N-H), 7,40-7,60 (m, 3H), 8,50 (s, 2H), 8,86-9,38 (m,2H).

Ejemplo 77

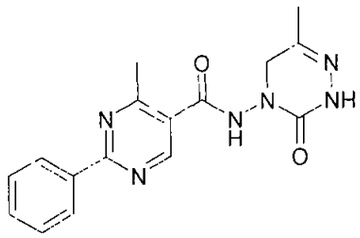
(2-Oxo-oxazolidin-3-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por hidrocloruro de 2-oxo-oxazolidin-3-ilamina, se prepara (2-oxo-oxazolidin-3-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (18%) en forma de un sólido. MS: 285 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 3,94 (t, 2H), 4,55 (t, 2H), 7,46-7,62 (m, 3H), 8,53 (d, 2H), 9,30 (d, 2H). CI_{50} = 49 nM.

Ejemplo 78

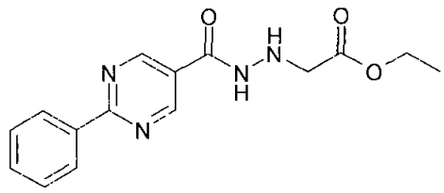
(6-Metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il]-amida del ácido 4-metil-2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-ilamina, se prepara (6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il]-amida del ácido 4-metil-2-fenil-pirimidina-5-carboxílico (87%) en forma de un sólido. MS: 325 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,95 (s, 3H), 3,72 (s, 3H), 4,30 (s, 2H), 7,34-7,58 (m, 4H), 7,72 (a, H), 8,92 (a, H), 8,43 (d, 2H), 8,87 (s, H), 9,46 (a, H).

Ejemplo 79

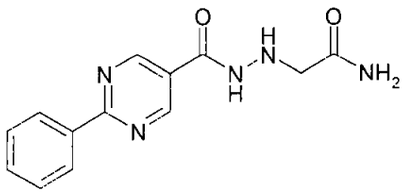
Éster etílico del ácido [N`-(2-fenil-pirimidina-5-carbonil)-hidrazino]-acético



Se añade Et_3N (13,15 mmol) a una solución agitada de cloruro del ácido 2-fenil-pirimidina-5-carboxílico (5,26 mmol) e hidrocloruro de éster etílico del ácido hidrazina-acético (5 mmol) en DCM (30 ml) a ta y la mezcla se agita a ta durante 5 h. La mezcla se inactiva con agua y se extrae con EtOAc (60 ml). La capa orgánica se lava con agua (20 ml) y salmuera (15 ml), se seca, se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 5-50% en heptano para producir éster etílico del ácido [N`-(2-fenil-pirimidina-5-carbonil)-hidrazino]-acético (256 mg, 16%) en forma de un sólido. MS: 301 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,35 (s, 3H), 4,20-4,40 (m, 4H), 4,56 (s, 2H), 7,54 (m, 3H), 8,53 (m, 2H), 9,24 (s, 2H).

Ejemplo 80

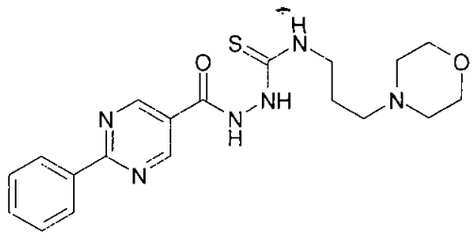
2-[N'-(2-Fenil-pirimidina-5-carbonil)-hidrazino]-acetamida



Una mezcla de éster etílico del ácido [N'-(2-fenil-pirimidina-5-carbonil)-hidrazino]-acético (0,37 mmol) en una solución al 25% de amoniaco (25 ml) se agita a ta durante una noche. El sólido se recoge por filtración y se seca para producir 2-[N'-(2-fenil-pirimidina-5-carbonil)-hidrazino]-acetamida (46%). MS: 272 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 4,45 (s, 2H), 7,45-7,56 (m, 3H), 8,40-8,50 (m, 2H), 9,18 (s, 2H).

Ejemplo 81

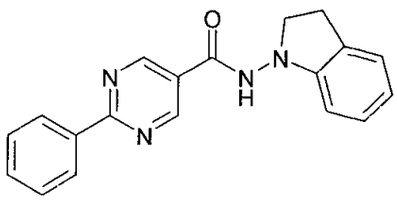
4-[3-(4-Morfolino)propil]-1-(2-fenil-pirimidina-5-carbonil)-3-tiosemicarbazida



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-[3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 4-[3-(4-morfolino)-propil]-3-tiosemicarbazida, se prepara 4-[3-(4-morfolino)propil]-1-(2-fenil-pirimidina-5-carbonil)-3-tiosemicarbazida (32%) en forma de un sólido. MS: 401 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 1,67-1,97 (m, 2H), 2,27-2,84 (m, 6H), 3,40-3,86 (m, 6H), 7,34-7,59 (m, 3H), 8,33-8,57 (m, 2H), 9,24 (s, 2H).

Ejemplo 82

(2,3-Dihidro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico

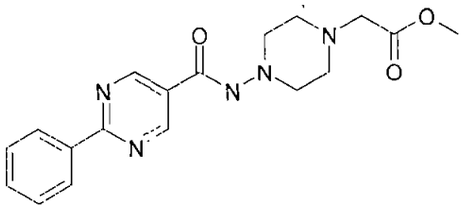


Se añade cloruro de oxalilo en DCM (2 M, 1,5 ml) a una solución de ácido 2-fenil-pirimidina-5-carboxílico (200 mg, 2 mmol) en DCM (20 ml) y la mezcla se agita a ta durante

2 h. La solución de reacción se concentra al vacío. El residuo se disuelve en DCM (20 ml). Se añaden N-amino-indolina (268 mg, 2 mmol) y trietilamina (404 mg, 4 mmol) y la mezcla se agita a ta durante una noche. La mezcla se concentra al vacío y el residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con EtOAc al 0-40% en heptano para producir (2,3-dihidro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (195 mg, 31%) en forma de un sólido. MS: 317 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 3,07 (t, 2H), 3,77 (t, 2H), 6,76 (m, H), 6,82-6,95 (m, H) 7,09-7,24 (m, 2H), 7,54-7,63 (m, 3H), 8,52 (d, 2H), 9,28 (s, 2H) y (indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (10 mg, 2%). MS: 315 (M+H). CI_{50} = 2 nM.

Ejemplo 83

Éster metílico del ácido {4-[2-fenil-pirimidina-5-carbonil)-amino]-piperazin-1-il}-acético



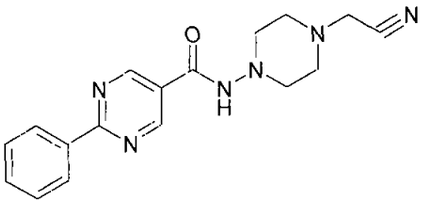
Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-[3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por piperazin-1-ilamina, se prepara piperazin-1-il-amida del ácido 2-fenil-pirimidina-5-carboxílico.

Etapa 2: Se disuelve piperazin-1-il-amida del ácido fenil-pirimidina-5-carboxílico en una solución de HCl y metanol y el metanol se evapora a sequedad para producir dihidrocloruro de piperazin-1-il-amida del ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido.

Etapa 3: Una solución suspendida de dihidrocloruro de piperazin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico (0,5 mmol), bromoacetato de metilo (0,5 mmol) y Na_2CO_3 (2,5 mmol) en THF húmedo (20 ml) se agita a ta durante 20 h. La mezcla se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con metanol al 1-5% en DCM para producir éster metílico del ácido {4-[2-fenil-pirimidina-5-carbonil)-amino]-piperazin-1-il}-acético (135 mg, 76%) en forma de un sólido. MS: 356 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,60-3,18 (m, 8H), 3,18-3,35 (d, 2H), 3,74 (s, 3H), 6,67 (a, 0,5 N-H) 7,03 (a, 0,5 N-H), 7,46-7,60 (m, 3H), 8,50 (d, 2H), 9,21 (d, 2H).

Ejemplo 84

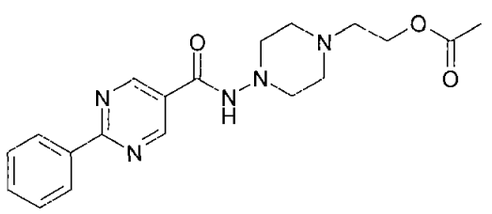
(4-Cianometil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Una solución de dihidrocloruro de piperazin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico (0,29 mmol), bromoacetonitrilo (0,29 mmol) y Na_2CO_3 (1,46 mmol) en THF húmedo (8 ml) se agita a ta durante una noche. La mezcla de reacción resultante se filtra y el filtrado se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con metanol al 1-2% en DCM para producir (4-cianometil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (38 mg, 40%) en forma de un sólido. MS: 323 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,60-3,30 (m, 8H), 3,55 (s, 2H), 6,63 (a, 0,5 N-H), 7,14 (a, 0,5 N-H), 7,52 (s, 3H), 8,53 (d, 2H), 9,06-9,38 (m, 2H).

Ejemplo 85

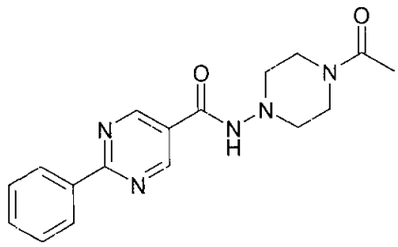
2-{4-[(2-Fenil-pirimidina-5-carbonil)-amino]-piperazin-1-il}-etil éster del ácido acético



Una solución de [4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico (0,21 mmol) y cloruro de acetilo (1,06 mmol) en piridina (4 ml) se agita a 80ºC durante una noche. La mezcla de reacción resultante se filtra y el filtrado se concentra al vacío. El residuo se disuelve en EtOAc (10 ml), se lava con agua (10 ml), Na_2CO_3 al 10% (10 ml) y salmuera (10 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con metanol al 0-5% en DCM para producir 2-{4-[(2-fenil-pirimidina-5-carbonil)-amino]-piperazin-1-il)-etil éster del ácido acético (12 mg, 15%) en forma de un sólido. MS: 370 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,08 (s, 3H), 2,42-3,20 (m, 8H), 3,20-3,80 (m, 3H), 4,10-4,52 (m, 2H) 7,42-7,65 (m, 3H), 8,52 (m, 2H), 9,07-9,38 (d, 2H).

Ejemplo 86

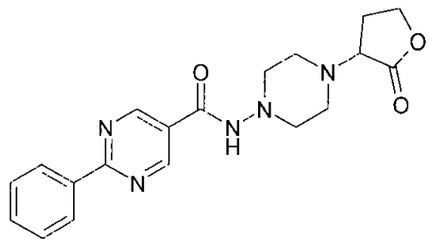
(4-Acetil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Una solución de dihidrocloruro de piperazin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico (0,43 mmol), cloruro de acetilo (1,28 mmol) y Et_3N (1,72 mmol) en DMF (8 ml) se agita a ta durante una noche y la mezcla se concentra al vacío. El residuo se disuelve en EtOAc (15 ml), se lava con agua y salmuera, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se tritura con éter para producir (4-acetil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (98 mg, 71%) en forma de un sólido. MS: 326 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,12 (s, 3H), 2,92-3,10 (m, 4H), 3,40-4,10 (m, 4H), 7,43-7,60 (m, 3H), 7,75 (a, N-H), 8,52 (m, 2H), 9,11-9,38 (a, 2H).

Ejemplo 87

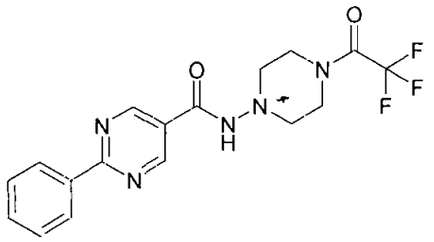
[4-(2-Oxo-tetrahidro-furan-3-il)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico



Una solución de dihidrocloruro de piperazin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico (0,45 mmol) y bromo-dihidro-furan-2-ona (1,8 mmol) en DMF (10 ml) se agita en una atmósfera de N_2 a 0ºC durante 15 min, después se añade NaH (al 60%, 1,8 mmol) y la mezcla se calienta a ta y se agita durante una noche. La mezcla se inactiva con agua y se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con metanol al 0-2% en DCM para dar [4-(2-oxo-tetrahidro-furan-3-il)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico (120 mg, 73%) en forma de un sólido. MS: 368 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,34 (s, 2H), 2,50-3,30 (m, 8H), 3,42-3,70 (m, H), 4,17-4,50 (m, 2H), 7,34-7,68 (m, 3H), 8,50 (d, 2H), 9,06-9,38 (d, 2H). CI_{50} = 26 nM.

Ejemplo 88

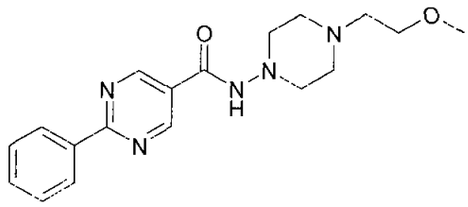
[4-(2,2,2-Trifluoro-acetil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico



Una solución de dihidrocloruro de piperazin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico (0,36 mmol), anhídrido trifluoroacético (1,08 mmol) y Et_3N (1,44 mmol) en DMF (8 ml) se agita en una atmósfera de N_2 a ta durante una noche. La mezcla de reacción se concentra al vacío. El residuo se disuelve en EtOAc (15 ml), se lava con agua (10 ml) y salmuera (15 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se tritura con éter para dar [4-(2,2,2-trifluoro-acetil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico (136 mg, ~100%) en forma de un sólido. MS: 380 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,95-3,40 (s, 4H), 3,60-4,10 (m, 4H), 7,41-7,68 (m, 3H), 8,52 (d, 2H), 9,03-9,40 (a, 2H). CI_{50} = 57 nM.

Ejemplo 89

[4-(2-Metoxi-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico

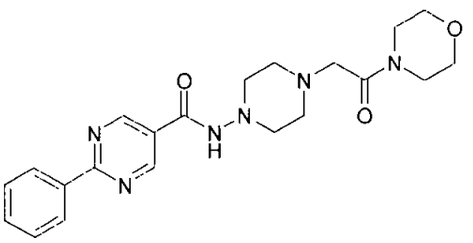


Etapa 1: A una solución suspendida de [4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico (0,83 mmol) en DCM (8 ml) en una atmósfera de N_2 se le añaden una solución de Et_3N (2,67 mmol) en DCM (1 ml), una solución de N,N-dimetil-4-aminopiridina (0,2 mmol) en DCM (1 ml) y una solución de dicarbonato de di-terc-butilo (1,48 mmol) en DCM (1 ml) a ta. La mezcla resultante se agita a ta durante 3 h y después se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con etanol al 6% en EtOAc para producir éster terc-butílico del ácido [4-(2-metoxi-etil)-piperazin-1-il]-(2-fenil-pirimidina-5-carbonil)-carbámico (70 mg, 20%) en forma de un sólido. MS: 428 (M+H).

Etapa 2: Una solución de éster terc-butílico del ácido [4-(2-metoxi-etil)-piperazin-1-il]-(2-fenil-pirimidina-5-carbonil)-carbámico (0,21 mmol), NaH (al 60%, 0,66 mmol) y yodometano (0,63 mmol) en DMF (8 ml) se agita en una atmósfera de N_2 a ta durante una noche. La mezcla de reacción se inactiva con agua y se extrae con EtOAc. La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con metanol al 0-2% en DCM para producir [4-(2-metoxi-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico (32 mg, 44%) en forma de un sólido. MS: 342 (M+H).

Ejemplo 90

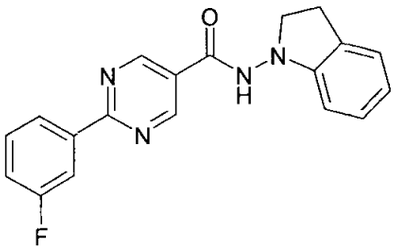
[4-(2-Morfolin-4-il-2-oxo-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico



Una solución de dihidrocloruro de piperazin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico (0,43 mmol) y NaH (al 60%, 2,15 mmol) en DMF (10 ml) se agita en una atmósfera de N_2 a ta durante 20 min. Se añade 2-cloro-1-morfolin-4-il-etanona (0,65 mmol) y la mezcla de reacción se agita a ta durante una noche. La mezcla de reacción se inactiva con agua y se extrae con EtOAc. La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con metanol al 0-4% en DCM para producir [4-(2-morfolin-4-il-2-oxo-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico (24 mg, 14%) en forma de un sólido. MS: 411 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,85-3,10 (m, 2H), 3,60-4,00 (m, 12H), 4,46 (d, 2H), 4,84 (s, 2H), 7,44-7,62 (m, 3H), 8,34-8,58 (m, 2H), 9,20-9,38 (d, 2H). CI_{50} = 831,5 nM.

Ejemplo 91

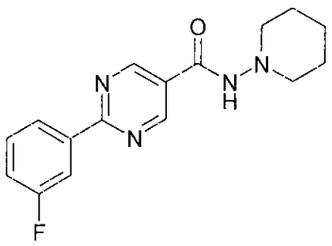
(2,3-Dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo ácido 2-fenil-4-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico, y sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 2,3-dihidro-indol-1-ilamina, se prepara (2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (83%) en forma de un sólido. MS: 335 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,00 (s, 2H), 3,70 (s, 2H), 6,53-7,34 (m, 5H), 7,45 (s, H), 8,00-8,38 (m, 2H), 9,20 (s, 2H). CI_{50} = 3 nM.

Ejemplo 92

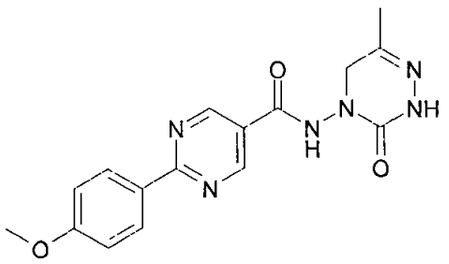
Piperadin-1-il-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo ácido 2-fenil-4-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico, y sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por piperidin-1-ilamina, se prepara piperidin-1-il-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (71%) en forma de un sólido. MS: 301 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,20-2,00 (m, 6H), 2,20-3,60 (m, 4H), 6,97-7,30 (m, H), 7,34-7,56 (m, H), 8,06-8,38 (m, 2H), 9,00-9,38 (d, 2H). CI_{50} = 19,5 nM.

Ejemplo 93

(6-Metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(4-metoxi-fenil)-pirimidina-5-carboxílico



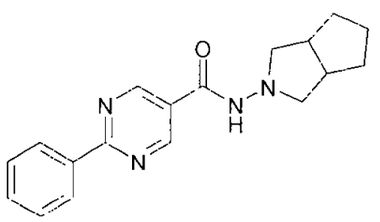
Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 1, pero sustituyendo ácido 3-metoxifenilborónico por ácido 4-metoxifenilborónico, se prepara éster metílico del ácido 2-(4-metoxi-fenil)-pirimidina-5-carboxílico.

Etapa 2: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 2, pero sustituyendo éster metílico del ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico por éster metílico del ácido 2-(4-metoxi-fenil)-pirimidina-5-carboxílico, se prepara ácido 2-(4-metoxi-fenil)-pirimidina-5-carboxílico.

Etapa 3: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 3, pero sustituyendo ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico por ácido 2-(4-metoxi-fenil)-pirimidina-5-carboxílico, se prepara (6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(4-metoxi-fenil)-pirimidina-5-carboxílico. MS: 341 (M+H); ^{1}H RMN (DMSO-d_6): δ 1,91 (s, 3H), 3,86 (s, 3H), 4,22 (s, 2H), 7,12 (d, J = 8,5 Hz, 1H), 7,95 (s, 1H), 8,42 (d, J = 8,6 Hz, 1H), 9,21 (s, 2H), 9,95 (s, 1H), 11,02 (s, 1H).

Ejemplo 94

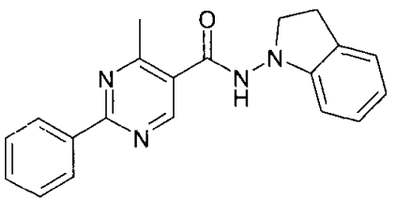
(Hexahidro-ciclopenta[c]pirrol-2-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por hexahidro-ciclopenta[c]pirrol-2-ilamina, se prepara (hexahidro-ciclopenta[c]pirrol-2-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (39%) en forma de un sólido. MS: 309 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,20-1,90 (m, 6H), 2,40-3,50 (m, 6H), 6,94 (s, N-H), 7,52 (s, 3H), 8,50 (s, 2H), 9,08-9,38 (d, 2H).

Ejemplo 95

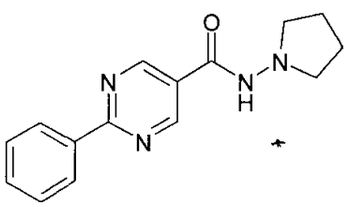
(2,3-Dihidro-indol-1-il)-amida del ácido 4-metil-2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo ácido 2-fenil-4-il-pirimidina-5-carboxílico por cloruro del ácido 4-metil-2-fenil-pirimidina-5-carboxílico, y sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 2,3-dihidro-indol-1-ilamina, se prepara (2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-fenil-pirimidina-5-carboxílico (80%) en forma de un sólido. MS: 331 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,69 (s, 3H), 2,74-3,10 (m, 2H), 3,64 (t, 2H), 6,58-6,97 (m, 2H), 7,03-7,30 (m, 2H), 7,49 (s, 3H), 7,96 (s, N-H), 8,44 (s, 2H), 8,72 (d, 2H). Cl_{50} = 5,5 nM.

Ejemplo 96

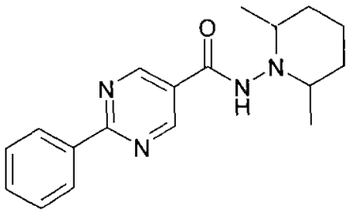
Pirrolidin-1-il-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por hidrocloruro de pirrolidin-1-ilamina, se prepara pirrolidin-1-il-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (67%) en forma de un sólido. MS: 269 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,70-2,20 (m, 4H), 2,70-3,46 (m, 4H), 7,55 (s, 3H), 8,42-8,67 (m, 2H), 9,14-9,49 (t, 2H).

Ejemplo 97

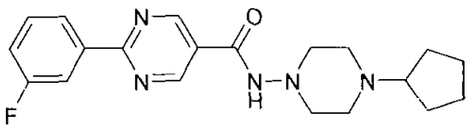
(2,6-Dimetil-piperidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 2,6-dimetil-piperidin-1-ilamina, se prepara (2,6-dimetil-piperidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (69%) en forma de un sólido. MS: 311 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 0,95-1,24 (m, 6H), 1,24-1,87 (m, 6H), 1,88-3,60 (m, 2H), 6,35 (a, N-H), 7,53 (s, 3H), 8,52 (s, 2H), 9,10-9,73 (m, 2H).

Ejemplo 98

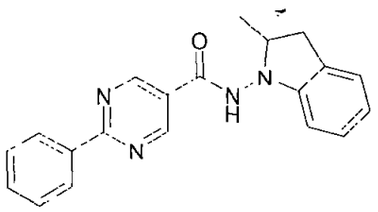
(4-Ciclopentil-piperazin-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo ácido 2-fenil-4-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico, y sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 4-ciclopentil-piperazin-1-ilamina, se prepara (4-ciclopentil-piperazin-1-il-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (64%) en forma de un sólido. MS: 370 (M+H).

Ejemplo 99

(2-Metil-2,3-dihidro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico

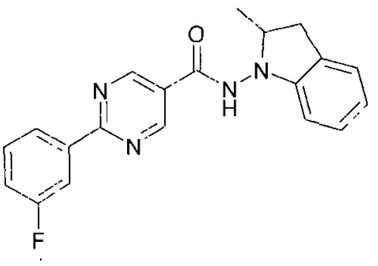


Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 2-metil-2,3-dihidro-indol-1-ilamina, se prepara (2-metil-2,3-dihidro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (32%) en forma de un sólido. MS: 331 (M+H); ^{1}H RMN (300 MHz,

$CDCl_3$): δ 1,05 (m, 3H), 2,50-2,79 (m, H), 3,03-3,24 (m, H), 3,40-3,58 (m, 0,5H), 3,92 (a, 0,5H), 6,67 (d, 0,5N-H), 6,77-7,33 (m, 4H), 7,51 (m, 3H), 7,98 (s, 0,5N-H), 8,52 (m, 2H), 9,23 (d, 2H). CI_{50} = 4 nM.

Ejemplo 100

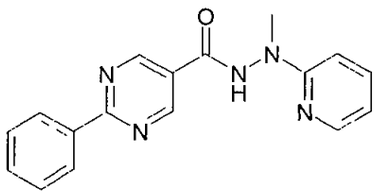
(2-Metil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo ácido 2-fenil-4-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico, y sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 2-metil-2,3-dihidro-indol-1-ilamina, se prepara (2-metil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (31%) en forma de un sólido. MS: 349 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,00-1,48 (m, 3H), 2,43-2,78 (m, 2H), 3,32-4,06 (m, H), 6,50-6,93 (m, 1,5H), 6,93-7,34 (m, 4H), 7,34-7,54 (d, H), 8,05-8,32 (m, 2H), 8,56 (s, 0,5N-H), 9,17 (d, 2H). CI_{50} = 4 nM.

Ejemplo 101

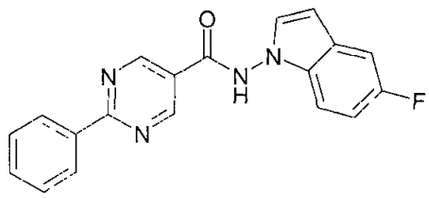
N'-Metil-N'-piridin-2-il-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por N'-metil-N'-piridin-2-il-hidrazina, se prepara N'-metil-N'-piridin-2-il-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico (31%) en forma de un sólido. MS: 306 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,48 (s, 3H), 6,88 (m, 2H), 7,40-7,70 (m, 4H), 8,23 (s, H), 8,52 (m, 2H), 9,13 (a, N-H), 9,28 (s, 2H).

Ejemplo 102

(5-Fluoro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico

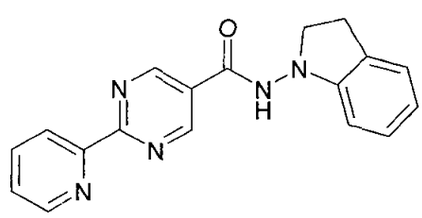


Etapa 1: Una solución de 5-fluoro-1H-indol (16,9 mmol) y terc-butóxido potásico (33,8 mmol) en DMF (76 ml) se agita a ta en una atmósfera de N_2 durante 2 h. Se añade gota a gota NH_2Cl 0,15 M en éter (169,2 ml) durante 15 minutos a ta. La mezcla de reacción se agita a ta durante 2 h, después se inactiva con una solución acuosa al 10% de $Na_2S_2O_3$ y se extrae con éter. La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 60-80% en heptano para producir 5-fluoro-indolo-1-ilamina (751 mg, 30%) en forma de un sólido. ^1H RMN (300 MHz, $CDCl_3$): δ 4,80 (a, 2N-H), 6,38 (d, H), 7,00 (m, H), 7,19-7,43 (m, 3H).

Etapa 2: Se añade dietil-iso-propilamina (2,30 mmol) a una solución agitada de cloruro del ácido 2-fenil-pirimidina-5-carboxílico (1,15 mmol) y 5-fluor-indol-1-ilamina (1,15 mmol) en DCM (20 ml) a ta. La mezcla de reacción se agita a ta durante una noche y se concentra al vacío. El residuo se disuelve en EtOAc (30 ml), después se lava con HCl al 5% (10 ml), agua (10 ml) y salmuera (10 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10-40% en heptano para producir (5-fluoro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (185 mg, 49%) en forma de un sólido. MS: 333 (M+H); ^1H RMN (300 MHz, $CDCl_3$): δ 6,56 (s, H) 7,02 (m, H), 7,10-7,38 (m, 4H), 7,55 (s, 3H), 8,53 (s, 2H), 8,70-9,40 (a, 2H). CI_{50} = 3 nM.

Ejemplo 103

(2,3-Dihidro-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico

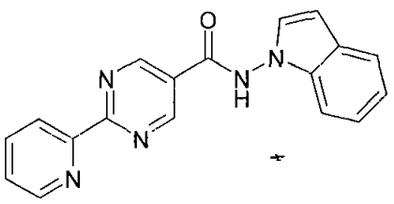


Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo ácido 2-fenil-4-il-pirimidina-5-carboxílico por ácido 2-piridin-2-il-pirimidina-5-carboxílico, y sustituyendo

éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 2,3-dihidro-indol-1-ilamina, se prepara (2,3-dihidro-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico (98%) en forma de un sólido. MS: 318 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,85-3,20 (m, 2H), 3,77 (t, 2H), 6,76 (d, 0,5N-H), 6,82-7,49 (m, 4H), 7,46 (d, H), 7,89 (d, H), 8,07 (a, 0,5N-H), 8,57 (m, H), 8,84 (d, H), 9,30 (s, 2H). CI_{50} = 3 nM.

Ejemplo 104

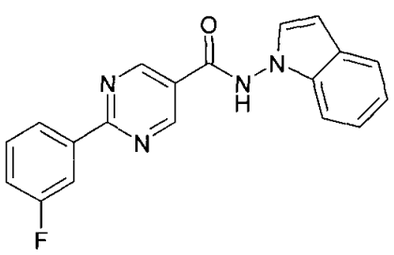
Indol-1-il-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico



Una solución suspendida de (2,3-dihidro-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico (0,28 mmol) y MnO2 (1,42 mmol) en DCM (8 ml) se agita a ta durante 2 h. La mezcla de reacción se filtra y el filtrado se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con metanol al 0-5% en DCM para producir indol-1-il-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico (45 mg, 50%) en forma de un sólido. MS: 316 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 6,48 (s, H), 6,72-7,48 (m, 5H), 7,56 (s, H), 7,88 (s, H), 8,52 (a, 2H), 9,08 (a, 2H), 11,56 (a, N-H). CI_{50} = 4,5 nM.

Ejemplo 105

Indol-1-il-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico

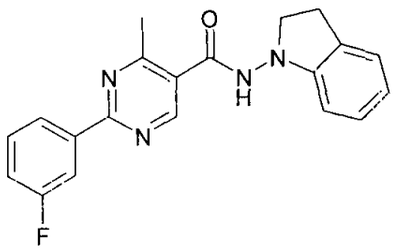


Una solución suspendida de (2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (0,39 mmol) y MnO2 (1,95 mmol) en DCM (10 ml) se agita a ta durante 40 min. La mezcla de reacción se filtra y el filtrado se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0-40% en heptano para producir indol-1-il-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (70 mg, 54%) en forma de un sólido. MS: 333 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 6,60 (s, H),

7,10 (d, H), 7,14-7,46 (m, 4H), 7,50 (a, H), 7,64 (d, H), 8,37 (d, 2H), 8,60-9,40 (a, 3H). CI_{50} = 5 nM.

Ejemplo 106

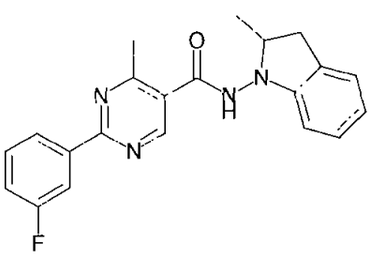
(2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo ácido 2-fenil-4-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico, y sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 2,3-dihidro-indol-1-ilamina, se prepara (2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (91%) en forma de un sólido. MS: 349 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,77-3,08 (m, 2H), 3,09-3,80 (m, 2H), 6,75-7,00 (m, 2H), 7,04-7,32 (m, 3H), 7,44 (c, H), 8,06-8,31 (m, 2H), 8,51 (d, 2H). CI_{50} = 23 nM.

Ejemplo 107

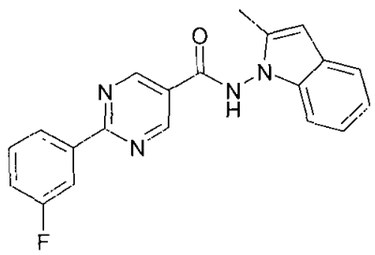
(2-Metil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo ácido 2-fenil-4-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico, y sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 2-metil-2,3-dihidro-indol-1-ilamina, se prepara (2-metil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (94%) en forma de un sólido. MS: 363 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,00-1,50 (d, 3H), 2,30-2,80 (m, 4H), 3,01 (m, H), 3,26-3,96 (m, H), 6,45-7,00 (m, 2H), 7,00-7,30 (m, 3H), 7,41 (c, H), 7,97-8,28 (m, 2H), 8,68 (d, H).

Ejemplo 108

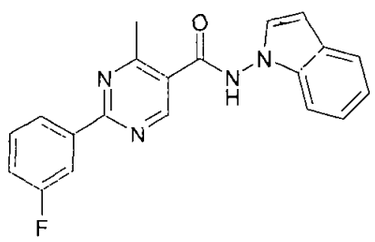
(2-Metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



Una solución suspendida de (2-metil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (0,98 mmol) y MnO2 (4,88 mmol) en DCM (15 ml) se agita a ta durante 2 h. La mezcla de reacción se filtra y el filtrado se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0-40% en heptano para producir (2-metil-indol-1-il)-amida del ácido 2-(3-fenil)-pirimidina-5-carboxílico (230 mg, 97%) en forma de un sólido. MS: 347 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,08-2,40 (m, 3H), 6,27 (s, H), 6,95-7,35 (m, 4H), 7,36-7,65 (m, 2H), 8,20-8,44 (m, 2H), 8,49-9,20 (d, 2H). CI_{50} = 6 nM.

Ejemplo 109

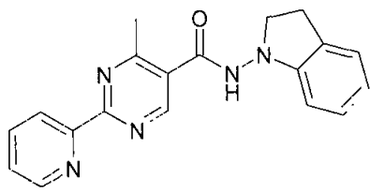
Indol-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Una solución suspendida de (2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (0,72 mmol) y MnO2 (3,60 mmol) en DCM (10 ml) se agita a ta durante 40 min. La mezcla de reacción se filtra y el filtrado se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0-40% en heptano para producir indol-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (185 mg, 75%) en forma de un sólido. MS: 347 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,73 (s, 3H), 6,53 (s, H), 7,03 (d, H), 7,08-7,36 (m, 4H), 7,37-7,75 (m, 2H), 8,04-8,40 (m, 2H), 8,56 (a, H), 8,81 (a, H). CI_{50} = 10 nM.

Ejemplo 110

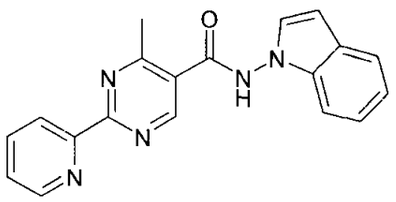
(2,3-Dihidro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo ácido 2-fenil-4-il-pirimidina-5-carboxílico por ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico, y sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 2,3-dihidro-indol-1-ilamina, se prepara (2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (96%) en forma de un sólido. MS: 332 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,78 (s, 3H), 3,09 (t, 2H), 3,77 (t, 2H), 6,70-7,01 (m, 2H), 7,09-7,23 (m, 2H), 7,36-7,46 (m, H), 7,85 (t, H), 8,43-8,64 (m, 2H), 8,80 (d, H). CI_{50} = 3 nM.

Ejemplo 111

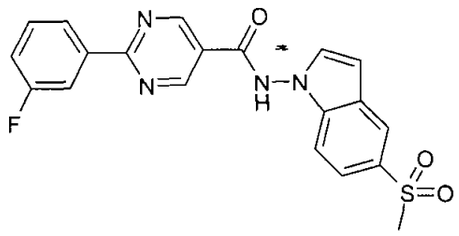
Indol-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Una solución suspendida de (2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (1,00 mmol) y MnO2 (5,00 mmol) en DCM (10 ml) se agita a ta durante 60 min. La mezcla de reacción se filtra y el filtrado se concentra al vacío. El residuo se purifica por cromatografía sobre gel de silice eluyendo con metanol al 0-5% en DCM para producir indol-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (196 mg, 60%) en forma de un sólido. MS: 330 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,77 (s, 3H), 6,58 (s, H), 7,15 (s, 2H), 7,26 (m, 3H), 7,84 (d, H), 8,44 (s, 2H), 8,73 (s, H), 10,94 (a, N-H). CI_{50} = 5 nM.

Ejemplo 112

(5-Metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



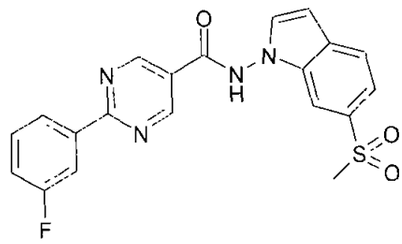
Etapa 1: Una solución de 5-metanosulfonil-indolina (4,11 mmol) y MnO2 (20,55 mmol) en DCM (20 ml) se agita a ta durante una noche. La mezcla de reacción se filtra y el filtrado se concentra al vacío para producir 5-metanosulfonil-1H-indol (782 mg, 100%) en forma de un sólido. MS: 196 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,09 (s, 3H), 6,71 (s, H), 7,39 (s, H), 7,53 (d, H), 7,74 (m, H), 8,30 (s, H), 8,66 (a, N-H).

Etapa 2: Una solución de 5-metanosulfonil-1H-indol (4,1 mmol) y terc-butóxido potásico (8,2 mmol) en DMF (20 ml) se agita a ta en una atmósfera de N_2 durante 2 h. Se añade gota a gota NH_2Cl 0,15 M en éter (41 ml) durante 15 min a ta y la mezcla de reacción se agita a ta durante 2 h. La mezcla de reacción se inactiva con una solución acuosa al 10% de $Na_2S_2O_3$ y se extrae con éter (3 x 40 ml). La capa orgánica combinada se lava con agua (2 x 30 ml) y salmuera (20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc y heptano para producir 5-metanosulfonil-indolo-1-ilamina (230 mg, 32%) en forma de un sólido. MS: 211 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,08 (s, 3H), 4,94 (a, 2N-H), 6,55 (d, H), 7,34 (m, H), 7,57 (d, H), 7,73 (m, H), 8,21 (m, H).

Etapa 3: Una solución de cloruro del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (0,62 mmol) en EtOAc (10 ml) se añade a una solución agitada de 5-metanosulfonil-indolo-1-ilamina (0,62 mmol) y K_2CO_3 (3,08 mmol) en EtOAc (10 ml) y H_2O (10 ml) a 0ºC, y la mezcla de reacción se calienta a ta y se agita durante una noche. El EtOAc se evapora al vacío y el sólido resultante se recoge por filtración. El sólido se tritura con DCM para producir (5-metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (85 mg, 34%) en forma de un sólido. MS: 411 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 3,13 (s, 3H), 6,81 (m, H) 7,25-7,39 (m, H), 7,49-7,67 (m, 3H), 7,72-7,84 (m, H), 8,21-8,32 (m, 2H), 8,39 (d, H), 9,41 (s, 2H).

Ejemplo 113

(6-Metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico

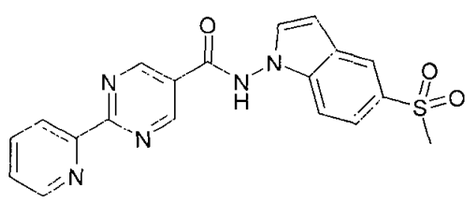


Etapa 1: Una solución de 6-metanosulfonil-1H-indol (2,66 mmol) y terc-butóxido potásico (5,32 mmol) en DMF (15 ml) se agita a ta en una atmósfera de N_2 durante 2 h. Se añade gota a gota NH_2Cl 0,15 M en éter (26,6 ml) durante 15 minutos a ta y la mezcla de reacción se agita a ta durante 2 h. La mezcla de reacción se inactiva con una solución acuosa al 10% de $Na_2S_2O_3$ y se extrae con éter (3 x 20 ml). La capa orgánica combinada se lava con salmuera (20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se tritura con EtOAc para dar 6-metanosulfonil-indolo-1-ilamina (270 mg, 51%) en forma de un sólido. MS: 211 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,09 (s, 3H), 6,49 (d, H), 7,41 (m, H), 7,61 (d, H), 7,71 (d, H), 8,12 (s, H).

Etapa 2: Una solución de cloruro del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (0,65 mmol) en EtOAc (15 ml) se añade a una solución agitada de 5-metanosulfonil-indolo-1-ilamina (0,65 mmol) y carbonato potásico (2,60 mmol) en EtOAc (10 ml) y H_2O (10 ml) a 0°C, y la mezcla de reacción se calienta a ta y se agita durante una noche. El EtOAc se evapora al vacío y el sólido resultante se recoge por filtración y se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 20-60% en heptano para producir (6-metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (85 mg, 33%) en forma de un sólido. MS: 411 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,08 (s, 3H), 6,62 (d, H) 7,33-7,44 (m, 2H), 7,46-7,59 (m, 2H), 7,75 (s, H), 8,29 (d, 2H), 8,39 (d, H), 9,42 (s, 2H), 10,80 (a, H). CI_{50} = 8 nM.

Ejemplo 114

(5-Metanosulfonil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico

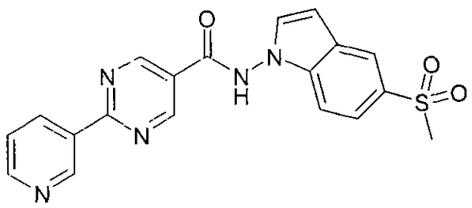


Se añade dietil-iso-propilamina (3,54 mmol) a una solución de ácido 2-piridin-2-il-pirimidina-5-carboxílico·HCl (1,18 mmol), 5-metanosulfonil-indol-1-ilamina (1,18 mmol) y

TBTU (1,77 mmol) en DMF anhidra (16 ml) a ta. La mezcla de reacción se agita a 90°C durante una noche y después se concentra al vacío. El residuo se disuelve en EtOAc (50 ml) y agua (50 ml). La capa orgánica se separa, se lava con agua (2 x 20 ml) y salmuera (20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se tritura con EtOAc y DCM para producir (5-metanosulfonil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico (125 mg, 27%) en forma de un sólido. MS: 394 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 3,14 (s, 3H), 6,82 (m, H) 7,50-7,72 (m, 3H), 7,80 (m, H), 8,07 (m, H), 8,30 (m, 2H), 8,70 (d, H), 8,80 (s, H), 9,51 (s, 2H).

Ejemplo 115

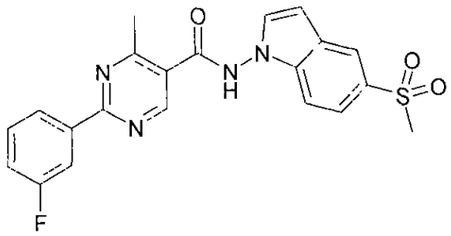
(5-Metanosulfonil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico



Se añade dietil-iso-propilamina (3,84 mmol) a una solución de hidrocloruro del ácido 2-piridin-2-il-pirimidina-5-carboxílico·HCl (1,28 mmol), 5-metanosulfonil-indol-1-ilamina (1,28 mmol) y TBTU (1,92 mmol) en DMF anhidra (16 ml) a ta. La mezcla de reacción se agita a 90°C durante una noche y después se concentra al vacío. El residuo se disuelve en EtOAc (60 ml) y se lava con agua (2 x 30 ml) y salmuera (20 ml). La capa orgánica se separa, se lava con agua (2 x 20 ml) y salmuera (20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 0-5% en DCM para producir (5-metanosulfonil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico (125 mg, 25%) en forma de un sólido. MS: 394 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,10 (s, 3H), 6,61 (m, H) 6,98 (m, H), 7,34 (s, H), 7,51 (m, H), 7,91 (s, H), 8,83 (m, 2H), 9,49 (s, H), 9,77 (s, H), 10,10 (s, N-H).

Ejemplo 116

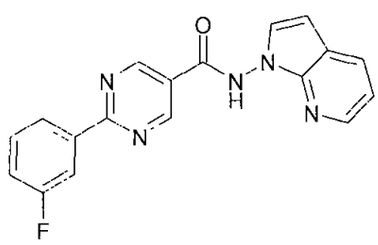
(5-Metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Se añade NaHMDS 2,0 M (bis(trimetilsilil)amida sódica) en THF a una solución agitada de cloruro del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (0,72 mmol) y 5-metanosulfonil-indol-1-ilamina (0,72 mmol) en piridina anhidra (10 ml) a ta. La mezcla de reacción se agita a 90°C durante una noche y después se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 1,5% en DCM para producir (5-metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (50 mg, 8%) en forma de un sólido. MS: 425 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,86 (s, 3H), 3,02 (s, 3H), 6,55 (s, H) 6,92 (d, H), 7,17-7,38 (m, 3H), 7,53 (m, H), 7,78 (s, H), 8,27 (d, H), 8,38 (d, H), 9,16 (s, H).

Ejemplo 117

Pirrolo[2,3-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



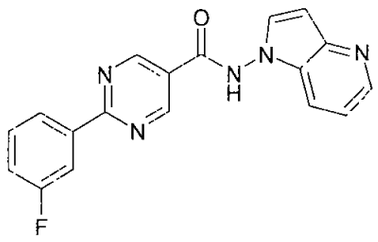
Etapa 1: Una solución de pirrolo[2,3-b]piridina (16,9 mmol) y terc-butóxido potásico (33,8 mmol) en DMF (76 ml) se agita a ta en una atmósfera de N_2 durante 2 h. Se añade gota a gota NH_2Cl 0,15 M en éter (169,2 ml) a ta y la mezcla de reacción se agita a ta durante 2 h. La mezcla de reacción se inactiva con una solución acuosa al 5% de $Na_2S_2O_3$ (100 ml) y se extrae tres veces con éter. La capa orgánica se lava con salmuera (20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 60-80% en heptano para producir pirrolo[2,3-b]piridin-1-ilamina (703 mg, 31%) en forma de un sólido. MS: 134 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 5,04 (a, 2N-H), 6,35 (d, H), 7,09 (m, H), 7,35 (m, H), 7,91 (m, H), 8,34 (d, H).

Etapa 2: Una solución de cloruro del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (1,13 mmol) en EtOAc (20 ml) se añade a una solución agitada de pirrolo[2,3-b]piridin-1-ilamina

(1,13 mmol) y K_2CO_3 (1,13 mmol) en EtOAc (10 ml) y H_2O (20 ml) a ta y la mezcla de reacción se agita a ta durante una noche. El EtOAc se evapora al vacío y el sólido resultante se recoge por filtración para producir pirrolo[2,3-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (305 mg, 81%) en forma de un sólido. MS: 334 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 6,57 (d, H) 7,13-7,55 (m, 4H), 7,99 (m, H), 8,10-8,40 (m, 3H), 9,27 (s, 2H), 12,57 (a, N-H).

Ejemplo 118

Pirrolo[3,2-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico

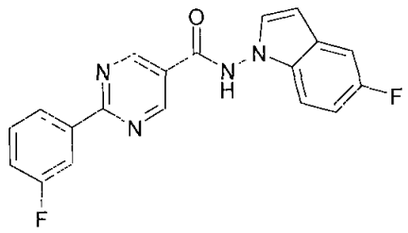


Etapa 1: Una solución de pirrolo[3,2-b]piridina (1,64 mmol) y terc-butóxido potásico (3,29 mmol) en DMF (7,3 ml) se agita a ta en una atmósfera de N_2 durante 2 h. Se añade gota a gota NH_2Cl 0,15 M en éter (16,3 ml) a ta y la mezcla de reacción se agita a ta durante 3 h. La mezcla de reacción se inactiva con una solución acuosa al 5% de $Na_2S_2O_3$ (10 ml) y se extrae tres veces con éter. La capa orgánica combinada se lava con salmuera, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc para producir pirrolo[3,2-b]piridin-1-ilamina (136 mg, 62%) en forma de un sólido. MS: 134 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,89 (a, 2N-H), 6,61 (d, H), 7,16 (m, H), 7,38 (d, H), 7,76 (d, H), 8,47 (d, H).

Etapa 2: Una solución de cloruro del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (0,45 mmol) en EtOAc (8 ml) se añade a una solución agitada de pirrolo[3,2-b]piridin-1-ilamina (0,45 mmol) y K_2CO_3 (0,45 mmol) en EtOAc (4 ml) y H_2O (8 ml) a ta, y la mezcla de reacción se agita a ta durante 30 min. El EtOAc se evapora y el sólido resultante se recoge por filtración para producir pirrolo[3,2-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (116 mg, 77%) en forma de un sólido. MS: 334 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 6,60 (d, H) 7,15-7,60 (m, 4H), 8,01 (m, H), 8,10-8,41 (m, 3H), 9,27 (s, 2H), 12,45 (a, N-H). CI_{50} = 18 nM.

Ejemplo 119

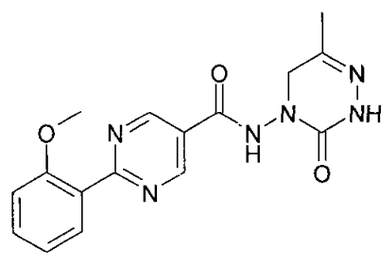
(5-Fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



Una solución de cloruro del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (1 mmol) en EtOAc (20 ml) se añade a una solución agitada de 5-fluoro-indol-1-ilamina (1 mmol) y carbonato potásico (1 mmol) en EtOAc (10 ml) y H_2O (20 ml) a ta y la mezcla de reacción se agita a ta durante una noche. El EtOAc se evapora al vacío y el sólido resultante se recoge por filtración para producir (5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (148 mg, 42%) en forma de un sólido. MS: 351 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 6,56 (m, H) 7,02 (m, H), 7,12-7,34 (m, 3H), 7,51 (m, H), 8,24 (d, H), 8,34 (s, H), 8,92 (a, H), 9,24 (a, 2H).

Ejemplo 120

(6-Metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(2-metoxi-fenil)-pirimidina-5-carboxílico



Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 1, pero sustituyendo ácido 3-metoxifenilborónico por ácido 2-metoxifenilborónico, se prepara éster metílico del ácido 2-(2-metoxi-fenil)-pirimidina-5-carboxílico.

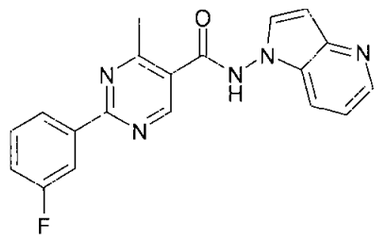
Etapa 2: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 2, pero sustituyendo éster metílico del ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico por éster metílico del ácido 2-(2-metoxi-fenil)-pirimidina-5-carboxílico, se prepara ácido 2-(2-metoxi-fenil)-pirimidina-5-carboxílico.

Etapa 3: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 3, pero sustituyendo ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico por ácido 2-(2-metoxi-fenil)-pirimidina-5-carboxílico, se prepara (6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-

(2-metoxi-fenil)-pirimidina-5-carboxílico. MS: 341 (M+H); ^{1}H RMN (DMSO-d_6): δ 1,91 (s, 3H), 3,79 (s, 2H), 4,22 (s, 2H), 7,09 (m, 1H), 7,19 (d, J = 8,2 Hz, 1H), 7,52 (m, 1H), 7,65 (m, 1H), 9,24 (s, 2H), 9,96 (s, 1H), 11,06 (s, 1H). CI_{50} = 199 nM.

Ejemplo 121

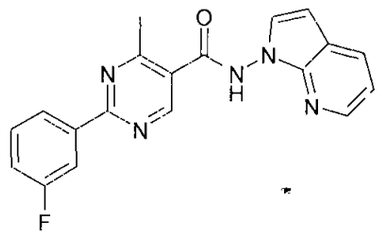
Pirrolo[3,2-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Una solución de cloruro del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (0,45 mmol) en EtOAc (8 ml) se añade a una solución agitada de pirrolo[3,2-b]piridin-1-ilamina (0,45 mmol) y carbonato potásico (0,45 mmol) en EtOAc (4 ml) y H_2O (8 ml) a ta y la mezcla de reacción se agita a ta durante una noche. El EtOAc se evapora al vacío y el sólido resultante se recoge por filtración. El sólido se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 20-80% en heptano para producir pirrolo[3,2-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (38 mg, 24%) en forma de un sólido. MS: 348 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,76 (s, 3H), 6,59 (m, H) 7,07-7,64 (m, 4H), 7,96 (m, H), 8,23 (m, H), 8,32 (m, 2H), 9,12 (s, H), 10,01 (a, N-H).

Ejemplo 122

Pirrolo[2,3-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

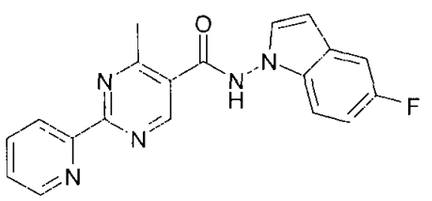


Una solución de cloruro del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (1 mmol) en EtOAc (10 ml) se añade a una solución agitada de pirrolo[2,3-b]piridin-1-ilamina (1 mmol) y K_2CO_3 (1 mmol) en EtOAc (20 ml) y H_2O (20 ml) a ta y después se agita a ta durante una noche. El EtOAc se evapora al vacío y el sólido resultante se recoge por filtración. El sólido se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 20-80% en heptano para producir pirrolo[3,2-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-

4-metil-pirimidina-5-carboxílico (162 mg, 47%) en forma de un sólido. MS: 348 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,78 (s, 3H), 6,59 (m, H) 7,09-7,58 (m, 4H), 7,96 (m, H), 8,22 (m, H), 8,31 (d, 2H), 9,14 (s, 2H). CI_{50} = 12 nM.

Ejemplo 123

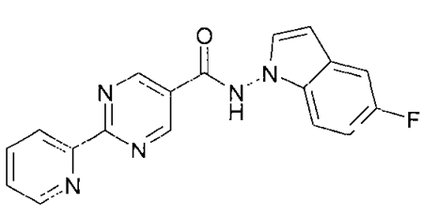
(5-Fluoro-2-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Una solución de cloruro del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (1 mmol) en EtOAc (20 ml) se añade a una solución agitada de 5-fluoro-indol-1-ilamina (1,20 mmol) y K_2CO_3 (2 mmol) en EtOAc (10 ml) y H_2O (20 ml) a ta y la mezcla de reacción se agita a ta durante una noche. La mezcla de reacción se extrae con EtOAc. La capa orgánica se lava con salmuera, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 0-10% en DCM para dar un sólido. El sólido se tritura con EtOAc/heptano para producir (5-fluoro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (122 mg, 35%) en forma de un sólido. MS: 348 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,77 (s, 3H), 6,55 (m, H) 7,06 (m, H), 7,32-7,66 (m, 4H), 8,02 (m, H), 8,45 (d, H), 8,79 (s, H), 9,26 (s, H), 12,00 (s, N-H). CI_{50} = 17 nM.

Ejemplo 124

(5-Fluoro-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico

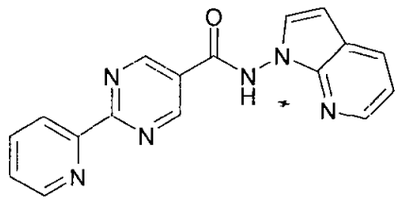


Una solución de cloruro del ácido 2-piridin-2-il-pirimidina-5-carboxílico (1 mmol) en EtOAc (20 ml) se añade a una solución agitada de 5-fluoro-indol-1-ilamina (1 mmol) y K_2CO_3 (2 mmol) en EtOAc (10 ml) y H_2O (20 ml) a ta y la mezcla de reacción se agita a ta durante una noche. El EtOAc se evapora al vacío y el sólido resultante se recoge por filtración. El sólido se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 0-10% en DCM para producir (5-fluoro-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-

5-carboxílico (65 mg, 20%) en forma de un sólido. MS: 334 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 6,56 (m, H) 7,04 (m, H), 7,28-7,79 (m, 3H), 8,04 (m, H), 8,49 (m, H), 8,81 (m, H), 9,48 (s, 2H), 12,22 (s, N-H). CI_{50} = 18 nM.

Ejemplo 125

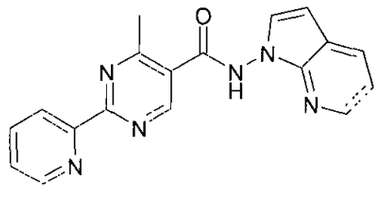
Pirrolo[2,3-b]piridina-1-ilamida del ácido 2-piridin-2-il-pirimidina-5-carboxílico



Se añade dietil-iso-propilamina (1,13 mmol), una solución de ácido 2-piridin-2-il-pirimidina-5-carboxílico (0,75 mmol), pirrolo[2,3-b]piridina-1-ilamina (0,75 mmol) y TBTU en DMF anhidra (7 ml) a ta y la mezcla de reacción se agita a 80°C durante una noche. La mezcla de reacción se concentra al vacío. El residuo se disuelve en EtOAc, se lava dos veces con agua, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 0-10% en DCM para dar un producto bruto. El producto se cristaliza en EtOAc para producir pirrolo[2,3-b]piridina-1-ilamida del ácido 2-piridin-2-il-pirimidina-5-carboxílico (78 mg, 25%) en forma de un sólido. MS: 317 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 6,56 (m, H) 7,24 (m, H), 7,53 (m, H), 7,61 (m, H), 8,01-8,17 (m, 2H), 8,27 (d, H), 8,69 (m, H), 8,78 (m, H), 9,51 (s, 2H).

Ejemplo 126

Pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico

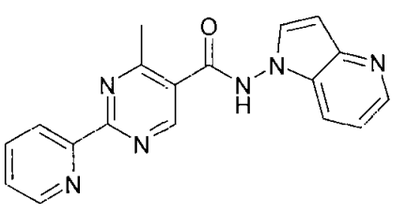


Se añade dietil-iso-propilamina (1,13 mmol) a una solución de ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (0,75 mmol), pirrolo[2,3-b]piridina-1-ilamina (0,75 mmol) y TBTU (0,9 mmol) en DMF anhidra (7 ml) a ta y la mezcla de reacción se agita a 80°C durante una noche. La mezcla de reacción se concentra al vacío. El residuo se disuelve en EtOAc, se lava con Na_2CO_3 acuoso saturado y agua, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con CH_3CN al 0-10% en DCM para dar un producto bruto. El producto bruto se cristaliza en EtOAc para producir

pirrol[2,3-b]piridina-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (95 mg, 38%) en forma de un sólido. MS: 331 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,89 (s, 3H), 6,65 (d, H), 7,23 (m, H), 7,48-7,66 (m, 2H), 8,01-8,15 (m, 2H), 8,29 (m, H), 8,64 (d, H), 8,77 (d, H), 9,33 (s, 2H).

Ejemplo 127

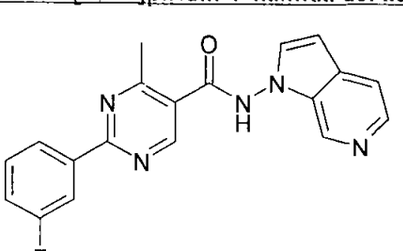
Pirrolo[3,2-b]piridin-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Se añade dietil-iso-propilamina (1,88 mmol) a una solución de ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (0,75 mmol), pirrolo[3,2-b]piridina-1-ilamina (0,75 mmol) y TBTU (0,9 mmol) en DMF anhidra (7 ml) a ta y la mezcla de reacción se agita a 80ºC durante 8 h. La mezcla de reacción se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 0-10% en DCM para producir pirrol[3,2-b]piridina-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (155 mg, 63%) en forma de un sólido. MS: 331 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,89 (s, 3H), 7,01 (d, H), 7,64-7,77 (m, 2H), 8,15 (m, H), 8,25 (m, H), 8,59-8,76 (m, 3H), 8,82 (d, H), 9,31 (s, 2H). CI_{50} = 13 nM.

Ejemplo 128

Pirrolo[2,3-c]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



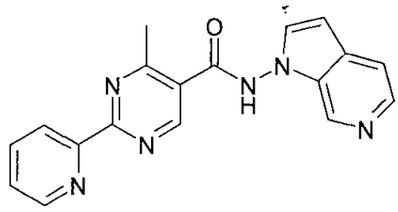
Etapa 1: Una solución de pirrolo[2,3-c]piridina (8,47 mmol) y terc-butóxido potásico (16,9 mmol) en DMF (38 ml) se agita a ta en una atmósfera de N_2 durante 2 h. Se añade gota a gota NH_2Cl 0,15 M en éter (84,6 ml) a ta y la mezcla de reacción se agita a ta durante 2 h, se inactiva con una solución acuosa al 5% de $Na_2S_2O_3$ (10 ml) y se extrae con éter. La capa orgánica se separa, se lava con salmuera, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 0-10% en

DCM para producir pirrolo[2,3-c]piridin-1-ilamina (226 mg, 11%) en forma de un sólido. MS: 134 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,96 (a, 2N-H), 6,43 (d, H), 7,29 (m, H), 7,50 (d, H), 8,29 (d, H), 8,89 (s, H).

Etapa 2: Se añade dietil-iso-propilamina (1,13 mmol) a una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (0,75 mmol), pirrolo[2,3-c]piridina-1-ilamina (0,75 mmol) y TBTU (0,9 mmol) en DMF anhidra (7 ml) a ta y la mezcla de reacción se agita a 80°C durante una noche. Se añade agua (150 ml) y la mezcla se extrae con EtOAc. La capa orgánica se separa, se lava con agua y salmuera, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 40-100% en DCM para producir pirrolo[2,3-c]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (117 mg, 45%) en forma de un sólido. MS: 348 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,84 (s, 3H), 6,72 (d, H), 7,29 (m, 2H), 7,55 (m, H), 7,71 (m, H), 8,14-8,29 (m, 2H), 8,36 (d, 3), 8,75 (s, H), 9,17 (s, H). CI_{50} = 28,5 nM.

Ejemplo 129

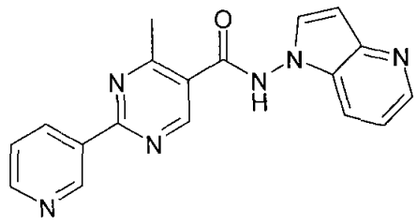
Pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 127 pero sustituyendo pirrolo[3,2-b]piridina-1-ilamina por pirrolo[2,3-c]piridina-1-ilamina, se prepara pirrol[2,3-c]piridina-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (46%) en forma de un sólido. MS: 331 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,79 (s, 3H), 6,64 (d, H), 7,53-7,65 (m, 2H), 7,78 (d, H), 8,02 (m, H), 8,22 (m, H), 8,46 (m, H), 8,80 (d, H), 8,87 (s, H), 9,30 (s, H).

Ejemplo 130

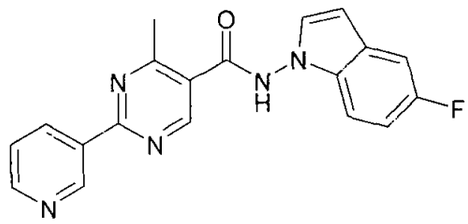
Pirrolo[3,2-b]piridin-1-ilamida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 127 pero sustituyendo ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico por ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico, se prepara pirrolo[3,2-b]piridina-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (40%) en forma de un sólido. MS: 331 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,86 (s, 3H), 6,74 (m, H), 7,31 (m, H), 7,61 (m, H), 7,71 (d, H), 7,92 (d, H), 8,41 (d, H), 8,71 (d, H), 8,91 (d, H), 9,20 (s, H), 9,64 (s, H). CI_{50} = 14 nM.

Ejemplo 131

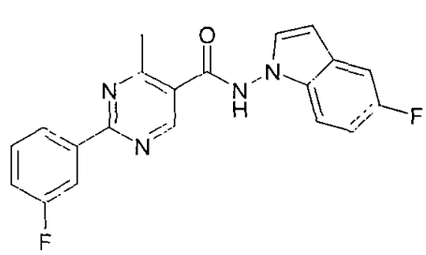
(5-Fluoro-2-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 127 pero sustituyendo ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico por ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico, y sustituyendo pirrolo[3,2-b]piridina-1-ilamina por 5-fluoro-indol-1-ilamina, se prepara (5-fluoro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (34%) en forma de un sólido. MS: 348 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,85 (s, 3H), 6,57 (m, H), 7,02 (m, H), 7,23-7,46 (m, 2H), 7,62 (m, H), 8,70 (d, H), 8,91 (d, H), 9,17 (s, H), 9,63 (s, H).

Ejemplo 132

(5-Fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

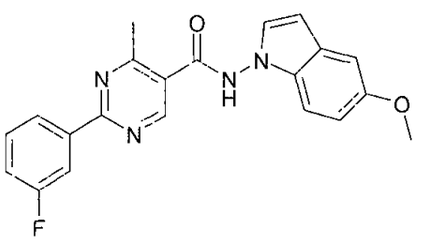


Método A: Siguiendo procedimientos similares a los del Ejemplo 127 pero sustituyendo ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico, y sustituyendo pirrolo[3,2-b]piridina-1-ilamina por 5-fluoro-indol-1-ilamina, se prepara (5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (17%) en forma de un sólido. MS: 365 (M+H): ^{1}H RMN (300 MHz, CD_3OD): δ 6,56 (d, H), 7,02 (m, H), 7,22-7,44 (m, 4H), 7,55 (m, H), 8,22 (d, H), 8,36 (d, H), 9,13 (s, H).

Método B: Una solución de cloruro del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (1 mmol) en EtOAc (20 ml) se añade a una solución agitada de 5-fluoro-indol-1-ilamina (1 mmol) y K_2CO_3 (1 mmol) en EtOAc (10 ml) y H_2O (20 ml) a ta, y después se agita a ta durante una noche. El EtOAc se evapora al vacío y el sólido resultante se recoge por filtración. El sólido se cristaliza en EtOAc/heptano para producir (5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (62 mg, 17%) en forma de un sólido. MS: 365 (M+H): ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,82 (s, H), 6,55 (s, H) 6,90-7,41 (m, 4H), 7,49 (m, H), 8,26 (d, 2H), 8,57 (a, H), 8,96 (a, H). CI_{50} = 19 nM.

Ejemplo 133

(5-Metoxi-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

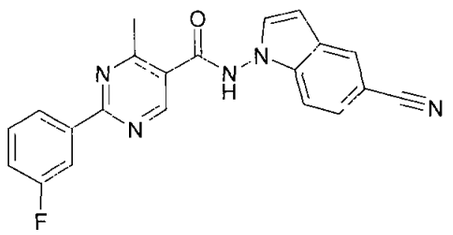


Etapa 1: Una solución de 5-metoxi-1H-indol (16,9 mmol) y terc-butóxido potásico (33,8 mmol) en DMF (76 ml) se agita a ta en una atmósfera de N_2 durante 2 h. Se añade gota a gota NH_2Cl 0,15 M en éter (169,2 ml) durante 15 minutos a ta. La mezcla de reacción se agita a ta durante 2 h, se inactiva con una solución acuosa al 5% de $Na_2S_2O_3$ (100 ml) y se agita a ta durante una noche. La mezcla se extrae con éter. La capa orgánica se separa, se lava con salmuera, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0-20% en heptano para producir 5-metoxi-indolo-1-ilamina (388 mg, 14%) en forma de un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,78 (a, 2N-H), 6,35 (d, H), 6,94 (d, H), 7,08 (d, H), 7,17 (d, H), 7,30 -7,39 (d, H).

Etapa 2: Siguiendo procedimientos similares a los del Ejemplo 127 pero sustituyendo ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico, y sustituyendo pirrolo[3,2-b]piridina-1-ilamina por 5-metoxi-indol-1-ilamina, se prepara (5-metoxi-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (43%) en forma de un sólido. MS: 377 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,83 (s, 3H), 3,84 (s, 3H), 6,50 (d, H), 6,90 (m, H), 7,12 (d, H), 7,22-7,36 (m, 3H), 7,55 (m, H), 8,22 (d, H), 8,36 (d, H), 9,11 (s, H). CI_{50} = 6 nM.

Ejemplo 134

(5-Ciano-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

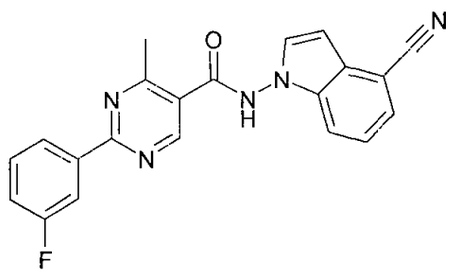


Etapa 1: Se añade en porciones NaH (al 60%, 60 mmol) a una solución de 5-ciano-1H-indol (20 mmol) en NMP (35 ml) y la mezcla de reacción se enfría a 0°C durante 1 h. Se añade gota a gota una solución de HOSA (60 mmol) en NMP (14 ml) a 0°C. La mezcla de reacción se calienta a ta y se agita durante una noche, después se inactiva con agua y se extrae con EtOAc. La capa orgánica se separa, se lava tres veces con agua y con salmuera, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 20-40% en heptano para producir 5-ciano-indolo-1-ilamina (531 mg, 16%) en forma de un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,88 (a, 2N-H), 6,53 (d, H), 7,32 (d, H), 7,54 (c, 2H), 7,98 (d, H).

Etapa 2: Siguiendo procedimientos similares a los del Ejemplo 127 pero sustituyendo ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico, y sustituyendo pirrolo[3,2-b]piridina-1-ilamina por 5-ciano-indol-1-ilamina, se prepara (5-ciano-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (39%) en forma de un sólido. MS: 372 (M+H); ^{1}H RMN (300 MHz, DMSO-d6): δ 2,77 (s, 3H), 6,73 (d, H), 7,45 (m, H), 7,53-7,82 (m, 4H), 8,08-8,23 (m, 2H), 8,32 (d, H), 9,27 (s, H), 12,15 (a, N-H).

Ejemplo 135

(4-Ciano-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

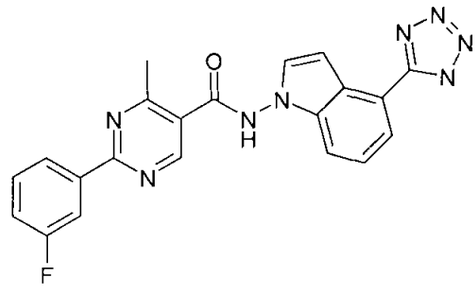


Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 134, etapa 1, pero sustituyendo 5-ciano-1H-indol por 4-ciano-1H-indol, se prepara 4-ciano-indolo-1-ilamina (33%) en forma de un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,1 (a, 2N-H), 6,88 (d, H), 7,22-7,40 (m, 2H), 7,51 (d, H), 7,72 (d, H).

Etapa 2: Siguiendo procedimientos similares a los del Ejemplo 127 pero sustituyendo ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico, y sustituyendo pirrolo[3,2-b]piridina-1-ilamina por 4-ciano-indol-1-ilamina, se prepara (4-ciano-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (29%) en forma de un sólido. MS: 372 (M+H): ^{1}H RMN (300 MHz, DMSO-d6): δ 2,77 (s, 3H), 6,71 (s, H), 7,32-7,51 (m, 2H), 7,57-7,69 (m, 2H), 7,88 (m, 2H), 8,16 (d, H), 8,31 (d, H), 9,25 (s, H).

Ejemplo 136

[4-(1H-Tetrazol-5-il)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

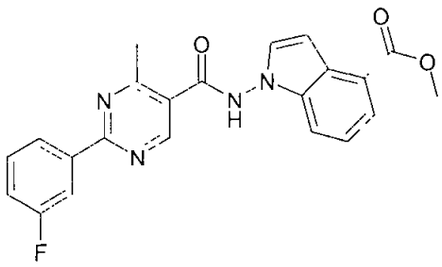


Una solución de (0,5 mmol), cloruro de amonio (6 mmol) y azida sódica (6 mmol) en DMF anhidra (6 ml) se calienta en el microondas a 200ºC durante 1 h. La mezcla de reacción se inactiva con una solución acuosa saturada de Na_2CO_3 y se lava con EtOAc. La capa acuosa se separa, se acidifica con HCl acuoso concentrado para ajustar el valor del valor del pH a ~1 y se extrae con EtOAc. La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 3% en DCM para producir [4-(1H-tetrazol-5-il)-indol-1-il]-amida del ácido 2-(3-fluoro-

fenil)-4-metil-pirimidina-5-carboxílico (18 mg, 9%) en forma de un sólido. MS: 415 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,85 (s, 3H), 7,20-7,35 (m, 2H), 7,44 (m, H), 7,52-7,59 (m, 2H), 7,65 (m, H), 7,77 (d, H), 8,23 (d, H), 8,37 (d, H), 9,18 (s, H).

Ejemplo 137

Éster metílico del ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-4-carboxílico

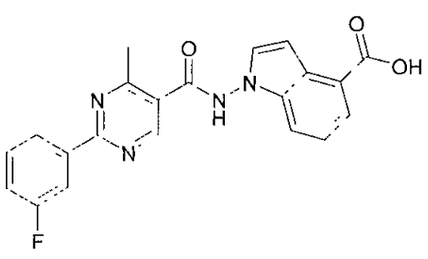


Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 133, etapa 1, pero sustituyendo 5-metoxi-1H-indol por éster metílico del ácido 1H-indolo-4-carboxílico, se prepara éster metílico del ácido 1-amino-1H-indolo-4-carboxílico (10%) en forma de un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,88 (a, 2N-H), 7,03 (d, H), 7,33 (m, H), 7,49 (d, 2H), 7,94 (d, H).

Etapa 2: Siguiendo procedimientos similares a los del Ejemplo 127, pero sustituyendo ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico, sustituyendo pirrolo[3,2-b]piridina-1-ilamina por éster metílico del ácido 1-amino-1H-indolo-4-carboxílico, y agitando la reacción a 150ºC durante 45 minutos, se prepara éster metílico del ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-4-carboxílico (33%) en forma de un sólido. MS: 405 (M+H); ^{1}H RMN (300 MHz, DMSO-d6): δ 2,77 (s, 3H), 3,92 (s, 3H), 7,44 (m, H), 7,63 (m, H), 7,72 (m, H), 7,76-7,88 (m, 2H), 8,17 (d, H), 8,31 (d, H), 9,26 (s, H), 12,06 (a, N-H).

Ejemplo 138

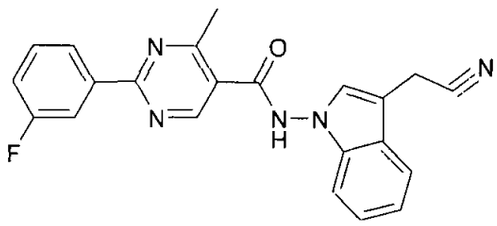
Ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-4-carboxílico



Una solución de éster metílico del ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-4-carboxílico (0,48 mmol) y LiOH (1,91 mmol) en metanol/THF/H2O (1:1:1, 6 ml) se agita a ta durante una noche. La mezcla de reacción se diluye con agua y se lava con DCM. La capa acuosa se separa y se acidifica con HCl acuoso al 10% para ajustar el valor del pH a ~1. La mezcla se extrae dos veces con éter. La capa orgánica se seca (Na_2SO_4), se filtra y se concentra al vacío para producir ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-4-carboxílico (186 mg, 99%) en forma de un sólido. MS: 391 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,85 (s, 3H), 7,20 (m, H), 7,24-7,40 (m, 2H), 7,46-7,61 (m, 2H), 7,66 (d, H), 7,92 (d, H), 8,23 (d, H), 8,37 (d, H), 9,16 (s, H).

Ejemplo 139

(3-Cianometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

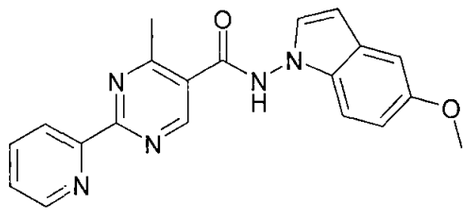


Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 133, etapa 1, pero sustituyendo 5-metoxi-1H-indol por 1H-indol-3-il-acetonitrilo, se prepara (1-amino-1H-indol-3-il)-acetonitrilo (17%) en forma de un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,83 (s, 2H), 4,80 (a, 2N-H), 7,17-7,25 (m, 2H), 7,33 (t, H), 7,46 (d, H), 7,59 (d, H).

Etapa 2: Siguiendo procedimientos similares a los del Ejemplo 127, pero sustituyendo ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico por ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico, sustituyendo pirrolo[3,2-b]piridina-1-ilamina por 3-cianometil-indol-1-ilamina, y agitando la reacción a 150ºC durante 1 h, se prepara (3-cianometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (42%) en forma de un sólido. MS: 386 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,84 (s, 3H), 4,03 (s, 2H), 7,15-7,48 (m, 5H), 7,55 (m, H), 7,70 (d, H), 8,23 (d, H), 8,37 (d, H), 9,14 (s, H).

Ejemplo 140

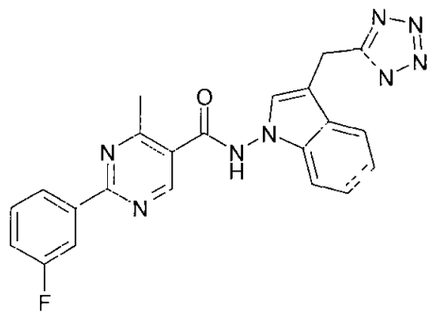
(5-Metoxi-2-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 127, pero sustituyendo pirrolo[3,2-b]piridina-1-ilamina por 5-metoxi-indol-1-ilamina, y agitando la reacción a 150°C durante 1 h, se prepara (5-metoxi-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico (22%) en forma de un sólido. MS: 360 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,88 (s, 3H), 3,84 (s, 3H), 6,50 (d, H) 6,90 (m, H), 7,13 (d, H), 7,25-7,34 (m, 2H), 7,60 (m, H), 8,05 (m, H), 8,65 (d, H), 8,79 (d, H), 9,20 (s, 2H).

Ejemplo 141

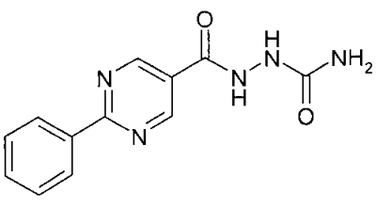
[3-(1H-Tetrazol-5-ilmetil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 136, pero sustituyendo (4-ciano-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico por (3-cianometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico, se prepara [3-(1H-tetrazol-5-ilmetil)-indol-1-il]-amida de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (12%) en forma de un sólido. MS: 429 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,85 (s, 3H), 4,52 (s, 2H), 7,15 (m, H), 7,24-7,35 (m, 2H), 7,36-7,50 (m, 2H), 7,55 (m, H), 8,23 (d, H), 8,37 (d, H), 9,15 (s, H).

Ejemplo 142

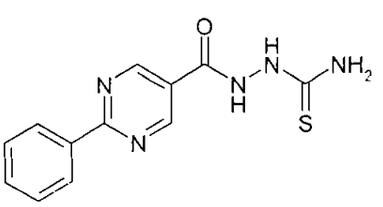
2-(2-Fenil-pirimidina-5-carbonil)-1-hidrazinacarboxamida



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por hidrocloruro de semicarbazida, se prepara 2-(2-fenil-pirimidina-5-carbonil)-1-hidrazinacarboximida (62%) en forma de un sólido. MS: 258 (M+H).

Ejemplo 143

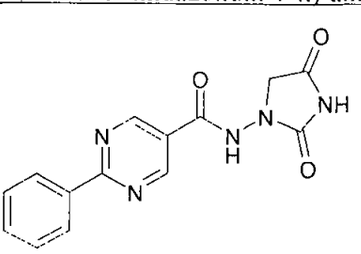
2-(2-Fenil-pirimidina-5-carbonil)-1-hidrazina-1-carbotioamida



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por tiosemicarbazida, se prepara 2-(2-fenil-pirimidina-5-carbonil)-1-hidrazina-1-carbotioamida (27%) en forma de un sólido. MS: 274 (M+H).

Ejemplo 144

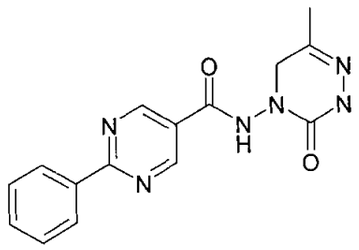
(2,4-Dioxo-imidazolidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 2,4-dioxo-imidazolidin-1-ilamina, se prepara (2,4-dioxo-imidazolidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (8%) en forma de un sólido. MS: 298 (M+H).

Ejemplo 145

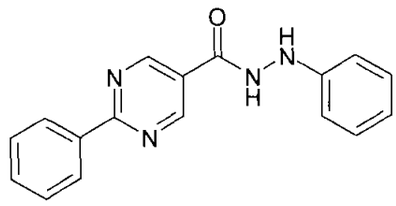
(6-Metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-ilamina, se prepara (6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico (39%) en forma de un sólido. MS: 311 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 1,98 (s, 3H), 4,32 (s, 2H), 7,45-7,63 (m, 3H), 8,50 (d, 2H), 9,24 (s, 2H).

Ejemplo 146

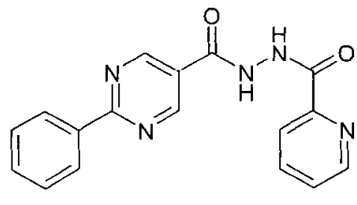
N'-Fenil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por N'-fenil-hidrazina, se prepara N'-fenil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico (18%) en forma de un sólido. MS: 291 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 6,34 (s, N-H), 6,82-7,04 (m, 2H), 7,15-7,39 (m, 3H), 7,40-7,63 (m, 3H), 7,94 (s, N-H), 8,51 (d, 2H), 9,20 (s, 2H).

Ejemplo 147

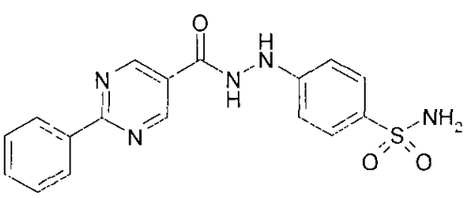
N'-(2-Fenil-pirimidina-5-carbonil)-hidrazida del ácido piridina-2-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64, pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por hidrazida del ácido 2-piridina-2-carboxílico, se prepara N'-(2-fenil-pirimidina-5-carbonil)-hidrazida del ácido piridina-2-carboxílico (52%) en forma de un sólido. MS: 320 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 7,75 (m, 4H), 7,98-8,14 (m, 2H), 8,46 (d, 2H), 8,73 (d, H), 9,32 (s, 2H), 10,81 (s, N-H), 10,96 (a, N-H).

Ejemplo 148

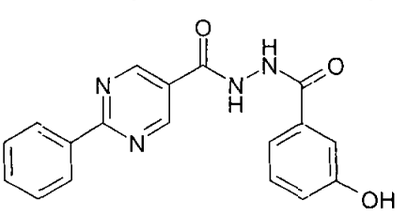
4-[N'-(2-Fenil-pirimidina-5-carbonil)-hidrazino]-bencenosulfonamida



Siguiendo procedimientos similares a los del Ejemplo 64, pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por 4-hidrazino-bencenosulfonamida, se prepara 4-[N'-(2-fenil-pirimidina-5-carbonil)-hidrazino]-bencenosulfonamida (36%) en forma de un sólido. MS: 370 (M+H).

Ejemplo 149

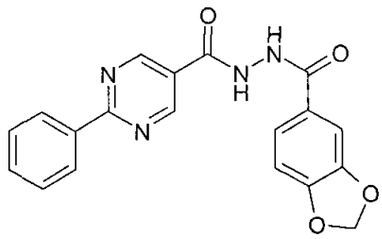
N'-(2-Fenil-pirimidina-5-carbonil)-hidrazida del ácido 3-hidroxi-benzoico



Siguiendo procedimientos similares a los del Ejemplo 64, pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por hidrazida del ácido 3-hidroxi-benzoico, se prepara N'-(2-fenil-pirimidina-5-carbonil)-hidrazida del ácido 3-hidroxi-benzoico (56%) en forma de un sólido. MS: 335 (M+H).

Ejemplo 150

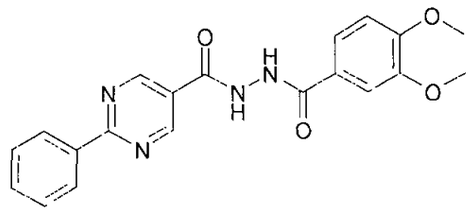
N'-(Fenil-pirimidina-5-carbonil)-hidrazida del ácido benzo[1,3]dioxo-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64, pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por hidrazida del ácido benzo[1,3]-dioxo-5-carboxílico, se prepara N`-(fenil-pirimidina-5-carbonil)-hidrazida del ácido benzo[1,3]dioxo-5-carboxílico (83%) en forma de un sólido. MS: 363 (M+H).

Ejemplo 151

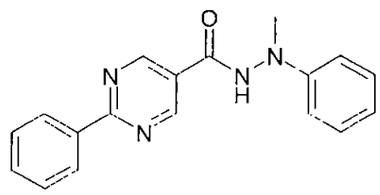
N`-(Fenil-pirimidina-5-carbonil)-hidrazida del ácido 3,4-dimetoxi-benzoico



Siguiendo procedimientos similares a los del Ejemplo 64 pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por hidrazida del ácido 3,4-dimetoxi-benzoico, se prepara N`-(fenil-pirimidina-5-carbonil)-hidrazida del ácido 3,4-dimetoxi-benzoico (76%) en forma de un sólido. MS: 379 (M+H).

Ejemplo 152

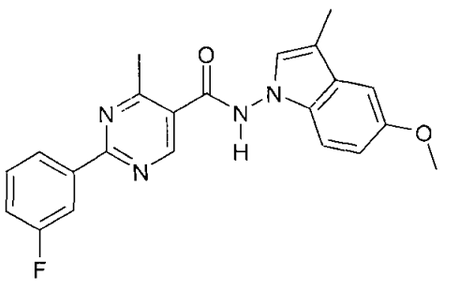
N`-Metil-N`-fenil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 64, pero sustituyendo éster metílico del ácido 3-{3-amino-2,4-dioxo-1,2,3,4-tetrahidro-pirimidin-5-propiónico por N'-metil-N'-fenil-hidrazina, se prepara N`-metil-N`-fenil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico (80 mg, 88%) en forma de un sólido. MS: 305 (M+H).

Ejemplo 153

(5-Metoxi-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

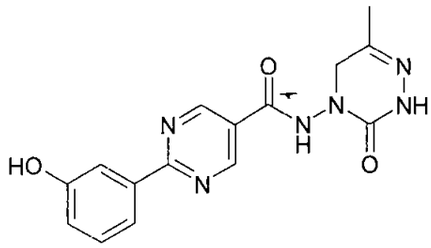


Etapa 1: Una solución de *terc*-butóxido potásico (5,23 g, 46,62 mmol) y 5-metoxi-3-metilindol (3,41 g, 21,15 mmol) en DMF (20 ml) se agita a ta durante 45 min. Se añade una solución de monocloroamina en éter (400 ml, 60 mmol) mediante un embudo de adición durante 15 min. La mezcla resultante se agita durante 2 h. El disolvente se retira y el residuo se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía en columna eluyendo con EtOAc al 10% en heptano para producir 5-metoxi-3-metil-indol-1-ilamina (1,42 g, 38%) en forma de un sólido. MS: 176 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,26-7,23 (m, 1H), 6,98-6,97 (m, 1H), 6,91-6,87 (m, 2H), 4,64 (s a, 2 H), 3,86 (s, 3H), 2,26-2,25 (m, 3H).

Etapa 2: Un vial para microondas (20 ml) se carga con ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (657 mg, 2,83 mmol), HOTT (1,16 g, 3,11 mmol), DIPEA (1,35 ml, 7,73 mmol) y DMF (6 ml). La mezcla se agita a 23°C en una atmósfera de N_2 durante 15 min. Se añade 5-metoxi-3-metil-indol-1-ilamina (456 mg, 2,59 mmol) y el vial se tapa. La mezcla resultante se calienta en un microondas (Biotage-Initiator) a 150°C durante 6 min. La mezcla se reparte entre EtOAc y agua. La fase orgánica se separa, se lava con $NaHCO_3$ acuoso saturado, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía en columna eluyendo con EtOAc al 45% en heptano para producir (5-metoxi-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (327 mg, 32%) en forma de un sólido. MS: 391 (M+H); ^{1}H RMN (300 MHz, d_6-DMSO): δ 11,75 (s, 1H), 9,19 (s, 1H), 8,32 (d, 1H), 8,18-8,16 (m, 1H), 7,66-7,62 (m, 1H), 7,45 (td, 1H), 7,30 (d, 1H), 7,22 (s, 1H), 7,05 (d, 1H), 6,85 (dd, 1H), 3,81 (s, 3H), 2,76 (s, 3H), 2,27 (s, 3H).

Ejemplo 154

(6-Metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-hidroxi-fenil)-pirimidina-5-carboxílico



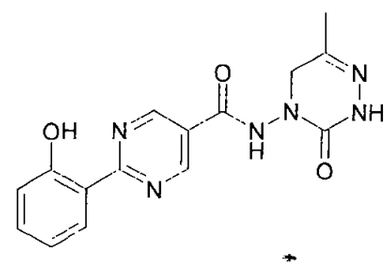
Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 1, pero sustituyendo ácido 3-metoxifenilborónico por ácido 3-hidroxifenilborónico, se prepara éster metílico del ácido 2-(3-hidroxi-fenil)-pirimidina-5-carboxílico.

Etapa 2: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 2, pero sustituyendo éster metílico del ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico por éster metílico del ácido 2-(3-hidroxi-fenil)-pirimidina-5-carboxílico, se prepara ácido 2-(3-hidroxi-fenil)-pirimidina-5-carboxílico.

Etapa 3: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 3, pero sustituyendo ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico por ácido 2-(3-hidroxi-fenil)-pirimidina-5-carboxílico, se prepara (6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-hidroxi-fenil)-pirimidina-5-carboxílico. MS: 327 (M+H); ^{1}H RMN (DMSO-d_6): δ 1,91 (s, 3H), 4,22 (s, 2H), 5,75 (s, 1H), 6,98 (m, 1H), 7,36 (m, 1H), 7,90 (m, 1H), 9,25 (s, 2H), 9,71 (s, 1H), 9,95 (s, 1H), 11,05 (s, 1H). CI_{50} = 21 nM.

Ejemplo 155

(6-Metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(2-hidroxi-fenil)-pirimidina-5-carboxílico



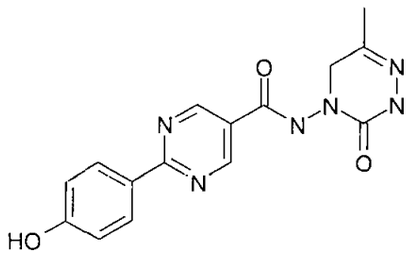
Etapa 1: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 1, pero sustituyendo ácido 3-metoxifenilborónico por ácido 2-hidroxifenilborónico, se prepara éster metílico del ácido 2-(2-hidroxi-fenil)-pirimidina-5-carboxílico.

Etapa 2: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 2, pero sustituyendo éster metílico del ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico por éster metílico del ácido 2-(2-hidroxi-fenil)-pirimidina-5-carboxílico, se prepara ácido 2-(2-hidroxi-fenil)-pirimidina-5-carboxílico.

Etapa 3: Siguiendo procedimientos similares a los del Ejemplo 59, etapa 3, pero sustituyendo ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico por ácido 2-(2-hidroxi-fenil)-pirimidina-5-carboxílico, se prepara (6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(2-hidroxi-fenil)-pirimidina-5-carboxílico. MS: 327 (M+H); 1H RMN (DMSO-d_6): δ = 1,91 (s, 3H), 4,22 (s, 2H), 7,02 (m, 2H), 7,50 (m, 1H), 8,46 (m, 1H), 9,32 (s, 2H), 9,97 (s, 1H), 11,12 (s, 1H), 12,95 (s, 1H).

Ejemplo 156

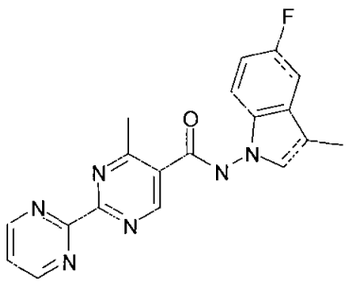
(6-Metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(4-hidroxi-fenil)-pirimidina-5-carboxílico



Una mezcla de (6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(4-metoxi-fenil)-pirimidina-5-carboxílico (100 mg, 0,29 mmol), metanotiolato sódico (206 mg, 2,9 mmol) y DMF (2 ml) se agita a 110ºC durante 6 h y después se enfría a ta. La mezcla de reacción se concentra al vacío y el residuo se purifica en una cromatografía HPLC de fase inversa para producir (6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(4-hidroxi-fenil)-pirimidina-5-carboxílico (32 mg). MS: 327 (M+H); ^{1}H RMN (DMSO-d_6): δ 1,87 (s, 3H), 4,17 (s, 2H), 6,74 (m, 2H), 8,21 (d, J = 6,9 Hz, 2H), 9,08 (s, 2H), 9,53 (s, 1H).

Ejemplo 157

(5-Fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico



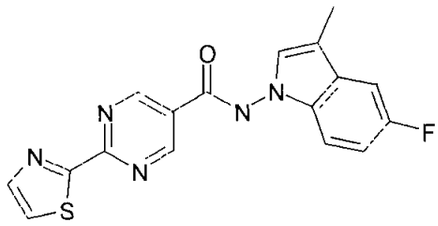
Etapa 1: Un matraz que contenía 2-cianopirimidina (16,6 g, 158 mmol), acetato amónico (14,6 g, 189,6 mmol), N-acetilcisteína (2,58 g, 15,8 mmol) y etanol (160 ml) se calienta a reflujo. Después de 1,25 h, la reacción se deja enfriar ligeramente (hasta aproximadamente 50ºC) y se añaden *terc*-butóxido sódico (15,18 g, 158 mmol) y etanol (160 ml). Después de agitar durante 10 minutos, se añade éster etílico del ácido 2-dimetilaminometileno-3-oxo-butírico (33,6 g, 181,7 mmol). Después, la reacción se calienta a reflujo durante 2 h más. Después, la reacción se deja enfriar a ta y se añade hidróxido sódico (12,6 g, 316 mmol) en agua (50 ml). Después de 2 h, la reacción se enfría en un baño de agua enfriada con hielo y el valor de pH de la reacción se ajusta a ~3 usando una solución de HCl acuoso ~12 M. Después, la mezcla de reacción se reduce al vacío hasta alcanzar un volumen de ~100 ml. Se añade más cantidad de agua (100 ml) y la suspensión se enfría en un baño de agua enfriada con hielo, se filtra y los sólidos se lavan con la cantidad mínima de agua enfriada. Después, los sólidos se secan al vacío para producir ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (85%).

MS: 217 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ = 2,80 (s, 3H), 7,66 (t, 1H), 9,01 (d, 2H), 9,14 (s, 1H).

Etapa 2: Se combina ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (0,5 g, 2,31 mmol) con cloruro de 5-fluoro-3-metil-indol-1-il-amonio (464 mg, 2,31 mmol), N-metilmorfolina (233 mg, 2,31 mmol) y DMF (10 ml). La suspensión se agita durante 5 minutos a ta y después se añade cloruro de 4-(4,6-dimetoxi-[1,3,5]triazin-2-il)-4-metil-morfolin-4-io (640 mg, 2,31 mmol). La reacción se calienta a 50ºC durante 4 h. Después, la reacción se vierte en agua (50 ml) y la suspensión se enfría durante 2 h en el frigorífico y después se filtra. Después, los sólidos se suspenden en acetonitrilo a 50ºC durante 4 h, se enfrían y después se filtran para producir (5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (60%). MS: 363 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ = 2,27 (s, 3H), 2,77 (s, 3H), 7,07 (dt, 1H), 7,36 (dd, 1H), 7,38 (s, 1H), 7,44-7,48 (m, 1H), 7,70 (t, 1H), 9,05 (d, 2H), 9,29 (s, 1H), 11,9 (s, 1H). CI_{50} = 4,5 nM.

Ejemplo 158

(5-Fluoro-3-metil-indol-1-il)-amida del ácido 2-tiazol-2-il-pirimidina-5-carboxílico



Etapa 1: Un matraz se carga con 2-cianotiazol (6,7 g, 60,9 mmol), acetato amónico (5,63 g, 73 mmol), N-acetilcisteína (993 mg, 6,09 mmol) y metanol (60 ml). Después, la reacción se calienta a reflujo durante una noche. La reacción se reduce al vacío para producir un residuo que se usa en la siguiente etapa sin modificaciones adicionales.

Etapa 2: El residuo bruto de la Etapa 1 se suspende en DMF (100 ml). A esto se le añade 2-etoxicarbonil-3-oxo-but-1-en-1-olato sódico (13,86 g, 70 mmol). Después, la reacción se calienta a 100°C durante 1,5 h y después la mezcla se deja enfriar a ta. Después, la reacción se vierte en agua enfriada con hielo (1 l). La suspensión se filtra y el filtrado se extrae sucesivamente con DCM (100 ml) y EtOAc (200 ml). Las capas orgánicas se secan (Na_2SO_4), se filtran y se concentran para producir un residuo (10,31 g).

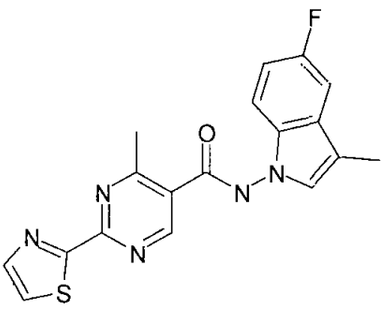
Etapa 3: El residuo de la Etapa 2 (6,26 g, 28,32 mmol) se combina con una solución de hidróxido sódico (2,26 g, 56,65 mmol) en agua (90 ml) y metanol (90 ml) y se agita a ta durante una noche. El volumen de la solución se reduce a la mitad al vacío y el valor del pH se ajusta a 3 con HCl acuoso (aproximadamente 12 M). El sólido se recoge por filtración y se seca al vacío para producir ácido 2-tiazol-2-il-pirimidina-5-carboxílico (56% en 3 etapas). MS: 208 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ = 8,11 (d, 1H), 8,16 (d, 1H), 9,32 (s, 2H).

Etapa 4: Una mezcla de ácido 2-tiazol-2-il-pirimidina-5-carboxílico (50 mg, 0,244 mmol), cloruro de 5-fluoro-3-metil-indol-1-il-amonio (49 mg, 0,244 mmol) y diisopropiletilamina (31,5 mg, 0,244 mmol) en DMF (1 ml) se agita a ta durante 5 min. Se añade cloruro de 4-(4,6-dimetoxi-[1,3,5]triazin-2-il)-4-metil-morfolin-4-io (37 mg, 0,244 mmol). La reacción se calienta a 50°C durante 1,5 h y después se concentra al vacío. El residuo se recoge en DMSO-d^6 y después se purifica por cromatografía HPLC C18 de fase inversa eluyendo con agua y acetonitrilo que contiene tampón de TFA al 0,1% para producir (5-fluoro-3-metil-indol-1-il)-amida del ácido 2-tiazol-2-il-pirimidina-5-carboxílico (58%). MS: 354 (M+H); ^{1}H

RMN (300 MHz, $CDCl_3$): δ = 2,27 (s, 3H), 7,05 (dt, 1H), 7,32 (s, 1H), 7,32-7,44 (m, 2H), 8,11 (d, 1H), 8,19 (d, 1H), 9,42 (s, 2H), 12,12 (s, 1H).

Ejemplo 159

(5-Fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico

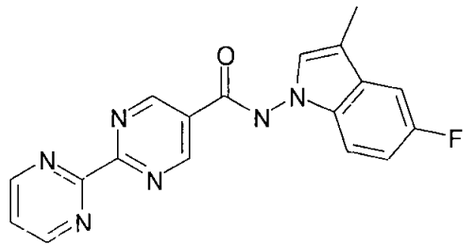


Etapa 1: Una solución de 2-cianotiazol (1,55 g, 14,2 mmol) en MeOH (12 ml) se trata con *N*-acetilcisteína (234 mg, 1,42 mmol) y acetato amónico (1,5 g, 18,5 mmol) y se calienta en un microondas a 120°C durante 15 min. Después, la mezcla se trata con éster etílico del ácido 2-dimetilaminometileno-3-oxo-butírico (3,2 g, 17,0 mmol) y KO*t*-Bu (2,2 g, 20 mmol) y se calienta en un microondas a 120°C durante 15 min más. Después, la mezcla se trata con una solución de KOH (1,2 g, 20 mmol) en H_2O (5 ml) y se calienta a reflujo durante 1 h. La mezcla se neutraliza con HCl acuoso concentrado. El precipitado se recoge por filtración y se seca para producir ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (1,95 g, 62%). MS: 222 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 13,77 (s, OH, 1H), 9,18 (s, 1H), 8,13 (d, 1H), 8,07 (d, 1H), 2,81 (s, 3H).

Etapa 2: Una mezcla de ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (221 mg, 1 mmol), cloruro de 5-fluoro-3-metil-indol-1-il-amonio (200 mg, 1 mmol) y N-metilmorfolina (101 mg, 1 mmol) en DMF (5 ml) se agita a ta durante 5 min. Se añade cloruro de 4-(4,6-dimetoxi-[1,3,5]triazin-2-il)-4-metil-morfolin-4-io (277 mg, 1 mmol) y la reacción se calienta a 50°C durante 4 h. Después, la mezcla de reacción se vierte en agua (50 ml). El precipitado se recoge por filtración y se seca al vacío para proporcionar (5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (68%). MS: 368 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ = 2,27 (s, 3H), 2,76 (s, 3H), 7,06 (dt, 1H), 7,35-7,38 (m, 2H), 7,42-7,47 (m, 1H), 8,07 (d, 1H), 8,14 (d, 1H), 9,22 (s, 1H), 11,9 (s, 1H).

Ejemplo 160

(5-Fluoro-3-metil-indol-1-il)-amida del ácido [2,2']bipirimidinil-5-carboxílico

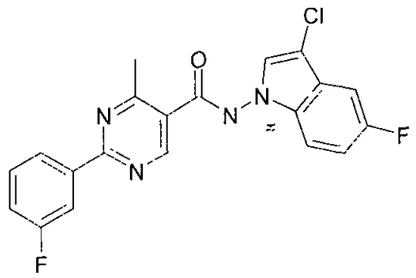


Etapa 1: Un recipiente a presión se carga con 2-cianopirimidina (7,88 g, 75 mmol), N-acetilcisteína (1,22 g, 7,5 mmol), acetato amónico (6,93 g, 90 mmol) y MeOH (75 ml). El recipiente se cierra herméticamente y se calienta a 110ºC durante 1,5 h, y después se enfría a ta. A la mezcla de reacción se le añaden 2-etoxicarbonil-3-oxo-but-1-en-1-olato sódico (17 g, 86,25 mmol) y MeOH (75 ml). La mezcla se calienta a reflujo durante 1,5 h y después se enfría a ta. Se añaden NaOH (6 g, 150 mmol) y agua (80 ml). La mezcla se agita durante 30 min o hasta que el análisis por LC-MS indica la hidrólisis completa del éster intermedio. El valor de pH de la mezcla de reacción se ajusta a ~3 con HCl acuoso concentrado (~12 M). El MeOH se evapora al vacío y el precipitado resultante se recoge por filtración y se lava con la cantidad mínima de agua enfriada para producir ácido [2,2']bipirimidinil-5-carboxílico (59%). MS: 203 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ = 7,71 (t, 1H), 9,06 (d, 2H), 9,40 (s, 2H).

Etapa 2: Una mezcla de ácido [2,2']bipirimidinil-5-carboxílico (166 mg, 0,82 mmol), cloruro de 5-fluoro-3-metil-indol-1-il-amonio (164 mg, 0,82 mmol) y DIPEA (106 mg, 0,82 mmol) en DMF (5 ml) se agita a ta durante 5 min. Se añade cloruro de 4-(4,6-dimetoxi-[1,3,5]triazin-2-il)-4-metil-morfolin-4-io (226 mg, 0,82 mmol). La mezcla de reacción se calienta a 50ºC durante 1,5 h y después se concentra al vacío. El residuo se recoge en DMSO- d^6 y después se purifica por cromatografía HPLC C18 de fase inversa eluyendo con agua y acetonitrilo que contiene tampón de TFA al 0,1% para producir (5-fluoro-3-metil-indol-1-il)-amida del ácido [2,2']bipirimidinil-5-carboxílico (56%). MS: 349 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ = 2,27 (s, 3H), 7,05 (dt, 1H), 7,33 (s, 1H), 7,36 (dd, 1H), 7,42-7,46 (m, 1H), 7,72 (t, 1H), 9,07 (d, 2H), 9,51 (s, 2H), 12,17 (s, 1H).

Ejemplo 161

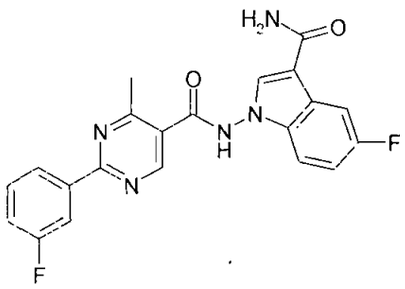
(3-Cloro-5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Una solución de (5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (300 mg, 0,824 mmol) en MeCN (20 ml) se trata con NCS (185 mg, 1,42 mmol) y la mezcla se agita a 60°C en un matraz cerrado herméticamente durante 2 h. Después, la mezcla se concentra, se diluye con $Na_2S_2O_8$ acuoso al 10% (20 ml) y se extrae con EtOAc (3 x 20 ml). La capa orgánica combinada se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10% - 20% en heptano para producir (3-cloro-5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (160 mg, 49%). MS: 399 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,79 (s, 1H), 8,04 (d, 1H), 7,92 (d, 1H), 7,18 (m, 1H), 7,04 (s, 1H), 7,00 (m, 3), 6,76 (m, 1), 2,52 (s, 3H).

Ejemplo 162

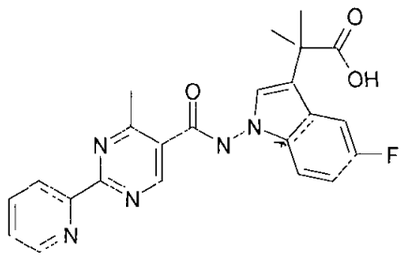
Amida del ácido 5-fluoro-1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indolo-3-carboxílico



Una solución de (5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (300 mg, 0,82 mmol) en 2-Me-THF (7 ml) se trata con isocianato de clorosulfonilo (CSI) (85 µl, 2,0 mmol) a 0°C y la mezcla se calienta a ta durante 2 h. Después, la mezcla se enfría a 0°C, se trata con NaOH 1 M (1 ml), se diluye con salmuera (20 ml) y se extrae con EtOAc (3 x 20 ml). La capa orgánica combinada se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío para producir amida del ácido 5-fluoro-1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indolo-3-carboxílico (275 mg, 83%). MS: 408 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,27 (s, 1H), 8,35 (d, 1H), 8,26 (s, 1H), 8,20 (d, 1H), 7,95 (d, 1H), 7,59 (m, 3H), 7,15 (m, 1H), 2,78 (s, 3H). CI_{50} = 8 nM.

Ejemplo 163

Ácido 2-{5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indol-3-il}-2-metil-propiónico



Etapa 1: Una solución de éster metílico del ácido (5-fluoro-1H-indol-3-il)-acético (3 g, 14,8 mmol) en MeCN (25 ml) se trata con Boc_2O (4,3 g, 16,3 mmol) y DMAP (200 mg, 1,63 mmol) y la mezcla se agita a ta durante 1 h. La mezcla se diluye con NH_4Cl acuoso saturado (50 ml) y se extrae con DCM (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 8% en heptano para producir éster *terc*-butílico del ácido 5-fluoro-3-metoxicarbonilmetil-indolo-1-carboxílico (1,6 g, 35%). MS: 371 (M+Na+ACN); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,09 (m, 1H), 7,59 (s, 1H), 7,17 (m, 1H), 7,04 (m, 1H), 3,72 (s, 3H), 3,67 (s, 2H), 1,55 (s, 9H).

Etapa 2: Una solución de éster *terc*-butílico del ácido 5-fluoro-3-metoxicarbonilmetil-indolo-1-carboxílico (1,6 g, 5,2 mmol) en 2-Me-THF (50 ml) a -78°C se trata con LDA (5,7 ml 1,8 M en THF, 10,4 mmol) y se agita durante 0,5 h. Se añade MeI (1,02 ml, 15,6 mmol) y la mezcla se calienta a 0°C durante 2 h. La mezcla se diluye con NH_4Cl acuoso saturado (50 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío para producir éster *terc*-butílico del ácido 5-fluoro-3-(1-metoxicarbonil-1-metil-etil)-indolo-1-carboxílico, que se usa en la siguiente etapa sin purificación adicional.

Etapa 3: Una solución de éster *terc*-butílico del ácido 5-fluoro-3-(1-metoxicarbonil-1-metil-etil)-indolo-1-carboxílico (5,2 mmol) en MeOH (25 ml) se trata con K_2CO_3 (720 mg, 5,2 mmol) y se calienta a reflujo durante 2 h. La mezcla se diluye con salmuera (50 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío para producir éster metílico del ácido 2-(5-fluoro-1H-indol-3-il)-2-metil-propiónico (650 mg, 53%, 2 etapas), que se usa en la siguiente etapa sin purificación

adicional. MS: 236 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 7,35 (m, 1H), 7,30 (m, 1H), 7,14 (m, 1H), 6,91 (m, 1H), 3,54 (s, 3H), 1,57 (s, 6H).

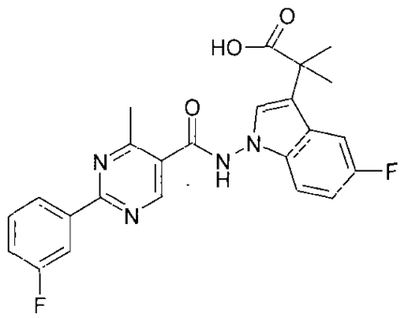
Etapa 4: Una suspensión de NaH (1,02 g, 25,5 mmol, al 60% en aceite mineral) en DMF (25 ml) a 0°C se trata con éster metílico del ácido 2-(5-fluoro-1H-indol-3-il)-2-metil-propiónico (400 mg, 1,7 mmol) y se agita a 0°C durante 0,5 h. La mezcla se trata en porciones con HOSA (960 mg, 8,5 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo, se filtra a través de una capa de Celite y se extrae con EtOAc (3 x 100 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío para producir éster metílico del ácido 2-(1-amino-5-fluoro-1H-indol-3-il)-2-metil-propiónico, que se usa en la siguiente etapa sin purificación adicional.

Etapa 5: Una solución de éster metílico del ácido 2-(1-amino-5-fluoro-1H-indol-3-il)-2-metil-propiónico (0,85 mmol) y ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (201 mg, 0,935 mmol) en DMF (8,5 ml) se agita a 40°C durante 0,5 h. La mezcla se trata con DMTMM (246 mg, 0,89 mmol) y se agita a 60°C durante 1 h. La mezcla se concentra al vacío, se diluye con Na_2CO_3 acuoso saturado (20 ml) y se extrae con EtOAc (3 x 20 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío para producir éster metílico del ácido 2-{5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indol-3-il}-2-metil-propiónico, que se usa en la siguiente etapa sin purificación adicional.

Etapa 6: Una solución de éster metílico del ácido 2-{5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indol-3-il}-2-metil-propiónico (0,85 mmol) en MeOH (5 ml) se trata con NaOH acuoso al 10% (2 ml) y se agita a ta durante una noche. Después, la mezcla se concentra, se diluye con EtOAc (50 ml) y se extrae con NaOH acuoso al 10% (3 x 50 ml). La capa acuosa se acidifica con HCl acuoso 12 M y se extrae con DCM (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra. El residuo se tritura con Et_2O para producir ácido 2-{5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indol-3-il}-2-metil-propiónico (100 mg, 27%, 3 etapas). MS: 434 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,26 (s, 1H), 8,79 (m, 1H), 8,44 (d, 1H), 8,03 (t, 1H), 7,59 (m, 1H), 7,53 (s, 1H), 7,49 (m, 1H), 7,35 (d, 1H), 7,08 (t, 1H), 2,79 (s, 3H), 1,59 (s, 6H).

Ejemplo 164

Ácido 2-(5-fluoro-1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-3-il)-2-metil-propiónico

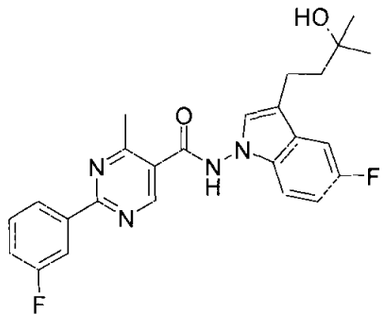


Etapa 1: Una solución de éster metílico del ácido 2-(1-amino-5-fluoro-1H-indol-3-il)-2-metil-propiónico (0,85 mmol) y ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (217 mg, 0,935 mmol) en DMF (8,5 ml) se agita a 40ºC durante 0,5 h. La mezcla se trata con DMTMM (246 mg, 0,89 mmol) y se agita a 60ºC durante 1 h. La mezcla se concentra al vacío, se diluye con Na_2CO_3 acuoso saturado (20 ml) y se extrae con EtOAc (3 x 20 ml). La capa orgánica combinada se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío para producir éster metílico del ácido 2-(5-fluoro-1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-3-il)-2-metil-propiónico, que se usa en la siguiente etapa sin purificación adicional.

Etapa 2: Una solución de éster metílico del ácido 2-{5-fluoro-1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-3-il)-2-metil-propiónico (0,85 mmol) en MeOH (5 ml) se trata con NaOH acuoso al 10% (2 ml) y se agita a ta durante una noche. Después, la mezcla se concentra, se diluye con EtOAc (50 ml) y se extrae con NaOH acuoso al 10% (3 x 50 ml). La capa acuosa se acidifica con HCl 12 M y se extrae con DCM (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra. El residuo se tritura con Et_2O para producir ácido 2-(5-fluoro-1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-3-il)-2-metil-propiónico (139 mg). MS: 451 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,22 (s, 1H), 8,33 (d, 1H), 8,18 (d, 1H), 7,63 (m, 1H), 7,50 (m, 3H), 7,33 (m, 1H), 7,07 (m, 1H), 2,78 (s, 3H), 1,59 (s, 6H). CI_{50} = 7 nM.

Ejemplo 165

[5-Fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Etapa 1: Una solución de 5-fluoroindol (10,5 g, 78 mmol) en MeCN (150 ml) a 0°C se trata con metil vinil cetona (9,5 ml, 117 mmol) y $Sc(OTf)_3$ (383 mg, 0,78 mmol) y se agita durante 1 h. Después, la mezcla se agita durante 6 h más a ta. La mezcla se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10% - 50% en heptano para producir 4-(5-fluoro-1H-indol-3-il)-butan-2-ona (11,1 g, 70%).

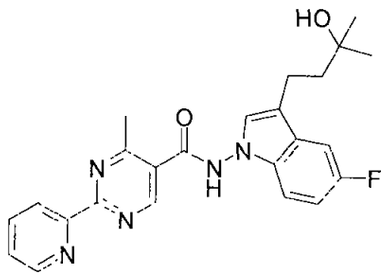
Etapa 2: Una solución de 4-(5-fluoro-1H-indol-3-il)-butan-2-ona (11,1 g, 54,1 mmol) en THF (200 ml) a 0°C se trata con MeMgBr (54,1 ml, 3 M en THF, 162,3 mmol), se agita a 0°C durante 2 h y se calienta a ta durante una noche. Después, la mezcla se vierte sobre hielo, se trata con NH_4Cl sólido (3 g) y se extrae con EtOAc (3 x 120 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10% - 60% en heptano para producir 4-(5-fluoro-1H-indol-3-il)-2-metil-butan-2-ol (3,07 g, 26%). MS: 222 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,94 (s, NH, 1H), 7,22 (m, 2H), 7,03 (s, 1H), 6,93 (m, 1H), 2,81 (m, 2H), 1,90 (m, 2H), 1,33 (s, 6H).

Etapa 3: Una suspensión de NaH (8,1 g, 204 mmol, al 60% en aceite mineral) en DMF (100 ml) a 0°C se trata con 4-(5-fluoro-1H-indol-3-il)-2-metil-butan-2-ol (3 g, 13,6 mmol) y se agita a 0°C durante 0,5 h. La mezcla se trata en porciones con HOSA (7,7 g, 68 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo, se filtra a través de una capa de Celite y se extrae con EtOAc (3 x 100 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por filtración a través de un lecho corto de gel de sílice para producir 4-(1-amino-5-fluoro-1H-indol-3-il)-2-metil-butan-2-ol, que se usa en la siguiente etapa sin purificación adicional. MS: 237 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,30 (m, 1H), 7,22 (m, 1H), 6,98 (m, 2H), 4,71 (s, NH_2, 2H), 2,75 (m, 2H), 1,86 (m, 2H), 1,31 (s, 6H).

Etapa 4: Una solución de ácido (278 mg, 1,2 mmol) y 4-(1-amino-5-fluoro-1H-indol-3-il)-2-metil-butan-2-ol (1,2 mmol) en DMF (10 ml) se agita a 50°C durante 1 h. La mezcla se trata con DMTMM (331 mg, 1,2 mmol) y se agita a 50°C durante 1 h. La mezcla se concentra al vacío, se diluye con Na_2CO_3 acuoso saturado (50 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc 50% en heptano para producir [5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (330 mg, 61%). MS: 451 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 9,10 (s, 1H), 8,36 (d, 1H), 8,23 (d, 1H), 7,55 (m, 1H), 7,32 (m, 3H), 7,18 (s, 1H), 7,03 (m, 1H), 3,91 (s, OH, 1H), 2,84 (s, 3H), 2,82 (m, 2H), 1,91 (m, 2H), 1,31 (s, 6H).

Ejemplo 166

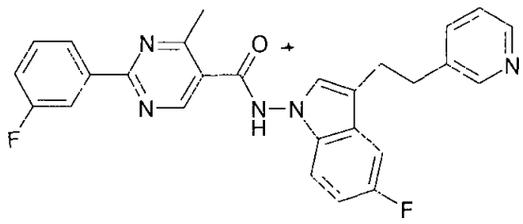
[5-Fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Una solución de ácido 2-(2-piridil)-4-metil-pirimidina-5-carboxílico (516 mg, 4 mmol) y 4-(1-amino-5-fluoro-1H-indol-3-il)-2-metil-butan-2-ol (566 mg, 4 mmol) en DMF (5 ml) se agita a 50°C durante 1 h. La mezcla se trata con DMTMM (662 mg, 4 mmol) y se agita a 50°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (50 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 4% - 10% en DCM para producir [5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (450 mg, 44%). MS: 434 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,25 (s, 1H), 8,81 (d, 1H), 8,47 (d, 1H), 8,02 (m, 1H), 7,58 (m, 1H), 7,43 (m, 3H), 7,06 (m, 1H), 4,29 (s, OH, 1H), 2,78 (s, 3H), 2,72 (m, 2H), 1,77 (m, 2H), 120 (s, 6H).

Ejemplo 167

[5-Fluoro-3-(2-piridin-3-il-etil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Etapa 1: Una solución de 5-fluorogramina (576 mg, 3 mmol) y piridina-3-carboxaldehído (531 mg, 3 mmol) en MeCN (6 ml) se trata con Bu_3P (1,12 ml, 4,5 mmol) y se agita a 90°C durante 24 h. La mezcla se concentra y se filtra a través de una capa de gel de sílice eluyendo con EtOAc al 30% en heptano para producir 5-fluoro-3-(2-piridin-3-il-vinil)-1H-indol en forma de una mezcla de isómeros de olefina, que se usa en la siguiente etapa sin purificación adicional.

Etapa 2: Una solución de 5-fluoro-3-(2-piridin-3-il-vinil)-1H-indol (3 mmol) en MeOH (10 ml) se trata con Pd/C (200 mg) y se agita en un aparato Parr a una presión de 40 atm de H_2 durante 18 h. La mezcla se filtra a través de Celite y el filtrado se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 0% - 10% en DCM para producir 5-fluoro-3-(2-piridin-3-il-etil)-1H-indol (360 mg, 50%, 2 etapas).

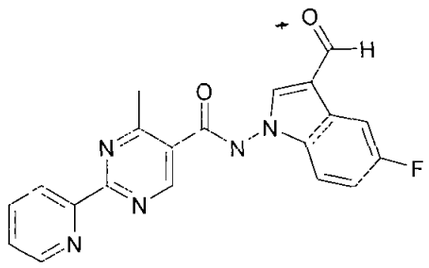
Etapa 3: Una suspensión de NaH (600 mg, 15 mmol, al 60% en aceite mineral) en DMF (10 ml) a 0°C se trata con 5-fluoro-3-(2-piridin-3-il-etil)-1H-indol (240 mg, 1 mmol) y se agita a 0°C durante 0,5 h. La mezcla se trata en porciones con HOSA (565 mg, 5 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo, se filtra a través de una capa de Celite y se extrae con EtOAc (3 x 1050 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío para producir 5-fluoro-3-(2-piridin-3-il-etil)-indol-1-ilamina, que se usa en la siguiente etapa sin purificación adicional.

Etapa 4: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (232 mg, 1 mmol) y 5-fluoro-3-(2-piridin-3-il-etil)-indol-1-ilamina (255 mmol) en DMF (10 ml) se agita a 50°C durante 10 min. La mezcla se trata con DMTMM (276 mg, 1 mmol) y se agita a 50°C durante 0,5 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (50 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por trituración en MeOH:H_2O (2:1) para producir [5-fluoro-3-(2-piridin-3-il-etil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (6 mg, 1%). MS: 470 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,21 (s, 1H),

8,51 (m, 1H), 8,40 (m, 1H), 8,33 (d, 1H), 8,19 (d, 1H), 7,74 (d, 1H), 7,63 (m, 1H), 7,45 (m, 4H), 7,33 (m, 1H), 7,06 (m, 1H), 3,29 (s, 2H), 3,01 (s, 2H), 2,77 (s, 3H).

Ejemplo 168

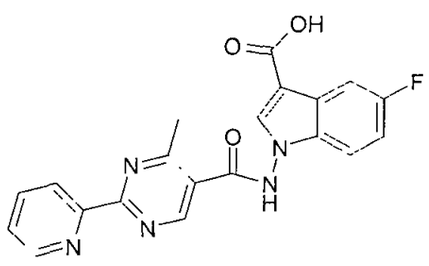
(5-Fluoro-3-formil-indol-1-il)amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Una solución de (5-fluoro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (250 mg, 0,55 mmol) en H_2O (5,5 ml) se trata con DDQ (369 mg, 1,6 mmol) en EtOAc (0,5 ml) y se agita a ta durante 2 h. La mezcla se diluye con EtOAc (50 ml), se lava con salmuera (50 ml) y se extrae con $NaHCO_3$ acuoso saturado (3 x 50 ml). La capa acuosa se acidifica a pH 2 con HCl (conc.) y se lava con Et_2O (50 ml). La capa acuosa se neutraliza con NaOH acuoso al 10% y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por trituración en Et_2O para producir (5-fluoro-3-formil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (87 mg, 43%). MS: 376 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,53 (s, NH, 1H), 10,00 (s, 1H), 9,34 (m, 1H), 8,81 (m, 1H), 8,66 (s, 1H), 8,48 (m, 1H), 8,04 (m, 1H), 7,86 (m, 1H), 7,72 (m, 1H), 7,61 (m, 1H), 7,27 (m, 1H), 2,80 (s, 3H).

Ejemplo 169

Ácido 5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indolo-3-carboxílico



Etapa 1: Una solución de éster metílico del ácido 5-fluoro-1H-indolo-3-carboxílico (510 mg, 2,6 mmol) en NMP (6,5 ml) a ta se trata con KO*t*-Bu (342 mg, 2,9 mmol) y se agita a ta durante 0,5 h. Se añade una solución de ácido *O*-amino-4-nitrobenzoico (558 mg, 3,0 mmol)

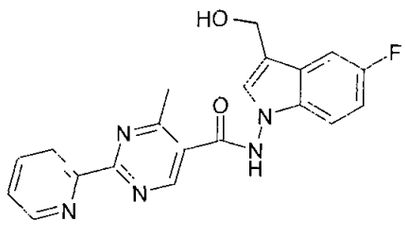
en NMP (2,5 ml) y la mezcla se agita durante 3 h. La mezcla se diluye con EtOAc (50 ml) y se lava con $NaHCO_3$ acuoso al 10% (50 ml). La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío para producir éster metílico del ácido 1-amino-5-fluoro-1H-indolo-3-carboxílico, que se usa en la siguiente etapa sin purificación adicional.

Etapa 2: Una solución de ácido 2-(2-piridil)-4-metil-pirimidina-5-carboxílico (559 mg, 2,6 mmol) y éster metílico del ácido 1-amino-5-fluoro-1H-indolo-3-carboxílico (540 mg, 2,6 mmol) en DMF (25 ml) se agita a 50°C durante 0,5 h. La mezcla se trata con DMTMM (718 mg, 2,6 mmol) y se agita a 50°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (50 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 1% - 10% en DCM para producir éster metílico del ácido 5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indolo-3-carboxílico.

Etapa 3: Una solución de éster metílico del ácido 5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indolo-3-carboxílico (2,6 mmol) en MeOH (10 ml) se trata con una solución acuosa de KOH (500 mg, 8,9 mmol) en H_2O (200 ml) y se calienta a reflujo durante 2 h. La mezcla se diluye con EtOAc (50 ml) y se extrae con KOH acuoso al 1% (3 x 50 ml). La capa acuosa combinada se neutraliza con HCl (conc.) y el precipitado se recoge por filtración y se seca al vacío para producir ácido 5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indolo-3-carboxílico (195 mg, 19%, 3 etapas). MS: 392 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,44 (s, OH, 1H), 12,31 (s, NH, 1H), 9,31 (s, 1H), 8,81 (d, 1H), 8,48 (d, 1H), 8,35 (s, 1H), 8,03 (m, 1H), 7,77 (m, 1H), 7,62 (m, 2H), 7,19 (m, 1H), 2,79 (s, 3H).

Ejemplo 170

(5-Fluoro-3-hidroximetil-indol-1-il)amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico

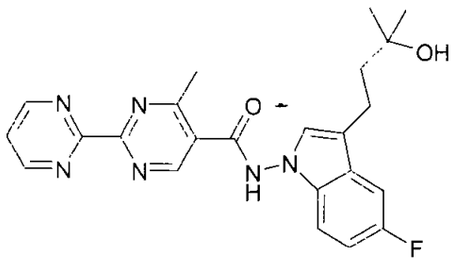


Una solución de (5-fluoro-3-formil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (230 mg, 0,614 mmol) en MeOH (10 ml) se trata con $NaBH_4$ (233

mg, 6,14 mmol) y se agita a ta durante 1 h. La mezcla se diluye con EtOAc (50 ml) y H_2O, se neutraliza con HCl (conc.) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por HPLC preparativa de fase inversa eluyendo con MeCN al 20% - 100% en H_2O para producir (5-fluoro-3-hidroximetil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (90 mg, 8%). MS: 378 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,92 (s, NH, 1H), 9,27 (s, 1H), 8.81 (d, 1H), 8,47 (d, 1H), 8,05 (m, 1H), 7,61 (m, 1H), 7,44 (m, 3H), 7,10 (m, 1H), 5,00 (t, OH, 1H), 4,66 (d, 2H), 2,78 (s, 3H).

Ejemplo 171

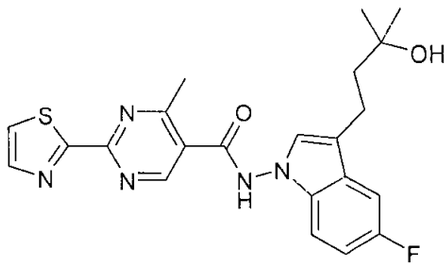
[5-Fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico



Una solución de ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (300 mg, 1.38 mmol) y 4-(1-amino-5-fluoro-1H-indol-3-il)-2-metil-butan-2-ol (325 mg, 1.38 mmol) en DMF (5 ml) se agita a 50°C durante 1 h. La mezcla se trata con DMTMM (380 mg, 1.38 mmol) y se agita a 50°C durante h. La mezcla se diluye con Na_2CO_3 acuoso saturado (50 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 0% - 7% en DCM para producir [5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (200 mg, 33%). MS: 435 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 9,26 (s, 1H), 9,09 (d, 2H), 7,70 (t, 1H), 7,29 (m, 2H), 7,22 (s, 1H), 7,01 (m, 1H), 2,90 (s, 3H), 2,82 (m, 2H), 1,91 (m, 2H), 1,31 (s, 6H).

Ejemplo 172

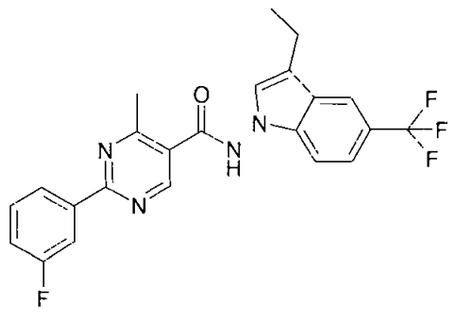
[5-Fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico



Una solución de ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (300 mg, 1,36 mmol) y 4-(1-amino-5-fluoro-1H-indol-3-il)-2-metil-butan-2-ol (325 mg, 1,38 mmol) en DMF (5 ml) se agita a 50°C durante 1 h. La mezcla se trata con DMTMM (380 mg, 1,38 mmol) y se agita a 50°C durante 2 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (50 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 0% - 7% en DCM para producir [5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-tiazol-2-piridin-2-il-pirimidina-5-carboxílico (155 mg, 26%). MS: 440 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,22 (s, 1H), 8,14 (d, 1H), 8,08 (d, 1H), 7,40 (m, 3H), 7,06 (m, 1H), 4,31 (s, OH, 1H), 2,76 (s, 3H), 2,71 (m, 2H), 1,77 (m, 2H), 1,20 (s, 6H). CI_{50} = 5 nM.

Ejemplo 173

(3-Etil-5-trifluorometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Etapa 1: Una solución de 2-yodo-4-trifluorometil-fenilamina (10 g, 34,8 mmol) en DCM (100 ml) se trata con TFAA (5,55 ml, 41,8 mmol) y piridina (3,4 ml, 41,8 mmol) y se agita a ta durante 1 h. La mezcla se diluye con H_2O (150 ml) y se extrae con DCM (3 x 150 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se diluye con MeCN (100 ml), se trata con bromuro de *trans*-crotilo (5,4 ml, 52,2 mmol) y K_2CO_3 (9,6 g, 69,6 mmol) y se calienta a reflujo durante 2 h. La mezcla se enfría, se filtra a través de una capa de Celite y se concentra. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0% - 10% en heptano para producir *N*-but-2-enil-2,2,2-

trifluoro-*N*-(2-yodo-4-trifluorometil-fenil)-acetamida (12,7 g, 84%). MS: 438 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,18 (s, 1H), 7,67 (s, 1H), 7,26 (m, 1H), 5,52 (m, 2H), 4,88 (m, 1H), 3,51 (m, 1H), 1,68 (d, 3H).

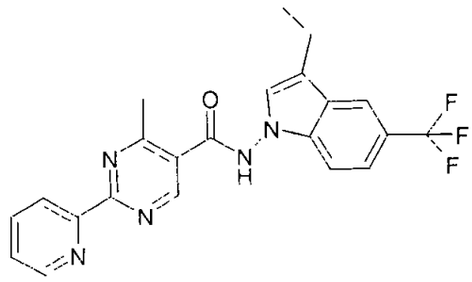
Etapa 2: Una solución de *N*-but-2-enil-2,2,2-trifluoro-*N*-(2-yodo-4-trifluorometil-fenil)-acetamida (12,7 g, 29 mmol) en DMF (60 ml) se trata con *n*-Bu_4NCl (8,8 g, 32 mmol) y $Pd(OAc)_2$ (131 mg, 0,58 mmol) y se agita a 100°C durante 2 h. La mezcla se enfría a ta, se diluye con EtOAc (150 ml), se filtra a través de una capa de gel de sílice y se lava con HCl 1 M (150 ml). La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10% - 30% en heptano para producir 3-etil-5-trifluorometil-1H-indol (2,6 g, 42%). MS: 214 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,08 (s, NH, 1H), 7,89 (s, 1H), 7,41 (m, 2H), 7,07 (m, 1H), 2,81 (c, 2H), 1,34 (t, 3H).

Etapa 3: Una suspensión de NaH (7 g, 176 mmol, al 60% en aceite mineral) en DMF (50 ml) a 0°C se trata con 3-etil-5-trifluorometil-1H-indol (2,4 g, 11,3 mmol) y se agita a 0°C durante 1 h. La mezcla se trata en porciones con HOSA (6,6 g, 59 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo, se filtra a través de una capa de Celite y se extrae con EtOAc (3 x 150 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10% - 50% en heptano para producir 3-etil-5-trifluorometil-indol-1-ilamina (1,3 g, 50%). MS: 229 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,84 (s, 1H), 7,45 (s, 2H), 7,02 (s, 1H), 4,74 (s, NH_2, 2H), 2,77 (c, 2H), 1,31 (t, 3H).

Etapa 4: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (232 mg, 1,0 mmol) y 3-etil-5-trifluorometil-indol-1-ilamina (228 mg, 1 mmol) en DMF (5 ml) se agita a 50°C durante 1 h. La mezcla se trata con DMTMM (276 mg, 1 mmol) y se agita a 50°C durante 2 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 5 min. El precipitado se recoge por filtración y se seca al vació para producir (3-etil-5-trifluorometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (240 mg, 54%). MS: 443 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,24 (s, 1H), 8,34 (d, 1H), 8,26 (d, 1H), 8,19 (s, 1H), 7,58 (m, 2H), 7,42 (m, 3H), 2,84 (c, 2H), 2,78 (s, 3H), 1,31 (t, 3H).

Ejemplo 174

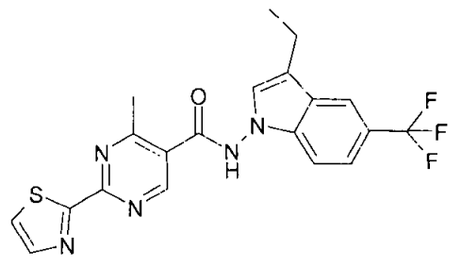
(3-Etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Una solución de ácido 2-(2-piridil)-4-metil-pirimidina-5-carboxílico (215 mg, 1 mmol) y 3-etil-5-trifluorometil-indol-1-ilamina (228 mg, 1 mmol) en DMF (5 ml) se agita a 50ºC durante 1 h. La mezcla se trata con DMTMM (276 mg, 1 mmol) y se agita a 50ºC durante 2 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 5 min. El precipitado se recoge por filtración y se seca al vacío para producir (3-etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (235 mg, 55%). MS: 426 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,28 (s, 1H), 8,81 (d, 1H), 8,48 (d, 1H), 8,03 (m, 1H), 7,99 (s, 1H), 7,60 (m, 4H), 2,82 (c, 2H), 2,79 (s, 3H), 1,31 (t, 3H).

Ejemplo 175

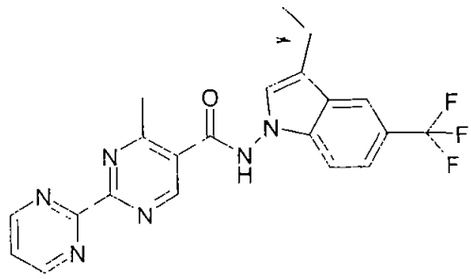
(3-Etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico



Una solución de ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (221 mg, 1 mmol) y 3-etil-5-trifluorometil-indol-1-ilamina (228 mg, 1 mmol) en DMF (5 ml) se agita a 50ºC durante 1 h. La mezcla se trata con DMTMM (276 mg, 1 mmol) y se agita a 50ºC durante 2 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 5 min. El precipitado se recoge por filtración y se seca al vacío para producir (3-etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (250 mg, 58%). MS: 432 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,07 (s, NH, 1H), 9,25 (s, 1H), 8,15 (d, 1H), 8,09 (d, 1H), 7,99 (s, 1H), 7,68 (d, 1H), 7,51 (m, 2H), 2,77 (s, 3H), 2,74 (c, 2H), 1,29 (t, 3H).

Ejemplo 176

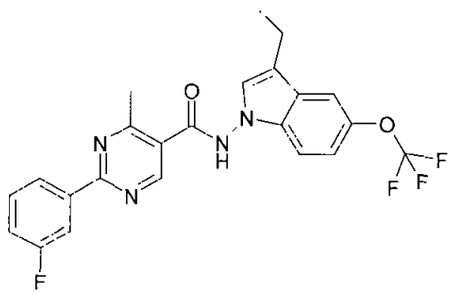
(3-etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico



Una solución de ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (216 mg, 1 mmol) y 3-etil-5-trifluorometil-indol-1-ilamina (228 mg, 1 mmol) en DMF (5 ml) se agita a 50°C durante 1 h. La mezcla se trata con DMTMM (276 mg, 1 mmol) y se agita a 50°C durante 2 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 5 min. El precipitado se recoge por filtración y se seca al vacío. El sólido se tritura en Et_2O para producir (3-etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (100 mg, 23%). MS: 427 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,11 (s, NH, 1H), 9,32 (s, 1H), 9,07 (d, 2H), 8,00 (s, 1H), 7,69 (m, 2H), 7,53 (m, 2H), 2,80 (c, 2H), 2,79 (s, 3H), 1,31 (t, 3H). CI_{50} = 8 nM.

Ejemplo 177

(3-Etil-5-trifluorometoxi-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Etapa 1: Una solución de 2-bromo-4-trifluorometoxi-fenilamina (7,6 g, 29,7 mmol) en DCM (60 ml) se trata con TFAA (5 ml, 35,6 mmol) y piridina (2,87 ml, 35,6 mmol) y se agita a ta durante una noche. La mezcla se diluye con H_2O (150 ml) y se extrae con DCM (3 x 150 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se diluye con MeCN (60 ml), se trata con bromuro de *trans*-crotilo (4,6 ml, 44,5 mmol) y K_2CO_3 (8,1 g, 59 mmol), se calienta a reflujo durante 1 h y después se agita a ta

durante 2 h. La mezcla se filtra a través de una capa de Celite y el filtrado se concentra. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0% - 15% en heptano para producir *N*-(2-bromo-4-trifluorometoxi-fenil)-*N*-but-2-enil-2,2,2-trifluoro-acetamida (10,5 g, 87%). MS: 406 (M+); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,56 (s, 1H), 7,22 (m, 2H), 5,52 (m, 2H), 4,86 (m, 1H), 3,57 (m, 1H), 1,65 (d, 3H).

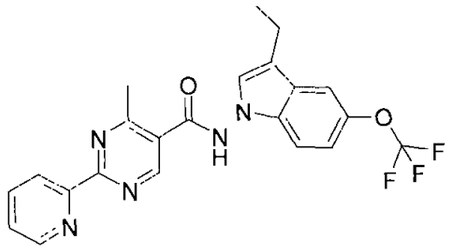
Etapa 2: Una solución de *N*-(2-bromo-4-trifluorometoxi-fenil)-*N*-but-2-enil-2,2,2-trifluoro-acetamida (10 g, 24,7 mmol) en DMF (50 ml) se trata con *n*-Bu_4NCl (7,5 g, 27,2 mmol) y $Pd(OAc)_2$ (221 mg, 0,98 mmol) y se agita a 100°C durante 1 h. Se añade H_2O (10 ml) y la mezcla se enfría a ta y se filtra a través de una capa de gel de sílice. El filtrado se extrae con heptano (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0% - 25% en heptano para producir 3-etil-5-trifluorometoxi-1H-indol (3,1 g, 55%). MS: 230 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,97 (s, NH, 1H), 7,44 (s, 1H), 7,29 (m, 1H), 7,07 (m, 2H), 2,77 (c, 2H), 1,32 (t, 3H).

Etapa 3: Una suspensión de NaH (7,9 g, 197 mmol, al 60% en aceite mineral) en DMF (60 ml) a 0°C se trata con 3-etil-5-trifluorometoxi-1H-indol (3 g, 13,1 mmol) y se agita a 0°C durante 1 h. La mezcla se trata en porciones con HOSA (7,4 g, 65,5 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo y se filtra a través de una capa de Celite. El filtrado se extrae con heptano (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10% - 30% en heptano para producir 3-etil-5-trifluorometoxi-indol-1-ilamina (2,05 g, 64%). MS: 245 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,37 (m, 2H), 7,11 (m, 1H), 7,00 (s, 1H), 4,72 (s, NH_2, 2H), 2,73 (c, 2H), 1,29 (t, 3H).

Etapa 4: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (250 mg, 1,1 mmol) y 3-etil-5-trifluorometoxi-indol-1-ilamina (244 mg, 1 mmol) en DMF (5 ml) se agita a 50°C durante 1 h. La mezcla se trata con DMTMM (276 mg, 1 mmol) y se agita a 50°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 10 min. El precipitado se recoge por filtración, se lava con H_2O (50 ml) y heptano (50 ml) y se seca al vacío para producir (3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (270 mg, 59%). MS: 459 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 11,51 (s, NH, 1H), 9,08 (s, 1H), 8,35 (d, 1H), 8,24 (d, 1H), 7,48 (m, 2H), 7,22 (m, 2H), 7,11 (m, 2H), 2,85 (s, 3H), 2,80 (c, 2H), 1,35 (t, 3H).

Ejemplo 178

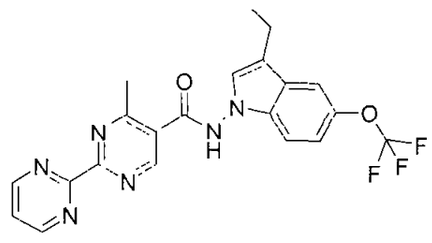
(3-Etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Una solución de ácido 2-(2-piridil)-4-metil-pirimidina-5-carboxílico (250 mg, 1,1 mmol) y 3-etil-5-trifluorometoxi-indol-1-ilamina (244 mg, 1,0 mmol) en DMF (5 ml) se agita a 50°C durante 1 h. La mezcla se trata con DMTMM (276 mg, 1,0 mmol) y se agita a 50°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 10 min. El precipitado se recoge por filtración, se lava con H_2O (50 ml) y heptano (50 ml) y se seca al vacío para producir (3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (300 mg, 68%). MS: 442 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,27 (s, 1H), 8,81 (d, 1H), 8,47 (d, 1H), 8,03 (m, 1H), 7,57 (m, 3H), 7,47 (s, 1H), 7,21 (d, 1H), 2,78 (s, 3H), 2,74 (c, 2H), 1,29 (t, 3H).

Ejemplo 179

(3-Etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico

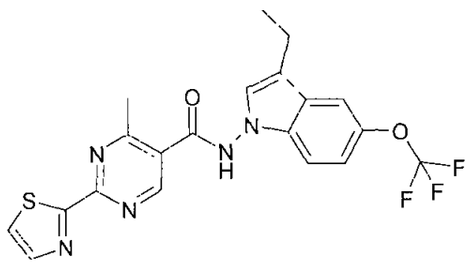


Una solución de ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (250 mg, 1,1 mmol) y 3-etil-5-trifluorometoxi-indol-1-ilamina (244 mg, 1 mmol) en DMF (5 ml) se agita a 50°C durante 1 h. La mezcla se trata con DMTMM (276 mg, 1,0 mmol) y se agita a 50°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 10 min. El precipitado se recoge por filtración, se lava con H_2O (50 ml) y heptano (50 ml) y se seca al vacío para producir (3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (130 mg, 29%). MS: 443 (M+H); ^{1}H RMN (300 MHz,

DMSO-d_6): δ 9,25 (s, 1H), 9,05 (d, 2H), 7,69 (t, 1H), 7,64 (s, 1H), 7,54 (m, 2H), 7,14 (d, 1H), 2,80 (s, 3H), 2,76 (c, 2H), 1,29 (t, 3H).

Ejemplo 180

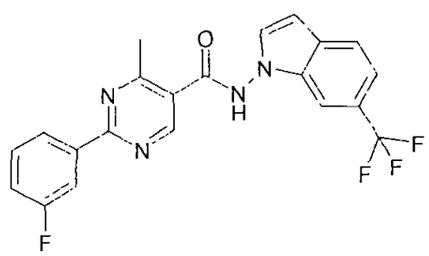
(3-Etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico



Una solución de ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (250 mg, 1,1 mmol) y 3-etil-5-trifluorometoxi-indol-1-ilamina (244 mg, 1,0 mmol) en DMF (5 ml) se agita a 50°C durante 1 h. La mezcla se trata con DMTMM (276 mg, 1,0 mmol) y se agita a 50°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 10 min. El precipitado se recoge por filtración, se lava con H_2O (50 ml) y heptano (50 ml) y se seca *al vacío* para producir (3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (250 mg, 56%). MS: 448 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,23 (s, 1H), 8,15 (m, 1H), 8,09 (m, 1H), 7,55 (m, 2H), 7,48 (s, 1H), 7,19 (d, 1H), 2,78 (s, 3H), 2,71 (m, 2H), 1,29 (t, 3H).

Ejemplo 181

(6-Trifluorometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



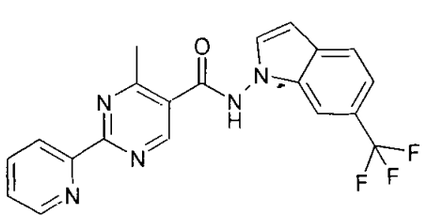
Etapa 1: Una suspensión de NaH (6,5 g, 162 mmol, al 60% en aceite mineral) en DMF (54 ml) a 0°C se trata con 6-trifluorometilindol (2,0 g, 10,8 mmol) y se agita a 0°C durante 0,5 h. La mezcla se trata en porciones con HOSA (6,1 g, 54 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo y se filtra a través de una capa de Celite. El filtrado

se extrae con Et_2O (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10% - 30% en heptano para producir 6-trifluorometil-indol-1-ilamina (1,79 g, 83%). MS: 201 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,74 (s, 1H), 7,67 (d, 1H), 7,35 (d, 1H), 7,30 (m, 1H), 6,45 (d, 1H), 4,83 (s, NH_2, 2H).

Etapa 2: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (278 mg, 1,2 mmol) y 6-trifluorometil-indol-1-ilamina (200 mg, 1 mmol) en DMF (5 ml) se agita a 50°C durante 0,5 h. La mezcla se trata con DMTMM (290 mg, 1,05 mmol) y se agita a 50°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se tritura con Et_2O/heptano durante una noche. El precipitado se recoge por filtración, se lava con H_2O (50 ml) y heptano (50 ml) y se seca al vacío para producir (6-trifluorometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (180 mg, 44%). MS: 415 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,09 (s, NH, 1H), 9,33 (s, 1H), 8,35 (d, 1H), 8,20 (d, 1H), 7,90 (s, 1H), 7,79 (m, 2H), 7,65 (m, 1H), 7,46 (m, 2H), 6,74 (d, 1H), 2,79 (s, 3H).

Ejemplo 182

(6-Trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico

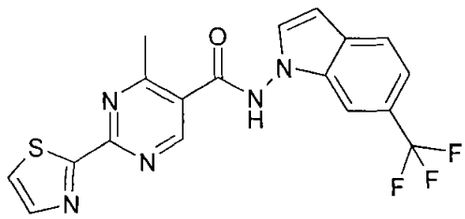


Una solución de ácido 2-(2-piridil)-4-metil-pirimidina-5-carboxílico (258 mg, 1,2 mmol) y 6-trifluorometil-indol-1-ilamina (200 mg, 1 mmol) en DMF (5 ml) se agita a 50°C durante 0,5 h. La mezcla se trata con DMTMM (290 mg, 1,05 mmol) y se agita a 50°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se tritura con Et_2O/heptano durante una noche. El precipitado se recoge por filtración, se lava con H_2O (50 ml) y heptano (50 ml) y se seca al vacío para producir (6-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (160 mg, 40%). MS: 398 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,13 (s, NH, 1H), 9,36 (s, 1H), 8,82 (d, 1H),

8,48 (d, 1H), 8,04 (m, 1H), 7,83 (m, 3H), 7,60 (m, 1H), 7,44 (d, 1H), 6,74 (d, 1H), 2,80 (s, 3H).

Ejemplo 183

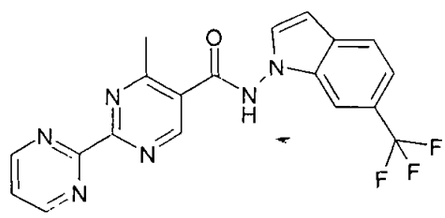
(6-Trifluorometil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico



Una solución de ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (265 mg, 1,2 mmol) y 6-trifluorometil-indol-1-ilamina (200 mg, 1 mmol) en DMF (5 ml) se agita a 50°C durante 0,5 h. La mezcla se trata con DMTMM (290 mg, 1,05 mmol) y se agita a 50°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se tritura con Et_2O/heptano durante una noche. El precipitado se recoge por filtración, se lava con H_2O (50 ml) y heptano (50 ml) y se seca al vacío para producir (6-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (160 mg, 40%). MS: 404 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,12 (s, NH, 1H), 9,33 (s, 1H), 8,15 (d, 1H), 8,05 (d, 1H), 7,91 (s, 1H), 7,79 (m, 2H), 7,44 (m, 1H), 6,73 (d, 1H), 2,77 (s, 3H).

Ejemplo 184

(6-Trifluorometil-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico

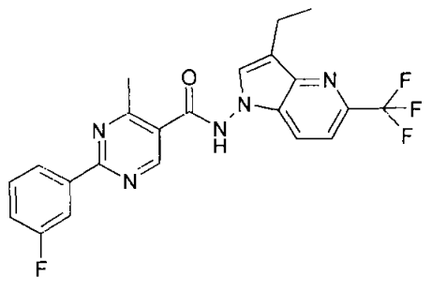


Una solución de ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (259 mg, 1,2 mmol) y 6-trifluorometil-indol-1-ilamina (200 mg, 1 mmol) en DMF (5 ml) se agita a 50°C durante 0,5 h. La mezcla se trata con DMTMM (290 mg, 1,05 mmol) y se agita a 50°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se tritura con Et_2O/heptano durante una noche. El precipitado se recoge por filtración, se lava con H_2O (50 ml) y heptano (50 ml) y se seca al vacío para producir (6-trifluorometil-indol-1-

il)-amida del ácido 4-metil-[2,2']bipiridinil-5-carboxílico (100 mg, 25%). MS: 399 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,16 (s, NH, 1H), 9,39 (s, 1H), 9,06 (d, 2H), 7,92 (s, 1H), 7,81 (m, 2H), 7,70 (t, 1H), 7,44 (d, 1H), 6,74 (d, 1H), 2,79 (s, 3H).

Ejemplo 185

(3-Etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Etapa 1: Una solución de 2-yodo-6-trifluorometil-piridin-3-ilamina (5,09 g, 17,7 mmol) en DCM (50 ml) se trata con TFAA (3 ml, 21,2 mmol) y piridina (1,7 ml, 21,2 mmol) y se agita a ta durante 1 h. La mezcla se diluye con H_2O (150 ml) y se extrae con DCM (3 x 150 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se diluye con MeCN (50 ml), se trata con bromuro de *trans*-crotilo (2,8 ml, 26,6 mmol) y K_2CO_3 (4,7 g, 34,4 mmol) y se calienta a reflujo durante 2 h. La mezcla se filtra a través de una capa de Celite. El filtrado se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0% - 25% en heptano para producir *N*-but-2-enil-2,2,2-trifluoro-*N*-(2-yodo-6-trifluorometil-piridin-3-il)-acetamida (5,5 g, 71%). MS: 439 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,71 (d, 1H), 7,53 (d, 1H), 5,52 (m, 2H), 4,98 (m, 1H), 3,58 (m, 1H), 1,68 (d, 3H).

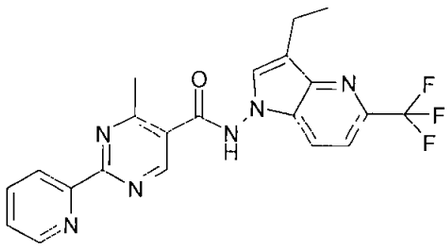
Etapa 2: Una solución de *N*-but-2-enil-2,2,2-trifluoro-*N*-(2-yodo-6-trifluorometil-piridin-3-il)-acetamida (5,2 g, 11,9 mmol) en DMF (24 ml) se trata con *n*-Bu_4NCl (3,6 g, 13,1 mmol) y $Pd(OAc)_2$ (107 mg, 0,48 mmol) y se agita a 100°C durante 1 h. Se añade H_2O (10 ml) y la mezcla se enfría a ta y se filtra a través de una capa de gel de sílice. El filtrado se extrae con EtOAc/heptano (3 x 50 ml) (1:1). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 5% - 50% en heptano para producir 3-etil-5-trifluorometil-1H-pirrolo[3,2-b]piridina (2,2 g, 86%). MS: 215 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,24 (s, NH, 1H), 7,73 (d, 1H), 7,50 (d, 1H), 7,34 (d, 1H), 2,93 (c, 2H), 1,36 (t, 3H).

Etapa 3: Una suspensión de NaH (4,65 g, 116 mmol, al 60% en aceite mineral) en DMF (40 ml) a 0ºC se trata con 3-etil-5-trifluorometil-1H-pirrolo[3,2-b]piridina (2 g, 7,75 mmol) y se agita a 0ºC durante 1 h. La mezcla se trata en porciones con HOSA (4,4 g, 38,8 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo, se trata con NH_4Cl sólido (3 g) y se filtra a través de una capa de Celite. El filtrado se extrae con Et_2O (3 x 150 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 30% - 50% en heptano para producir 3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-ilamina (1,5 g, 84%). MS: 230 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 7,97 (d, 1H), 7,59 (d, 1H), 7,54 (s, 1H), 6,12 (s, NH_2, 2H), 2,78 (c, 2H), 1,28 (t, 3H).

Etapa 4: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (278 mg, 1,1 mmol) y 3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-ilamina (230 mg, 1 mmol) en DMF (5 ml) se agita a 50ºC durante 1 h. La mezcla se trata con DMTMM (290 mg, 1,05 mmol) y se agita a 50ºC durante una noche. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 10 min. El precipitado se recoge por filtración, se lava con H_2O (50 ml) y heptano (50 ml) y se seca al vacío para producir (3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (195 mg, 44%). MS: 444 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 12,16 (s, NH, 1H), 9,28 (s, 1H), 8,34 (d, 1H), 8,18 (m, 2H), 7,86 (s, 1H), 7,65 (m, 2H), 7,45 (m, 1H), 2,83 (c, 2H), 2,78 (s, 3H), 1,35 (t, 3H).

Ejemplo 186

(3-Etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico

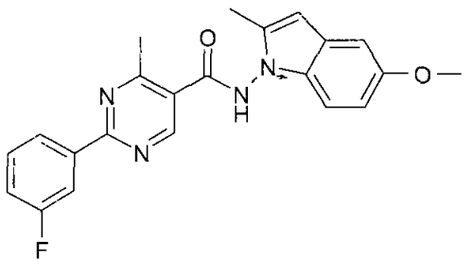


Una solución de ácido 2-(2-piridil)-4-metil-pirimidina-5-carboxílico (258 mg, 1,1 mmol) y 3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-ilamina (230 mg, 1,0 mmol) en DMF (5 ml) se agita a 50ºC durante 1 h. La mezcla se trata con DMTMM (290 mg, 1,05 mmol) y se agita a 50ºC durante una noche. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita

Una solución de ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (259 mg, 1,2 mmol) y 3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-ilamina (230 mg, 1,0 mmol) en DMF (5 ml) se agita a 50°C durante 0,5 h. La mezcla se trata con DMTMM (290 mg, 1,05 mmol) y se agita a 50°C durante una noche. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por HPLC preparativa de fase inversa eluyendo con MeCN al 20% - 100% en H_2O para producir (3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (230 mg, 54%). MS: 428 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,28 (s, 1H), 9,05 (d, 2H), 8,11 (d, 1H), 7,98 (s, 1H), 7,69 (t, 1H), 7,64 (d, 1H), 2,83 (c, 2H), 2,80 (s, 3H), 1,34 (t, 3H).

Ejemplo 189

(5-Metoxi-2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Etapa 1: Una suspensión de NaH (1,25 g, 51 mmol, al 60% en aceite mineral) en DMF (47 ml) a 0°C se trata con 5-metoxi-2-metilindol (500 mg, 3,1 mmol) y se agita a 0°C durante 0,5 h. La mezcla se trata en porciones con HOSA (1,92 g, 17,0 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío para producir 5-metoxi-2-metil-indol-1-ilamina, que se usa en la siguiente etapa sin purificación adicional.

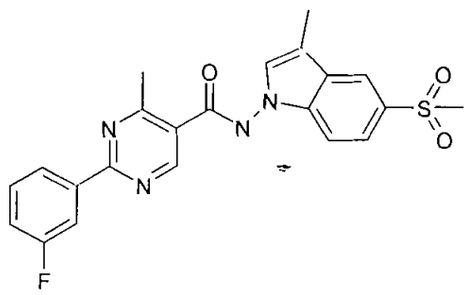
Etapa 2: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (719 mg, 3,1 mmol) y 5-metoxi-2-metil-indol-1-ilamina (550 mg, 3,1 mmol) en DMF (4 ml) se agita a 50°C durante 15 min. La mezcla se trata con DMTMM (856 mg, 3,1 mmol) y se agita a 50°C durante 1 h. La mezcla se concentra al vacío, se diluye con EtOAc (50 ml) y se lava con Na_2CO_3 acuoso saturado (50 ml). La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 30% en heptano para producir (5-metoxi-2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (180 mg, 15%, 2 etapas). MS: 391 (M+H); ^{1}H

Etapa 1: Una suspensión de NaH (805 mg, 20,1 mmol, al 60% en aceite mineral) en DMF (5 ml) a 0°C se trata con 7-fluoro-3-metilindol (200 mg, 1,34 mmol) y se agita a 0°C durante 1 h. La mezcla se trata en porciones con HOSA (757 mg, 6,7 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo, y se extrae con EtOAc (3 x 100 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío para producir 7-fluoro-3-metil-indol-1-ilamina, que se usa en la siguiente etapa sin purificación adicional.

Etapa 2: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (1,34 mmol) y 7-fluoro-3-metil-indol-1-ilamina (342 mg, 1,47 mmol) en DMF (15 ml) se agita a 50°C durante 1 h. La mezcla se trata con DMTMM (407 mg, 1,47 mmol) y se agita a 50°C durante 4 h. La mezcla se concentra al vacío, se diluye con Et_2O (50 ml) y se lava con Na_2CO_3 acuoso saturado (50 ml). La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con DCM al 0% -100% en EtOAc para producir (7-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (241 mg, 48%). MS: 379 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,05 (s, 1H), 8,32 (d, 1H), 8,18 (d, 1H), 7,64 (m, 1H), 7,45 (m, 1H), 7,40 (m, 1H), 7,31 (s, 1H), 7,05 (m, 2H), 2,74 (s, 3H), 2,29 (s, 3H).

Ejemplo 192

(5-Metanosulfonil-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



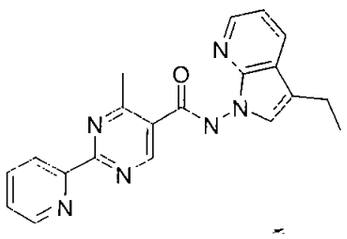
Etapa 1: Una solución de alil-(2-yodo-4-metanosulfonil-fenil)-amina (1,43 g, 4,1 mmol) en DMF (20 ml) se trata con *n*-Bu_4NCl (1,47 g, 5,32 mmol) y $Pd(OAc)_2$ (56,6 mg, 0,2 mmol) y se agita a 100°C durante 1 h. Se añade HCl (5,3 ml, 3 M) y la mezcla se enfría a ta, se filtra a través de una capa de Celite y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de silice eluyendo con EtOAc al 60% en heptano para producir 5-metanosulfonil-3-metil-1H-indol (370 mg, 43%).

Etapa 2: Una suspensión de NaH (1,06 g, 26,6 mmol, al 60% en aceite mineral) en DMF (15 ml) a 0ºC se trata con 5-metanosulfonil-3-metil-1H-indol (370 mg, 1,77 mmol) y se agita a 0ºC durante 1 h. La mezcla se trata en porciones con HOSA (1 g, 8,85 mmol) y se calienta a ta durante una noche. Después, la mezcla se vierte sobre hielo y se extrae con EtOAc (3 x 100 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío para producir 5-metanosulfonil-3-metil-indol-1-ilamina, que se usa en la siguiente etapa sin purificación adicional.

Etapa 3: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (1,77 mmol) y 5-metanosulfonil-3-metil-indol-1-ilamina (452 mg, 1,95 mmol) en DMF (15 ml) se agita a ta durante 1 h. La mezcla se trata con DMTMM (538 mg, 1,95 mmol) y se agita a 60ºC durante 1,5 h. La mezcla se diluye con EtOAc (50 ml) y se lava con Na_2CO_3 acuoso saturado (50 ml). La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0% -100% en heptano y después por trituración en Et_2O para producir (5-metanosulfonil-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (106 mg, 14%). MS: 439 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,15 (s, 1H), 8,37 (d, 1H), 8,24 (m, 2H), 7,82 (m, 1H), 7,59 (d, 1H), 7,54 (m, 1H), 7,34 (s, 1H), 7,29 (m, 1H), 3,13 (s, 3H), 2,83 (s, 3H), 2,42 (s, 3H).

Ejemplo 193

Sal del ácido trifluoroacético de (3-etil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Etapa 1: (Ref.: J. Org. Chem. 2002, 67, 6226-6227) Se añade 7-azaindol (5 g, 42,3 mmol) a una suspensión agitada de $AlCl_3$ (22,6 g, 169 mmol) en DCM (300 ml). Después de agitar a ta durante 1 h, se añade gota a gota cloruro de acetilo (13,3 g, 169 mmol) y la mezcla resultante se agita durante 18 h. La mezcla se enfría a 0ºC, se inactiva con MeOH (150 ml) y se agita durante 1 h. A la mezcla se le añade gel de sílice, los disolventes se retiran al vacío y el residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 10% en

DCM para producir 1-(1H-pirrolo [2,3-b]piridin-3-il)-etanona (1,6 g). ^{1}H RMN (300 MHz, CH_3OD): δ 8,93 (d, 1H), 8,45 (s, 2H), 7,50 (t, 1H), 3,30 (s, 3H).

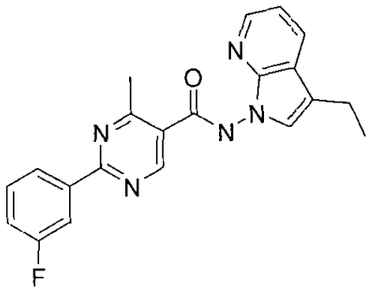
Etapa 2: A una solución de 1-(1H-pirrolo[2,3-b]piridin-3-il)-etanona (1,34 g, 8,38 mmol) en TFA (25 ml) se le añade trietilsilano (6,09 g, 52,4 mmol) y se agita a ta durante 18 h. La mezcla se concentra, se diluye con una solución acuosa 2 N de KOH y se extrae tres veces con DCM. La capa orgánica combinada se seca (Na_2SO_4), se filtra y se evapora. El residuo resultante se cromatografía a través de gel de sílice eluyendo con MeOH al 10% en DCM para producir 3-etil-1H-pirrolo[2,3-b]piridina (0,91 g). MS: 147 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 9,23 (s ancho, 1H), 8,32 (d, 1H), 7,94 (s,1H), 7,05-7,14 (m, 2H), 2,80 (c, 2H), 1,35 (t,3H).

Etapa 3: Se disuelven 3-etil-1H-pirrolo[2,3-b]piridina (0,91 g, 6,2 mmol) y KO*t*Bu (1,39 g, 12,4 mmol) en DMF (28 ml) y la mezcla se agita durante 2 h a ta. Mientras se rocía vigorosamente con nitrógeno, se añade en porciones NH_2Cl (92 ml 0,15 M en éter). La mezcla de reacción se agita a ta durante 2 h. La mezcla se enfría a 0ºC y después se inactiva con $Na_2S_2O_3$ (2,7 g) en agua (50 ml). Después de dejar en reposo a ta durante 18 h, la mezcla se concentra, se tritura en DCM y se filtra. El filtrado se concentra y se cromatografía a través de gel de sílice eluyendo con MeOH al 10% en DCM para producir 3-etil-pirrolo[2,3-b]piridin-1-il- amina (380 mg). MS: 162 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,32 (d, 1H), 7,90 (d, 1H), 7,04-7,13 (m, 2H), 4,96 (s ancho, 2H), 2,76 (c, 2H), 1,33 (t, 3H).

Etapa 4: Una mezcla de 3-etil-pirrolo[2,3-b]piridin-1-ilamina (126 mg, 0,78 mmol), ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (168 mg, 0,78 mmol), HATU (356 mg, 0,936 mmol) y DIPEA (302 mg, 2,34 mmol) en DMF (4 ml) se calienta a 150ºC durante 1 h. La reacción se interrumpe con agua y se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se cromatografía primero a través de gel de sílice eluyendo con MeOH al 10% en DCM. El producto resultante se cromatografía de nuevo usando HPLC de fase inversa eluyendo con TFA al 0,1% en agua y acetonitrilo para producir sal del ácido trifluoroacético de (3-etil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (29 mg). MS: 359 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 9,45 (s, 1H), 9,04 (d, 1H), 8,93 (d, 1H), 8,67 (t, 1H), 8,31 (d, 1H), 8,19-8,08 (m, 2H), 7,34 (s, 1H), 7,27 (dd, 1H), 2,96 (s, 3H), 2,85 (c, 2H), 1,39 (t, 3H).

Ejemplo 194

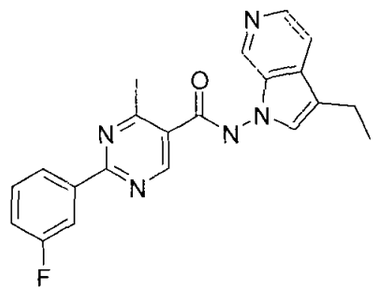
(3-Etil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Una mezcla de 3-etil-pirrolo[2,3-b]piridin-1-ilamina (126 mg, 0,78 mmol), ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (180 mg, 0,78 mmol), HATU (356 mg, 0,036 mmol) y DIPEA (302 mg, 2,34 mmol) en DMF (4 ml) se calienta a 150°C durante 1 h. La reacción se interrumpe con agua y se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se cromatografía a través de gel de sílice eluyendo con acetato de etilo al 0-100% en heptano para producir (3-etil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (128 mg). MS: 376 (M+H); ^{1}H RMN (300 MHz, DMSO-d6): δ 9,10 (s, 1H), 8,25-8,33 (m, 2H), 8,16 (d, 1H), 8,05 (d, 1H), 7,62 (c, 1H), 7,39-7,48 (m, 2H), 7,16 (dd, 1H), 2,78 (s, 3H), 2,75 (c, 2H), 1,29 (t, 3H).

Ejemplo 195

(3-Etil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

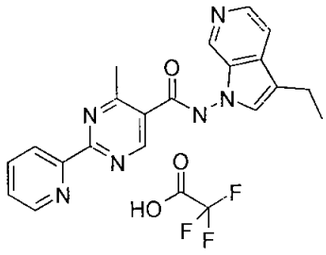


Una mezcla de 3-etil-pirrolo[2,3-c]piridin-1-ilamina (93 mg, 0,577 mmol), ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (134 mg, 0,757 mmol), HATU (263 mg, 0,692 mmol) y DIPEA (223 mg, 1,73 mmol) en DMF (3 ml) se calienta a 150°C durante 1 h. La reacción se interrumpe con agua y se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con acetato de etilo al 0-100% en heptano para producir (3-etil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (86 mg).

MS: 376 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 9,15 (s, 1H), 8,69 (s, 1H), 8,37 (d, 1H), 8,15-8,26 (m, 2H), 7,70 (d, 1H), 7,55 (c, 1H), 7,49 (s, 1H), 7,29 (t, 1H), 2,80-2,90 (m, 5 H), 1,38 (t, 3H). CI_{50} = 7 nM.

Ejemplo 196

Sal del ácido trifluoroacético de (3-etil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Etapa 1: (Ref.: J. Org. Chem. 2002, 67, 6226-6227) Se añade 6-azaindol (2,5 g, 21,25 mmol) a una suspensión agitada de $AlCl_3$ (11,3 g, 84,5 mmol) en CH_2Cl_2 (150 ml). Después de agitar a ta durante 1 h, se añade gota a gota cloruro de acetilo (6,65 g, 84,5 mmol) y la mezcla resultante se agita durante 18 h. La mezcla se enfría a 0°C, se inactiva con MeOH (75 ml) y se agita durante 1 h. A la mezcla se le añaden gel de sílice (40 ml), MeOH y DCM, los disolventes se retiran al vacío y el residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 10% en DCM para producir 1-(1H-pirrolo[2,3-c]piridin-3-il)-etanona (1,52 g, 45%). MS: 161 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 9,20 (s, 1H), 8,95 (s, H), 7,82 (d, 1H), 8,72 (d, 1H), 8,43 (d, 1-H), 2,64 (s, 3H).

Etapa 2: A una solución de 1-(1H-pirrolo[2,3-c]piridin-3-il)-etanona (1,53 g, 9,55 mmol) en TFA (29 ml) se le añade trietilsilano (6,88 g, 59,21 mmol) y se agita a ta durante 18 h. La mezcla se concentra y se extrae con EtOAc. La capa orgánica se lava con KOH acuoso 2 N, se seca (Na_2SO_4), se filtra y se evapora. El residuo resultante se cromatografía a través de gel de sílice eluyendo con MeOH al 10% en DCM para producir 3-etil-1H-pirrolo[2,3-c]piridina (1,35 g, 97%). MS: 147 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 13,3 (ancho, N-H) 9,46 (s, 1H), 8,04 (s, 1H), 7,71-7,88 (m, 2H), 2,88 (c, 2H), 1,39 (t, 3H).

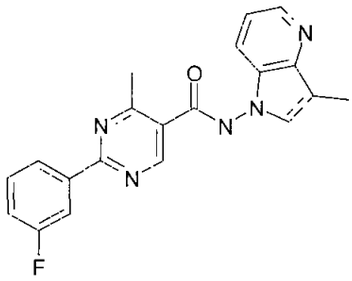
Etapa 3: Se disuelven 3-etil-1H-pirrolo[2,3-c]piridina (1,21 g, 8,29 mmol) y KO*t*Bu (1,86 g, 16,57 mmol) en DMF (47 ml) y la mezcla se agita durante 2 h a ta. Mientras se purga vigorosamente con nitrógeno, se añade en porciones NH_2Cl (101 ml 0,15 M en éter). La mezcla de reacción se agita a ta durante 1 h. Después, la mezcla se enfría a 0°C y se inactiva

con $Na_2S_2O_3$ (4,3 g) en agua (80 ml). Después de dejar en reposo a ta durante 2 días, las capas se separan. A la capa acuosa se le añade salmuera y después se extrae con EtOAc. Las capas orgánicas se combinan y se secan (Na_2SO_4) para dar una mezcla de 3-etil-pirrolo[2,3-c]piridin-1-ilamina y material de partida. Esta mezcla se purifica por cromatografía a través de gel de sílice eluyendo con MeOH al 10% en DCM para producir 3-etil-pirrolo[2,3-c]piridin-1-ilamina (93 mg). La mezcla restante del material de partida y el producto se recoge y se disuelve en DCM. Esta solución se enfría a 0°C y se carga con BOC_2O (164 mg, 0,75 mmol). La mezcla resultante se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 10% en DCM para producir más cantidad de 3-etil-pirrolo[2,3-c]piridin-1-ilamina (145 mg). ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,85 (s, 1H), 8,25 (d, 1H), 7,48 (d, 1H), 7,10 (s, 1H), 4,88 (s, 2H), 2,75 (c, 2H), 1,35(t, 3H).

Etapa 4: Una mezcla de 3-etil-pirrolo[2,3-c]piridin-1-ilamina (122 mg, 0,757 mmol), ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (163 mg, 0,757 mmol), HATU (356 mg, 0,936 mmol) y DIPEA (294 mg, 2,27 mmol) en DMF (4 ml) se calienta a 150°C durante 1 h. La reacción se interrumpe con agua y se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se cromatografía a través de gel de sílice eluyendo con MeOH al 10% en DCM. El producto resultante se cromatografía de nuevo usando HPLC de fase inversa eluyendo con TFA al 0.1% en agua y acetonitrilo para producir sal del ácido trifluoroacético de (3-etil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (42 mg, 9,5%). MS: 359 (M+H); ^{1}H RMN (300 MHz, DMSO-d6): δ 9,43 (s, 1H), 9,37 (s, 1H), 8,80 (d, 1H), 8,45 (t, 2H), 8,26 (s, 1H), 8,22 (d, 1H), 8,03 (t, 1H), 7,59 (t, 1H), 2,86 (c, 2H), 2,80 (s, 3H), 1,32 (t, 3H).

Ejemplo 197

(3-Metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

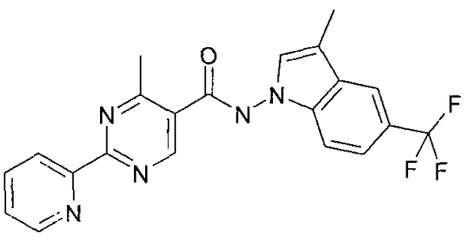


Una mezcla de 3-metil-pirrolo[3,2-b]piridin-1-ilamina (75% de pureza) (240 mg, <1,63 mmol), ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (379 mg, 1,63 mmol),

HATU (744 mg, 1,96 mmol) y DIPEA (388 mg, 4,89 mmol) en DMF (5 ml) se calienta a 150°C durante 1 h. La reacción se interrumpe con agua y se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se cromatografía a través de gel de sílice eluyendo con MeOH al 10% en DCM. El producto resultante se recristaliza con éter para producir (3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (197 mg, 44%). MS: 362 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 9,14 (s, 1H), 8,40 (d, 1H), 8,36 (d, 1H), 8,22 (d, 1H), 7,85 (d, 1H), 7,55 (c, 1H), 7,47 (s, 1H), 7,25-7,34 (m, 2H), 2,83 (s, 3H), 2,42 (s, 3H). CI_{50} = 2 nM.

Ejemplo 198

(3-Metil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Etapa 1: A una mezcla de 2-yodo-4-trifluorometil-anilina (5 g, 17,4 mmol), KO*t*-Bu (2,05 g, 18,3 mmol) y THF (200 ml) a -78°C se le añade bromuro de alilo (2,21 g, 18,3 mmol). La mezcla resultante se calienta a ta y se agita durante 18 h. Se añade agua y la mezcla se extrae con EtOAc. La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra. El residuo se cromatografía a través de gel de sílice eluyendo con EtOAc al 0-50% en heptano para producir alil-(2-yodo-4-trifluorometil-fenil)-amina (1,9 g, 33%). MS 328 (M + H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,90 (s, 1H), 7,45 (d, 1 H), 5,88-6,02 (m, 1H), 5,33 (d, 1 H), 5,25 (d, 1H), 4,72(s ancho, 1H), 3,90 (s, 2H).

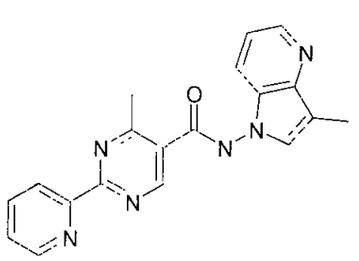
Etapa 2: Una mezcla de alil-(2-yodo-4-trifluorometil-fenil)-amina (1,75 g, 5,35 mmol), cloruro de tetrabutilamonio (1,68 g, 5,35 mmol), acetato de paladio (120 mg, 0,54 mmol) y carbonato potásico (2,22 g, 16,0 mmol) en DMF (50 ml) se calienta a 80°C durante 1,5 h. La reacción se interrumpe con agua y se extrae tres veces con DCM. La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra. El residuo se cromatografía a través de gel de sílice eluyendo con EtOAc al 0-40% en heptano para producir 3-metil-5-trifluorometil-1H-indol (401 mg). ^{1}H RMN (300 MHz, $CDCl_3$): δ = 8,09 (s ancho, 1H), 7,90 (s, 1 H), 7,44 (s, 1H), 7,10 (s, 1H), 2,38 (s, 3H).

Etapa 3: Se añade en porciones NaH al 60% (1,21 g, 30,2 mmol) a una solución agitada de 3-metil-5-trifluorometil-1H-indol (400 mg, 2,01 mmol) en DMF (6 ml) a 0ºC. La mezcla se agita a 0ºC durante 1 h, se añade en porciones HOSA (1,14 g, 10,0 mmol) a 0ºC y la mezcla se deja calentar a ta durante 2 h. La reacción se interrumpe con cloruro de amonio acuoso saturado, y se extrae tres veces con DCM. La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra. El residuo se cromatografía a través de gel de sílice eluyendo con EtOAc al 0-40% en heptano para producir 3-metil-5-trifluorometil-indol-1-ilamina (223 mg, 52%). MS: 215 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ = 7,84 (s, 1H), 7,48 (s, 2H), 7,04 (s, 1H), 4,77 (s, 2H), 2,34 (s, 3H).

Etapa 4: Una mezcla de 3-metil-5-trifluorometil-indol-1-ilamina (223 mg, 1,04 mmol), ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (224 g, 1,04 mmol), HATU (475 mg, 1,25 mmol) y DIPEA (404 mg 3,13 mmol) se agita en DMF a 150ºC durante 1 h. La reacción se interrumpe con agua y se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se cromatografía a través de gel de sílice eluyendo con MeOH al 10% en DCM para producir (3-metil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (122 mg, 28%). MS: 412 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 9,22 (s, 1H), 8,79 (d, 1H), 8,66 (d, 1H), 8,06 (t, 1H), 7,91 (s, 1H), 7,60 (dd, 1H), 7,51 (s, 2H), 7,29 (s, 3H), 2,88 (s, 3H), 2,40 (s, 3H).

Ejemplo 199

(3-Metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Etapa 1: A una solución de 3-amino-2-cloropiridina (5 g 38,9 mmol) en THF (35 ml) se le añade NaHMDS 2 M en THF (38,9 ml, 77,8 mmol). Después de agitar a ta durante 15 min, se añade en una porción BOC_2O (7,7 g, 35,6 mmol) en THF (20 ml) y después la mezcla se agita durante 5 h a ta. Se añade HCl acuoso al 0,1%. La mezcla se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se cromatografía a través de gel de sílice eluyendo con EtOAc al 0-50% en heptano para producir éster terc-butílico

del ácido (2-cloro-piridin-3-il)-carbámico (7,18 g, 89%). MS: 229 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,52 (d, 1H), 8,05 (dd, 1H), 7,23 (dd, 1H), 7,02 (s ancho, 1H), 1,55 (s, 9H).

Etapa 2: Una mezcla de éster terc-butílico del ácido (2-cloro-piridin-3-il)-carbámico (7 g, 30,7 mmol), bromuro de alilo (5,26 g, 40,8 mmol) y carbonato de cesio (20,8 g, 63,8 mmol) en DMF (280 ml) se calienta a 60ºC durante 1 h. La reacción se interrumpe con agua y se extrae con EtOAc. La capa orgánica se seca (Na_2SO_4), se filtra y se concentra para producir éster terc-butílico del ácido alil-(2-cloro-piridin-3-il)-carbámico (8,03 g, 98%), que se usa en la siguiente etapa sin purificación adicional.

Etapa 3: Una mezcla de éster terc-butílico del ácido alil-(2-cloro-piridin-3-il)-carbámico (8,03 g, 30 mmol), cloruro de tetrabutilamonio (9,4 g, 30 mmol), acetato de paladio (673 mg, 3 mmol) y carbonato potásico (12,4 g, 3 mmol) en DMF (300 ml) se calienta a 80ºC durante 1,5 h. La reacción se interrumpe con DCM y se lava con agua. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se cromatografía a través de gel de sílice eluyendo con EtOAc al 0-40% en heptano para producir éster terc-butílico del ácido 3-metil-pirrolo[3,2-b]piridina-1-carboxílico y éster terc-butílico del ácido 3-metileno-2,3-dihidro-pirrolo[3,2-b]piridina-1-carboxílico (1,58 g).

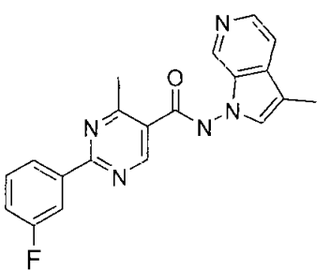
Etapa 4: Después, la mezcla anterior se agita en DCM (10 ml) y TFA (10 ml) a ta durante 3 h. La reacción se concentra y se añaden una solución acuosa 2 M de KOH y DCM. El precipitado se recoge por filtración para producir la sal potásica de 3-metil-1H-pirrolo[3,2-b]piridina (1 g, 20%). MS: 133 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 8,26 (d, 1H), 7,75 (d, 1H), 7,33 (s, 1H), 7,12 (dd, 1H), 2,36 (s, 3H).

Etapa 5: Una mezcla de la sal potásica de 3-metil-1H-pirrolo[3,2-b]piridina (1 g, 5,88 mmol) y KOtBu (660 mg, 5,88 mmol) en DMF (26 ml) se purga con N_2 y se agita a ta durante 2 h. Se añade cloramina en éter (0,15 M, 29 ml) y la mezcla se agita durante 45 min. La reacción se enfría a 0ºC, se añade $Na_2S_2O_3$ (3,4 g) en agua (70 ml) y la mezcla se agita durante 15 min. La mezcla se concentra al vacío. El residuo se tritura con DCM y después se filtra. El filtrado se lava con KOH acuoso 2 M, se seca (Na_2SO_4), se filtra y se concentra. El residuo se cromatografía a través de gel de sílice eluyendo con MeOH al 10% en DCM para producir una mezcla de material de partida y 3-metil-pirrolo[3,2-b]piridin-1-il amina (839 mg,~64%, pureza de ~66% en mol), que se usa en la siguiente etapa sin purificación adicional.

Etapa 6: Una mezcla de 3-metil-pirrolo[3,2-b]piridin-1-ilamina (839 mg, <5,71 mmol), ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (1,32 g, 6,13 mmol), HATU (2,6 g, 6,85 mmol) y DIPEA (2,21 g 17,1 mmol) en DMF (17 ml) se agita a 150ºC durante 1 h. La reacción se interrumpe con agua y éter. La capa de agua se concentra al vacío. El residuo se cromatografía a través de gel de sílice eluyendo con una mezcla de DCM, MeOH y trietilamina (9,5:0,5:0,05) para producir (3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (134 mg). MS: 345 345 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 9,22 (s, 1H), 8,79 (d, 1H), 8,64 (d, 1H), 8,40 (d, 1H), 8,05 (t, 1H), 7,87 (d, 1H), 7,60 (t, 1H), 7,49 (s, 1H) 7,30 (dd, 1H), 2,87 (s, 3H), 2,42 (s, 3H).

Ejemplo 200

(3-Metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



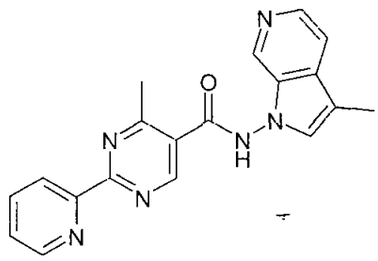
Etapa 1: Se añade en porciones hidruro sódico al 60% (6,69 g, 167 mmol) a una solución agitada de 3-metil-1H-pirrolo[2,3-c]piridina (1,47 g, 11,2 mmol) en DMF (33 ml) a 0ºC durante 1 h. Se añade en porciones ácido hidroxilamina-O-sulfónico (6,3 g, 55,8 mmol) a 0ºC y se agita durante 2 h a 0ºC. La mezcla de reacción se inactiva a 0ºC con agua y se concentra al vacío para retirar la DMF. El residuo se tritura en DCM. El sólido se retira por filtración y el filtrado se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 10% en DCM para producir 3-metil-pirrolo[2,3-c]piridin-1-ilamina (1 g, 61%). MS: 148 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,85 (s, 1H), 8,27 (d, 1H), 7,46 (d, 1H), 7,09 (s, 1H), 2,30 (s, 3H).

Etapa 2: Una mezcla de 3-metil-pirrolo[2,3-c]piridin-1-ilamina (224 mg, 1,53 mmol), ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (354 mg, 1,53 mmol), HATU (693 mg, 1,82 mmol) y DIPEA (593 mg, 4,59 mmol) en DMF (8 ml) se agita a 150ºC durante 1 h. La reacción se interrumpe con agua y se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0-100% en heptano para producir (3-metil-pirrolo[2,3-c]piridin-1-il)-

amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (55 mg). MS: 362 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 9,15 (s, 1H), 8,69 (s, 1H), 8,37 (d, 1H), 8,24 (s, 1H), 8,20 (d, 1H), 7,68 (d, 1H), 7,55 (c, 1H), 7,47 (s, 1H), 7,29 (t, 1H), 2,84 (s, 3H), 2,39 (s, 3H).

Ejemplo 201

(3-Metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Etapa 1: A una solución de 3-amino-4-cloropiridina (6,56 g 51 mmol) en THF (46 ml) se le añade NaHMDS 2 M en THF (50 ml, 100 mmol). Después de agitar a ta durante 15 min, se añade en una porción BOC_2O (10,1 g, 46,4 mmol) en THF (26 ml) y la mezcla se agita durante 3 h a ta. Se añade HCl acuoso al 0,1% (590 ml). La mezcla se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0-50% en heptano para producir éster terc-butílico del ácido (4-cloro-piridin-3-il)-carbámico (6,78 g, 76%). MS: 229 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 9,38 (ms, 1H), 8,23 (d, 1H), 7,30 (dd, 1H), 6,85 (s ancho, 1H), 1,57 (s, 9H).

Etapa 2: Una mezcla de éster terc-butílico del ácido (4-cloro-piridin-3-il)-carbámico (6,78 g, 29,7 mmol), bromuro de alilo (5,1 g, 40,8 mmol) y carbonato de cesio (20,1 g, 61,8 mmol) en DMF (200 ml) se calienta a 60° C durante 1 h. La reacción se interrumpe con agua y se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con EtOAc al 0-40% en heptano para producir éster terc-butílico del ácido alil-(4-cloro-piridin-3-il)-carbámico (5,66 g, 71%). MS: 269 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,42 (d, 1H), 7,40 (d, 1H), 5,80-5,98 (m, 1H), 4,35-4,51 (m, 1H), 3,90-4,07 (m, 1H).

Etapa 3: Una mezcla de éster terc-butílico del ácido alil-(4-cloro-piridin-3-il)-carbámico (7,68 g, 28,7 mmol), cloruro de tetrabutilamonio (9,0 g, 28,7 mmol), acetato de paladio (643

mg, 2,87 mmol) y carbonato potásico (11,9 g, 86,0 mmol) en DMF (200 ml) se calienta a 80°C durante 1,5 h. La mezcla de reacción se diluye con DCM y se lava tres veces con agua. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con EtOAc al 0-40% en heptano para producir una mezcla de éster terc-butílico del ácido 3-metil-pirrolo[2,3-c]piridina-1-carboxílico y éster terc-butílico del ácido 3-metileno-2,3-dihidro-pirrolo[2,3-c]piridina-1-carboxílico (total 3,1 g).

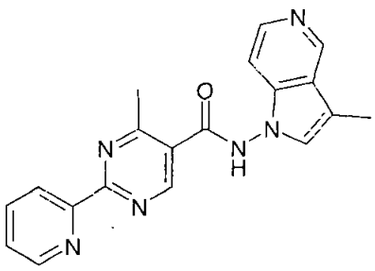
Etapa 4: La mezcla anterior se agita en DCM (10 ml) y TFA (10 ml) a ta durante 18 h y después se concentra al vacío. Se añade KOH acuoso 2 M. La mezcla se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con MeOH al 10% en DCM para producir 3-metil-1H-pirrolo[2,3-c]piridina (1.98 g, 69%). MS: 133 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 9,10 (s ancho, 1H), 8,79 (s, 1H), 8,28 (d, 1H), 7,52 (d, 1H), 7,20 (s, 1H) 2,36 (s, 2H).

Etapa 5: Una mezcla de 3-metil-1H-pirrolo[2,3-c]piridina (1,21 g, 9,16 mmol) y KOtBu (2,05 g, 18,3 mmol) en DMF (41 ml) se purga con N_2 y se agita a ta durante 2 h. Se añade cloramina en éter (0,15 M, 92 ml) y la mezcla se agita durante 20 min. La reacción se enfría a 0°C y se añade una solución de $Na_2S_2O_3$ (5 g) en agua (80 ml). La mezcla se agita durante 10 min y después se concentra al vacío. El residuo se tritura en DCM y se filtra. Se añade DCM, se enfría a 0°C y se carga con BOC_2O (541 mg, 2,48 mmol). La mezcla resultante se separa por cromatografía sobre gel de sílice eluyendo con MeOH al 10% en DCM para producir 3-metil-pirrolo[2,3-c]piridin-1-il amina (468 mg, 35%). MS: 148 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,85 (s, 1H), 8,27 (d, 1H), 7,46 (d, 1H), 7,09 (s, 1H), 2,30 (s, 3H).

Etapa 6: Una mezcla de 3-metil-pirrolo[2,3-c]piridin-1-ilamina (467 mg, 3,18 mmol), ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (683 g, 3,18 mmol), HATU (1,45 g, 3,81 mmol) y DIPEA (1,23 g 9,54 mmol) en DMF (10 ml) se agita a 150°C durante 1 h. La reacción se interrumpe con agua y se añaden $NaHCO_3$ (320 mg, 3,81 mmol) y EtOAc. El sólido resultante se recoge por filtración y después se tritura con agua caliente. La mezcla se filtra de nuevo y el sólido se seca al vacío para producir (3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (484 mg). MS: 345 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 9,24 (s, 1H), 8,79 (d, 2H), 8,65 (d, 1H), 8,21 (d, 1H), 8,05 (t, 1H), 7,72 (d, 1H), 7,60 (s, 1H), 7,57 (s, 1H), 2,88 (s, 3H), 2,40 (s, 3H).

Ejemplo 202

(3-Metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Etapa 1: A una solución de 4-amino-3-cloropiridina (15 g 116,7 mmol) en THF (60 ml) se le añade NaHMDS en THF (1 M, 233 ml, 233 mmol). Después de agitar a ta durante 30 min, se añade en una porción BOC_2O (23,2 g, 106 mmol) en THF (45 ml) y la mezcla se agita durante 3 h a ta. Se añade más cantidad de BOC_2O (2 g, 9,0 mmol) en THF (40 ml) y la reacción se agita durante 18 h a ta. Se añade HCl acuoso al 0,1% (1,35 l). La mezcla se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se recristaliza en éter para producir éster terc-butílico del ácido (3-cloro-piridin-4-il)-carbámico (4 g). Las aguas madre se purifican por cromatografía en columna sobre gel de sílice eluyendo con EtOAc al 0-50% en heptano. El producto recogido se cristaliza en éter para producir 4,5 g más de éster terc-butílico del ácido (3-cloro-piridin-4-il)-carbámico (rendimiento total 8,5 g). MS: 229 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,48 (s, 1H), 8,38 (d, 1H), 8,17 (d, 1H), 7,18 (s ancho, 1H) 1,57 (s, 9H).

Etapa 2: Una mezcla de éster terc-butílico del ácido (3-cloro-piridin-3-il)-carbámico (8,4 g, 36,8 mmol), bromuro de alilo (7,46 g, 39,1 mmol) y carbonato de cesio (24,9 g, 76,4 mmol) en DMF (100 ml) se calienta a 60° C durante 1 h. La reacción se interrumpe con agua y se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0-40% en heptano para producir éster terc-butílico del ácido alil-(3-cloro-piridin-3-il)-carbámico (8,4 g, 85%). MS: 269 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ = 8,66 (s, 1H), 8,49 (d, 1H), 7,18 (d, 1H), 5,80-5,96 (m, 1H) 5,15 (s, 1H), 5,10 (d, 1H), 4,2 (s ancho, 1H), 1,43 (s, 9H).

Etapa 3: Una mezcla de éster terc-butílico del ácido alil-(3-cloro-piridin-4-il)-carbámico (8,25 g, 30,8 mmol), cloruro de tetrabutilamonio (9,67 g, 30,8 mmol), acetato de paladio (691 mg, 3,08 mmol) y carbonato potásico (12,8 g, 92,3 mmol) en DMF (100 ml) se calienta

a 80°C durante 1,5 h. La reacción se diluye con DCM y se lava tres veces con agua. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se cromatografía a través de gel de sílice eluyendo con EtOAc al 0-40% en heptano para producir una mezcla de éster terc-butílico del ácido 3-metil-pirrolo[3,2-c]piridina-1-carboxílico y éster terc-butílico del ácido 3-metileno-2,3-dihidro-pirrolo[3,2-c]piridina-1-carboxílico (4,21 g, total).

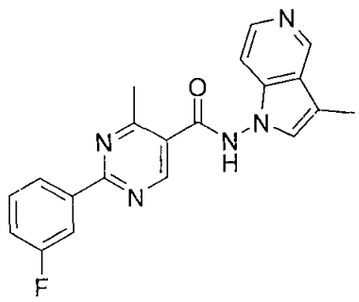
Etapa 4: La mezcla de la etapa 3 se agita en DCM (10 ml) y TFA (10 ml) a ta durante 18 h. La reacción se concentra. Se añade una solución acuosa 2 M de KOH y la mezcla se extrae con EtOAc. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo resultante se cromatografía a través de gel de sílice eluyendo con MeOH al 10% en DCM para producir 3-metil-1H-pirrolo[3,2-c]piridina (1,91 g, 47%). MS: 133 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,89 (s, 1H), 8,24 (d, 1H), 7,37 (d, 1H), 7,11 (s, 1H) 2,40 (s, 3H).

Etapa 5: Una mezcla de 3-metil-1H-pirrolo[3,2-c]piridina (1,91 g, 14,47 mmol) y KO*t*Bu (3,25 g, 28,9 mmol) en DMF (65 ml) se purga con N_2 y se agita a ta durante 2 h. Se añade cloramina en éter (0,15 M, 145 ml) y la mezcla se agita durante 20 min. La reacción se enfría a 0°C y se añade una solución de $Na_2S_2O_3$ (800 mg) en agua (130 ml). La mezcla se agita durante 10 min a 0°C y después se concentra al vacío. El residuo se tritura en DCM y se filtra. Al filtrado se le añade DCM, se enfría a 0°C y se trata con BOC_2O (793 mg, 3,6 mmol). La mezcla se concentra al vacío y el residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 10% en DCM para producir 3-metil-pirrolo[3,2-c]piridin-1-il amina (842 mg, 35%). MS: 148 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,85 (s, 1H), 8,36 (d, 1H), 7,32 (d, 1H), 6,95 (s, 1H) 4,77 (s, 2H), 2,37 (s, 3H).

Etapa 6: Una mezcla de 3-metil-pirrolo[3,2-c]piridin-1-ilamina (223 mg, 1,52 mmol), ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (329 mg, 1,52 mmol), HATU (693 mg, 1,82 mmol) y DIPEA (593 mg, 4,59 mmol) en DMF (8 ml) se agita a 150°C durante 1 h. La reacción se interrumpe con agua y $NaHCO_3$ (168 mg, 2 mmol). La mezcla se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 10% en DCM para producir (3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (91 mg, 17%). MS: 345 (M+H); ^{1}H RMN (300 MHz, DMSO-d6): δ = 9,34 (s, 2H), 8,79 (d, 1H), 8,53 (d, 1H), 8,45 (d, 1H), 8,13 (d, 1H), 8,02 (t, 1H), 7,86 (s, 1H), 7,59 (t, 1H), 2,77 (s, 3H), 2,43 (s, 3H).

Ejemplo 203

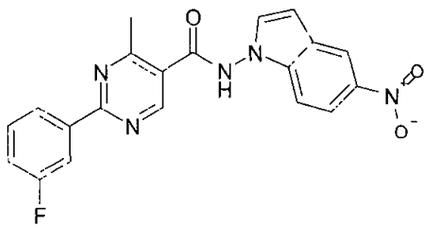
(3-Metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Una mezcla de 3-metil-pirrolo[3,2-c]piridin-1-ilamina (224 mg, 1,52 mmol), ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (354 mg, 1,52 mmol), HATU (693 mg, 1,82 mmol) y DIPEA (593 mg, 4,59 mmol) en DMF (8 ml) se calienta a 150°C durante 1 h. La reacción se interrumpe con agua, se añade $NaHCO_3$ (168 mg, 2 mmol) y la mezcla se extrae con EtOAc. La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra. El residuo se purifica primero por cromatografía en columna sobre gel de sílice eluyendo con MeOH al 10% en DCM y después se recristaliza en EtOAc para producir (3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (198 mg). MS: 362 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 9,12 (s, 1H), 8,86 (s, 1H), 8,35 (d, 1H), 8,15-8,31 (m, 2H), 7,47-7,60 (m, 2H), 7,35 (s, 1H), 7,29 (t, 1H), 2,84 (s, 3H), 2,44 (s, 3H).

Ejemplo 204

(5-Nitro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



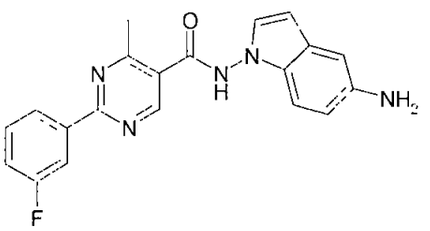
Etapa 1: Se añade en porciones NaH (al 60%, 421,5 mmol) a una solución de 5-nitro-1H-indol (28,1 mmol) en DMF anhidra (80 ml) a 0°C y la mezcla se agita a 0°C en una atmósfera de N_2 durante 10 min. Se añade en porciones HOSA (140,5 mmol) durante 30 minutos y la mezcla se agita a 0°C durante 2 h. La reacción se interrumpe con agua. Se añade más cantidad de agua (250 ml) y la mezcla se extrae con EtOAc (3 x 100 ml). La capa orgánica combinada se lava con agua (2 x 30 ml) y salmuera (30 ml), se seca (Na_2SO_4), se filtra y se concentra. El residuo se lava con heptano (2 x 20 ml) y se recristaliza en EtOAc

para producir 5-nitro-indolo-1-ilamina (4,84 g, 97%) en forma de un sólido. MS: 178 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,93(a, 2N-H), 6,62 (d, H), 7,30 (d, H), 7,52 (d, H), 8,17 (d, H), 8,58 (s, H).

Etapa 2: Se añade DIPEA (12,65 mmol) a una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (4,22 mmol), 5-nitro-indolo-1-ilamina (4,22 mmol) y HOTT (hexafluorofosfato de S-(1-oxido-2-piridil)-tio-N,N,N',N'-tetrametiluronio) (7,6 mmol) en DMF anhidra (15 ml) y la mezcla se calienta a 80-90ºC durante una noche. Después de la evaporación del disolvente, el residuo se disuelve en EtOAc (150 ml) y se lava con agua (20 ml), sulfato sódico al 5% (20 ml), agua (ml) y salmuera (20 ml). La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se mantiene a ta durante una noche para producir (5-nitro-indol-1-il)-amida del ácido 4-metil-2-(3-fluoro-fenil)-pirimidina-5-carboxílico (730 mg, 44%) en forma de un sólido. MS: 392 (M+H); ^{1}H RMN (300 MHz, DMSO-d6): δ 2,78 (s, 3H), 6,88(d, H), 7,38-7,53 (m, H), 7,57-7,76 (m, 2H), 7,81 (d, H), 8,06-8,32 (m, 2H), 8,34 (d, H), 8,65 (d, H), 9,27 (s, 2H).

Ejemplo 205

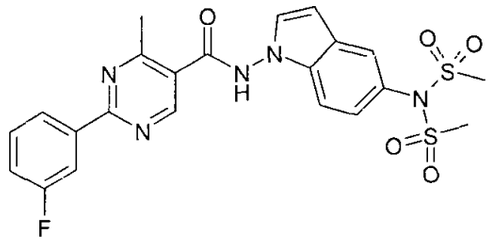
(5-Amino-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Una solución de (5-nitro-indol-1-il)-amida del ácido 4-metil-2-(3-fluoro-fenil)-pirimidina-5-carboxílico (1,64 mmol) en MeOH (45 ml) y Pd al 10%/C (0,16 mmol) se hidrogena en un recipiente Parr de 500 ml a 344,74 kPa (50 psi) a ta durante una noche. El Pd/C se retira por filtración. El filtrado se concentra para producir (5-amino-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (545 mg, 92%) en forma de un sólido. MS: 362 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 3,84 (s, H), 6,37 (d, H), 6,81 (dd, H), 7,01 (d, H), 7,16-7,36 (m, 3H), 7,55 (m, H), 8,23 (d, H), 8,36 (d, H), 9,50 (s, H).

Ejemplo 206

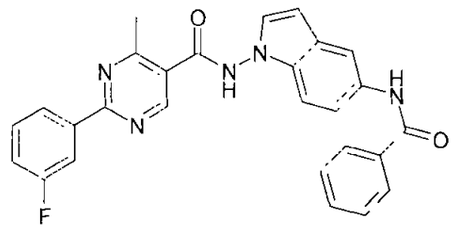
[5-(Dimetanosulfonil)-amino-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Una mezcla de (5-amino-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (0,43 mmol) y cloruro de metanosulfonilo (0,52 mmol) en DCM anhidro (10 ml) se agita a 0ºC y se añade trietilamina (1,29 mmol). La mezcla de reacción se agita a 0ºC durante 1 h y después se calienta a ta y se agita durante 30 minutos. Se añade DCM (20 ml) y la mezcla se lava con HCl al 4% (15 ml), agua (10 ml) y salmuera (15 ml). La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se purifica por cromatografía usando gel de sílice eluyendo con EtOAc al 0-60% en DCM para producir [5-(dimetanosulfonil)-amino-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (85 mg, 38%) en forma de un sólido. MS: 518 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,75 (s, 3H), 2,90 (s, 3H), 3,66 (s, 3H), 6,51 (s, H), 7,04-7,53 (m, 6H), 8,03 (d, H), 8,12 (d, H), 8,60 (s, H).

Ejemplo 207

(5-Benzoilamino-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

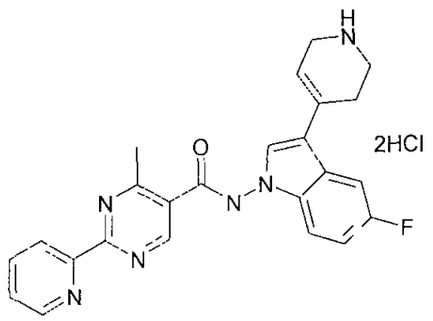


Una solución de cloruro de benzoílo (0,85 mmol) en DCM anhidro (2 ml) se añade gota a gota a una solución de (5-amino-indol-1-il)-amida del ácido 4-metil-2-(3-fluoro-fenil)-pirimidina-5-carboxílico (0,47 mmol) y trietilamina (1,41 mmol) en DCM anhidro (16 ml) y la mezcla se agita a ta durante una noche. La mezcla de reacción se concentra al vacío. El residuo se disuelve en EtOAc (25 ml) y se lava con agua (2 x 20 ml) y salmuera (10 ml). La capa orgánica se seca ($MgSO_4$), se filtra y se concentra. El residuo se tritura con EtOAc para producir (5-benzoilamino-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (95 mg, 43%) en forma de un sólido. MS: 466 (M+H); ^{1}H RMN (300 MHz,

DMSO-d6): δ 2,99 (s, 3H), 6,72 (d, H), 7,38-7,48 (m, H), 7,48-7,80 (m, 6H), 7,83-8,016 (m, 3H), 8,07-8,20 (m, H), 8,23-8,35 (m, 2H), 9,24 (s, H), 10,25 (a, H).

Ejemplo 208

Dihidrocloruro de [5-fluoro-3-(1,2,3,6-tetrahidro-piridin-4-il)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Etapa 1: Una mezcla de 5-fluoroindol (6,65 g, 49,2 mmol) e hidrocloruro de 4-piperidona hidrato (18,9 g, 123 mmol) en una solución en metanol de KOH 2 N (90 ml) se calienta a reflujo durante 6 h. Después de enfriar a ta, se añade agua (150 ml) y la mezcla se agita a ta durante 30 minutos. El precipitado resultante se filtra, se lava con agua (10 ml) y éter (15 ml) y se seca al vacío para producir 5-fluoro-3-(1,2,3,6-tetrahidropiridin-4-il)-indol (6,34 g, 60%). MS: 217 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,40 (a, H), 7,57 (dd, H), 7,24-7,37 (m, H), 7,23 (s, H), 6,98 (t, H), 6,20 (s, H), 3,62 (m, 2H), 3,16 (m, 2H), 2,50 (s, 2H).

Etapa 2: Una solución de dicarbonato de di-terc-butilo (504 mg, 2,31 mmol) en DCM (10 ml) se añade a una solución agitada de 5-fluoro-3-(1,2,3,6-tetrahidropiridin-4-il)-indol (500 mg, 2,31 mmol) en DCM (20 ml) a ta y la mezcla se agita a ta durante una noche. La mezcla de reacción se concentra al vacío para producir éster terc-butílico del ácido 4-(5-fluoro-1H-indol-3-il)-3,6-dihidro-2H-piridina-1-carboxílico (730 mg). MS: 317 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,17 (a, H), 7,56 (d, H), 7,31 (m, H), 7,26 (s, H), 6,99 (t, H), 6,13 (s, H), 4,17 (m, 2H), 3,70 (m, 2H), 2,57 (s, 2H), 1,54 (s, 9H).

Etapa 3: Una solución de éster terc-butílico del ácido 4-(5-fluoro-1H-indol-3-il)-3,6-dihidro-2H-piridina-1-carboxílico (730 mg, 2,31 mmol) en DMF anhidra se añade lentamente a una solución agitada de NaH al 60% (1108 mg, 27,72 mmol) en DMF anhidra (20 ml) a 0°C en una atmósfera de N_2 y se agita a ta durante una hora. Se añade en porciones HOSA (1305 mg, 11,55 mmol) a 0°C, se agita a 0°C durante 5 horas, se vierte en hielo/agua (350 ml) y se extrae con éter (3 x 35 ml). El extracto orgánico combinado se separa, se lava con agua (2 x

20 ml) y salmuera (20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se lava con heptano (3 x 5 ml) para producir éster terc-butílico del ácido 4-(1-amino-5-fluoro-1H-indol-3-il)-3,6-dihidro-2H-piridina-1-carboxílico (715 mg, 94%) en forma de un sólido. MS: 332 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,52 (d, H), 7,36 (m, H), 7,20 (s, H), 7,04 (t, H), 6,06 (s, H), 4,78 (s, 2H), 4,15 (m, 2H), 3,69 (t, 2H), 2,54 (s, 2H), 1,55 (s, 9H).

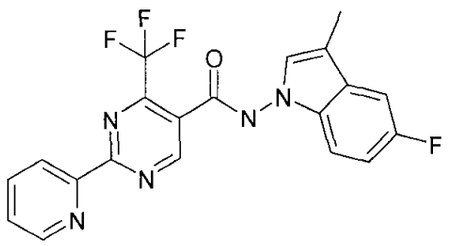
Etapa 4: Se añade trietilamina (2,6 mmol) a una solución agitada de ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (1,30 mmol) y cloroformiato de iso-butilo (1,95 mmol) en DCM anhidro (20 ml) a ta en una atmósfera de N_2 y se agita a ta durante 2 h. La mezcla de reacción se concentra al vacío. El residuo se seca al vacío y se añade THF (30 ml). La mezcla se filtra y el filtrado se concentra para producir [1-(4-metil-2-piridin-2-il-pirimidin-5-il)]-carbonato de iso-butilo (350 mg, 85%).

Etapa 5: Se añade bis(trimetilsilil)amida sódica (2 N) en THF (0,83 ml) a una solución agitada de éster terc-butílico del ácido 4-(1-amino-5-fluoro-1H-indol-3-il)-3,6-dihidro-2H-piridina-1-carboxílico (367 mg,1,11 mmol) en DMF anhidra (20 ml) a ta en una atmósfera de N_2 y después la mezcla se agita a ta durante 15 min. Se añade lentamente una solución de [1-(4-metil-2-piridin-2-il-pirimidin-5-il]]-carbonato de iso-butilo (350 mg, 1,11 mmol) en DMF anhidra (5 ml) a ta y la mezcla se agita a 60°C durante 18 horas en una atmósfera de N_2. La DMF se retira por evaporación. El residuo se disuelve en EtOAc (60 ml), se lava con agua (3 x 20 ml) y salmuera (20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 0-20% en DCM para producir éster terc-butílico del ácido 4-{5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indol-3-il}-3,6-dihidro-2H-piridina-1-carboxílico (158 mg, 28%).

Etapa 6: Una solución de éster terc-butílico del ácido 4-{5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indol-3-il}-3,6-dihidro-2H-piridina-1-carboxílico (158 mg) en DCM (15 ml) se burbujea con gas HCl durante 10 min a ta y después se agita a ta durante 18 h. El DCM se retira por evaporación y el residuo se tritura con MeOH (2 ml). El sólido se recoge por filtración y se seca para producir dihidrocloruro de [5-fluoro-3-(1,2,3,6-tetrahidro-piridin-4-il)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (81 mg, 54%). MS: 429 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ =2,89 (m, 2H), 2,96 (s, 3H), 3,53 (t, 2H), 3,94 (m, H), 6,27 (s, H), 7,12(t, H), 7,46 (c, H), 7,59-7,71 (m, H), 8,28 (t, H), 8,85 (t, H), 8,99 (d, H), 9,15 (d, H), 9,41 (s, H).

Ejemplo 209

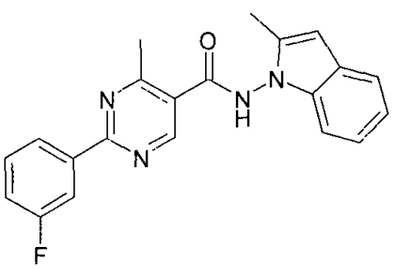
(5-Fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-2-il-4-trifluorometil-pirimidina-5-carboxílico



Una solución de ácido 2-piridin-2-il-4-trifluorometil-pirimidina-5-carboxílico (219 mg, 0,81 mmol), 5-fluoro-3-metil-indol-1-ilamina (0,98 mmol), DIPEA (158 mg, 1,23 mmol) y HATU (1,06 mmol) en DMF anhidra (8 ml) se agita a 80°C durante una noche. La mezcla de reacción se diluye con EtOAc (40 ml) y se lava con agua (4 x 20 ml) y salmuera (20 ml). La capa orgánica se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 1%-50% en DCM. El producto recogido se recristaliza en DCM para producir (5-fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-2-il-4-trifluorometil-pirimidina-5-carboxílico (105 mg, 31%) en forma de un sólido. MS: 416 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ = 2,32 (s, 3H), 7,04 (t, H), 7,16 (s, H), 7,25 (dd, H), 7,34 (c, H), 7,67 (dd, H), 8,11 (t, H), 8,70 (d, H), 8,82 (d, H), 9,57 (s, H). CI_{50} = 8 nM.

Ejemplo 210

(2-Metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico

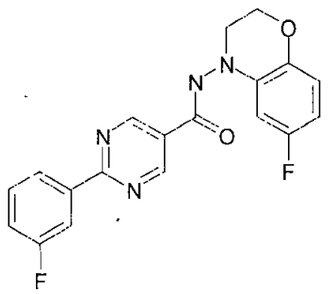


Una mezcla de (2-metil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (246 mg, 0,68 mmol) y MnO_2 (296 mg, 3,4 mmol) en DCM (10 ml) se agita a ta durante 1,5 h. La mezcla de reacción se filtra y el filtrado se concentra al vacío. El residuo se tritura con éter para producir (2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (158, 65%). MS: 361 (M+H); ^{1}H RMN (300 MHz,

$CDCl_3$): δ 2,39 (s, 3H), 2,83 (s, 3H), 6,36 (s, H), 7,10-7,29 (m, 3H), 7,44-7,62 (m, H), 8,17 (s, H), 8,25 (d, H), 8,35 (d, H), 8,97 (s, H).

Ejemplo 211

(6-Fluoro-2,3-dihidro-1,4-benzoxazin-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico



Etapa 1: Se añade $LiAlH_4$ (14,7 mmol, solución 1 M en THF) a una solución de 6-fluoro-4H-benzo[1,4]oxazin-3-ona (1,23 g, 7,35 mmol) en THF a ta y la mezcla se calienta a reflujo durante 2 h. La mezcla de reacción se inactiva con unas gotas de agua seguido de la lenta adición de acetato de etilo (10 ml). El sólido se retira por filtración y se lava con EtOAc. El filtrado se concentra al vacío para producir 6-fluoro-3,4-dihidro-2H-benzo[1,4]oxazina (1 g). MS: 154 (M+H).

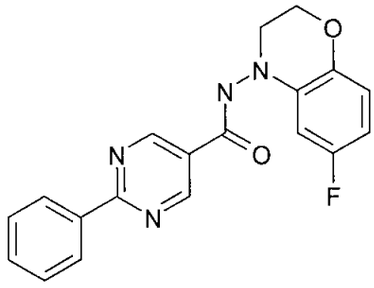
Etapa 2: Se añade nitrito de isoamilo a una solución de 6-fluoro-3,4-dihidro-2H-benzo[1,4]oxazina (1 g) en DCM (15 ml) y la mezcla se calienta a reflujo durante una noche. La mezcla de reacción se concentra al vacío y el residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10% en heptano para dar 6-fluoro-4-nitroso-3,4-dihidro-2H-benzo[1,4]oxazina (0,83 g).

Etapa 3: Se añade $LiAlH_4$ en THF (1 M, 6,58 ml) a una solución de 6-fluoro-4-nitroso-3,4-dihidro-2H-benzo[1,4]oxazina (0,8 g) en THF (10 ml) a 0°C y después la mezcla se agita a ta durante una noche. La mezcla de reacción se inactiva con unas gotas de agua seguido de la adición de EtOAc (10 ml). El sólido se retira por filtración y se lava con EtOAc (15 ml). El filtrado se concentra al vacío y el residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con EtOAc al 15% en heptano para producir 6-fluoro-2,3-dihidro-benzo[1,4]oxazin-4-ilamina (0,44 mg).

Etapa 4: Se añade DIPEA (174 µl) a una mezcla de ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (218 mg), HATU (380 mg) y 6-fluoro-2,3-dihidro-benzo[1,4]oxazin-4-ilamina (220 mg) en DMF (15 ml) y después la mezcla se calienta a 80°C durante una noche. La mezcla de reacción se concentra al vacío y el residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con EtOAc al 30% en heptano para producir (6-fluoro-2,3-dihidro-1,4-benzoxazin-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico (81 mg). MS: 369 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,05 (s, 1H), 9,35 (s, 2H), 8,32 (dd, 1H), 8,18 (dd, 1H), 7,65 (m, 1H), 7,5 (m, 1H), 6,8-6,7 (m, 2H), 6,52-6,45 (m, 1H), 4,36 - 4,33 (m, 2H), 3,65 (m, 2H). CI_{50} = 12 nM.

Ejemplo 212

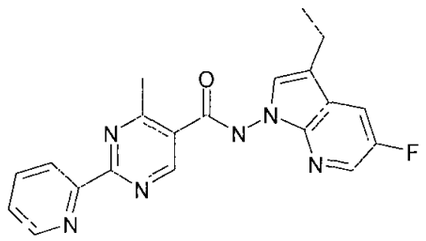
(6-Fluoro-2,3-dihidro-1,4-benzoxazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los de la etapa 4 del Ejemplo 211, pero sustituyendo ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico por ácido 2-fenil-pirimidina-5-carboxílico, se prepara (6-fluoro-2,3-dihidro-1,4-benzoxazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico en forma de un sólido. MS: 351 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,03 (s, 1H), 9,33 (s, 2H), 8,49-8,46 (m, 2H), 7,61-7,55 (m, 3H), 6,8-6,7 (m, 2H), 6,52-6,45 (m, 1H), 4,36 - 4,33 (m, 2H), 3,65-3,25 (m, 2H). CI_{50} = 21 nM.

Ejemplo 213

(3-Etil-5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Etapa 1: Una solución de 5-fluoro-3-yodo-piridin-2-ilamina (3 g, 12,6 mmol) en DCM (40 ml) se trata con TFAA (2,1 ml, 15,1 mmol) y piridina (1,2 ml, 15,1 mmol) y la mezcla se agita a ta durante 2 h. La mezcla se diluye con H_2O (150 ml) y se extrae con DCM (3 x 150 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se diluye con MeCN (40 ml), se trata con bromuro de *trans*-crotilo (2 ml, 18,9 mmol) y K_2CO_3 (3,5 g, 25,2 mmol) y se calienta a reflujo durante 2 h. La mezcla se enfría, se filtra a través de una capa de Celite y se concentra. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 5% - 30% en heptano para producir N-but-2-enil-2,2,2-trifluoro-*N*-(5-fluoro-3-yodo-piridin-2-il)-acetamida (2,5 g, 51%). MS: 389 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,36 (m, 1H), 7,98 (s, 1H), 5,55 (m, 2H), 4,62 (m, 1H), 3,96 (m, 1H), 1,61 (m, 3H).

Etapa 2: Una solución de *N*-but-2-enil-2,2,2-trifluoro-*N*-(5-fluoro-3-yodo-piridin-2-il)-acetamida (2,57 g, 6,5 mmol) en DMF (10 ml) se trata con *n*-Bu_4NCl (2 g, 7,15 mmol) y $Pd(OAc)_2$ (59 mg, 0,26 mmol) y se agita a 100°C durante 2 h. La mezcla se enfría a ta, se diluye con EtOAc (50 ml), se filtra a través de una capa de gel de sílice y se lava con HCl 1 M (50 ml). La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 25% - 70% en heptano para producir 3-etil-5-fluoro-1H-pirrolo[2,3-b]piridina (0,75 g, 70%). MS: 165 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 9,62 (s, NH, 1H), 8,17 (m, 1H), 7,60 (m, 1H), 7,16 (s, 1H), 2,74 (c, 2H), 1,31 (t, 3H).

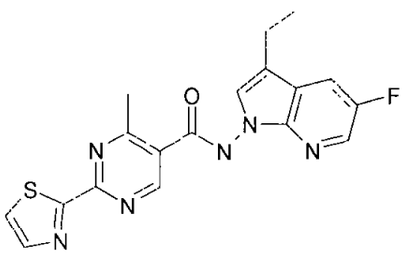
Etapa 3: Una suspensión de NaH (2,7 g, 68 mmol, al 60% en aceite mineral) en DMF (20 ml) a 0°C se trata con 3-etil-5-fluoro-1H-pirrolo[2,3-b]piridina (745 mg, 4,5 mmol) y se agita a 0°C durante 1 h. La mezcla se trata en porciones con HOSA (2,5 g, 22,5 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo, se filtra a través de una capa de Celite y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 30% - 50% en heptano para producir 3-etil-5-fluoropirrolo[2,3-b]piridin-1-ilamina (685 mg, 84%). MS: 180 (M+H); ^{1}H RMN (300 MHz,

$CDCl_3$): δ 8,16 (s, 1H), 7,56 (m, 1H), 7,14 (s, 1H), 4,93 (s, NH_2, 2H), 2,697 (c, 2H), 1,28 (t, 3H).

Etapa 4: Una solución de ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (490 mg, 2,28 mmol) y 3-etil-5-fluoropirrolo[2,3-b]piridin-1-ilamina (340 mg, 1,9 mmol) en DMF (6 ml) se agita a 40ºC durante 1 h. La mezcla se trata con DMTMM (524 mg, 1,9 mmol) y se agita a 40ºC durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 5 min. El precipitado se recoge por filtración y se seca al vacío para producir (3-etil-5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-pirjdin-2-il-pirimidina-5-carboxílico (427 mg, 60%). MS: 377 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,94 (s, NH, 1H), 9,14 (s, 1H), 8,81 (d, 1H), 8,47 (d, 1H), 8,30 (s, 1H), 8,03 (m, 2H), 7,61 (m, 2H), 2,81 (s, 3H), 2,75 (c, 2H), 1,29 (t, 3H).

Ejemplo 214

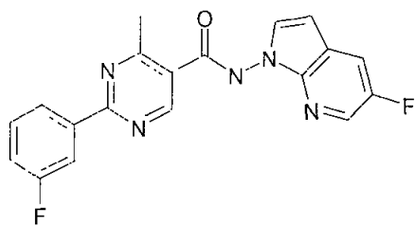
(3-Etil-5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico



Una solución de ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (509 mg, 2,28 mmol) y 3-etil-5-fluoropirrolo[2,3-b]piridin-1-ilamina (340 mg, 1,9 mmol) en DMF (6 ml) se agita a 40ºC durante 1 h. La mezcla se trata con DMTMM (524 mg, 1,9 mmol) y se agita a 40ºC durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 5 min. El precipitado se recoge por filtración y se seca al vacío para producir (3-etil-5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (481 mg, 66%). MS: 383 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,95 (s, NH, 1H), 9,10 (s, 1H), 8,29 (s, 1H), 8,14 (d, 1H), 8,08 (d, 1H), 8,00 (m, 1H), 7,57 (s, 1H), 2,79 (s, 3H), 2,75 (c, 2H), 1,29 (t, 3H).

Ejemplo 215

(5-Fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Etapa 1: Una solución de 5-fluoro-3-yodo-piridin-2-ilamina (4 g, 16,8 mmol) en THF (50 ml) y trimetilsililacetileno (4,7 ml, 33,6 mmol) se trata con $PdCl_2(PPh_3)_4$ (353 mg, 0,5 mmol), CuI (96 mg, 0,5 mmol) y trietilamina (7 ml, 50,4 mmol) y la mezcla se agita a ta durante 2 h. La mezcla se filtra a través de Celite y se concentra. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10% - 35% en heptano para producir 5-fluoro-3-trimetilsilaniletinil-piridin-2-ilamina (3,3 g, 94%). MS: 209 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,90 (d, 1H), 7,30 (m, 1H), 4,89 (s, NH_2, 2H), 0,25 (s, 9H).

Etapa 2: Una solución de 5-fluoro-3-trimetilsilaniletinil-piridin-2-ilamina (3,2 g, 15,4 mmol) en MeOH (77 ml) y K_2CO_3 (1,1 g, 7,7 mmol) se agita a ta durante 0,5 h. La mezcla se filtra a través de Celite y se concentra. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 15% - 55% en heptano para producir 3-etinil-5-fluoro-piridin-2-ilamina (1,55 g, 74%). MS: 137 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,94 (d, 1H), 7,35 (m, 1H), 4,91 (s, NH_2, 2H), 3,44 (s, 1H).

Etapa 3: Una solución de 3-etinil-5-fluoro-piridin-2-ilamina (1,25 g, 9,2 mmol) en DMF (20 ml) se trata con $(Rh(cod)_2Cl)_2$ (23 mg, 0,023 mmol) y tris-(4-fluoro-fenil)-fosfano (115 mg, 0,368 mmol) y se agita a 85°C durante 0,5 h. Después, la mezcla se vierte sobre salmuera (50 ml) y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 35% - 75% en heptano para producir 5-fluoro-1H-pirrolo[2,3-b]piridina (1,05 g, 84%). MS: 137 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 9,15 (s, NH, 1H), 7,99 (s, 1H), 7,44 (d, 1H), 7,18 (s, 1H), 6,28 (s, 1H).

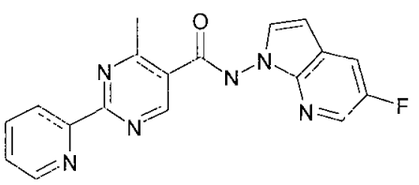
Etapa 4: Una suspensión de NaH (4,4 g, 110 mmol, al 60% en aceite mineral) en DMF (37 ml) a 0°C se trata con 3-etil-5-fluoro-1H-pirrolo[2,3-b]piridina (1,0 g, 7,4 mmol) y se agita a 0°C durante 1 h. La mezcla se trata en porciones con HOSA (4,2 g, 37 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo, se filtra a través de una capa de Celite y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice

eluyendo con EtOAc al 30% - 70% en heptano para producir 5-fluoro-pirrolo[2,3-b]piridin-1-ilamina (980 mg, 88%). MS: 152 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 8,20 (s, 1H), 7,60 (m, 1H), 7,42 (m, 1H), 6,36 (s, 1H), 5,01 (s, NH_2, 2H).

Etapa 5: Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (529 mg, 2,28 mmol) y 5-fluoro-pirrolo[2,3-b]piridin-1-ilamina (288 mg, 1,9 mmol) en DMF (6 ml) se agita a 40°C durante 1 h. La mezcla se trata con DMTMM (524 mg, 1,9 mmol) y se agita a 40°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 5 min. El precipitado se recoge por filtración y se seca al vacío para producir (5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (475 mg, 68%). MS: 366 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,12 (s, 1H), 8,30 (m, 2H), 8,18 (d, 1H), 7,97 (d, 1H), 7,82 (d, 1H), 7,59 (m, 1H), 7,44 (m, 1H), 6,59 (d, 1H), 2,80 (s, 3H).

Ejemplo 216

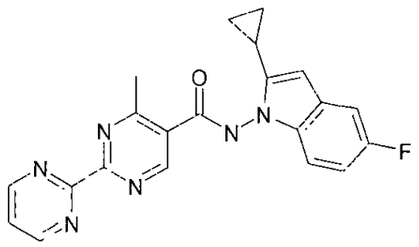
(5-Fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Una solución de ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (440 mg, 2,28 mmol) y 5-fluoro-pirrolo[2,3-b]pirjdin-1-ilamina (288 mg, 1,9 mmol) en DMF (6 ml) se agita a 40°C durante 1 h. La mezcla se trata con DMTMM (524 mg, 1,9 mmol) y se agita a 40°C durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 5 min. El precipitado se recoge por filtración y se seca al vacío para producir (5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (343 mg, 52%). MS: 349 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,17 (s, 1H), 8,81 (d, 1H), 8,53 (d, 1H), 8,27 (s, 1H), 8,01 (m, 1H), 7,90 (m, 1H), 7,77 (d, 1H), 7,57 (m, 1H), 6,60 (d, 1H), 2,84 (s, 3H).

Ejemplo 217

(2-Ciclopropil-5-fluoro-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico



Etapa 1: Una solución de 4-fluoro-2-yodoanilina (2 g, 8,4 mmol) en THF (15 ml) y ciclopropilacetileno (1,4 ml, 16,9 mmol) se trata con $PdCl_2(PPh_3)_4$ (177 mg, 0,25 mmol), CuI (48 mg, 0,25 mmol) y trietilamina (3,5 ml, 25,2 mmol) y se agita a ta durante 2 h. La mezcla se filtra a través de Celite y se concentra. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0% - 35% en heptano para producir 2-ciclopropiletinil-4-fluoro-fenilamina (1,1 g, 74%). MS: 176 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 6,93 (m, 1H), 6,81 (m, 1H), 6,59 (m, 1H), 4,00 (s, NH_2, 2H), 1,49 (m, 1H), 0,82 (m, 4H).

Etapa 2: Una solución de 2-ciclopropiletinil-4-fluoro-fenilamina (0,80 g, 4,5 mmol) en PhMe (16 ml) se trata con $InBr_3$ (80 mg, 0,23 mmol) y se agita a 110ºC durante 0,5 h. Después, la mezcla se vierte sobre salmuera (20 ml) y se extrae con EtOAc (3 x 20 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 0% - 25% en heptano para producir 2-ciclopropil-5-fluoro-1H-indol (610 mg, 78%). MS: 176 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,88 (s, NH, 1H), 7,12 (m, 2H), 6,83 (m, 1H), 6,09 (s, 1H), 1,90 (m, 1H), 0,95 (m, 2H), 0,77 (m, 2H).

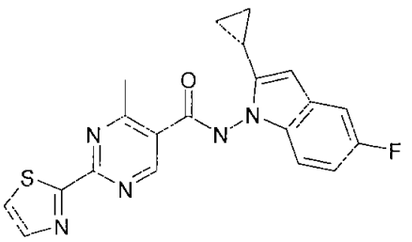
Etapa 3: Una suspensión de NaH (1,9 g, 47 mmol, al 60% en aceite mineral) en DMF (20 ml) a 0ºC se trata con 2-ciclopropil-5-fluoro-1H-indol (550 mg, 3,14 mmol) y se agita a 0ºC durante 1 h. La mezcla se trata en porciones con HOSA (1,8 g, 15,7 mmol) y se calienta a ta durante 2 h. Después, la mezcla se vierte sobre hielo, se filtra a través de una capa de Celite y se extrae con EtOAc (3 x 50 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 5% - 35% en heptano para producir 2-ciclopropil-5-fluoro-indol-1-ilamina (420 mg, 70%). MS: 191 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,30 (m, 1H), 7,11 (m, 1H), 6,92 (m, 1H), 5,90 (s, 1H), 4,57 (s, NH_2, 2H), 2,07 (m, 1H), 1,02 (m, 2H), 0,75 (m, 2H).

Etapa 4: Una solución de ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (184 mg, 0,85 mmol) y 2-ciclopropil-5-fluoro-indol-1-ilamina (135 mg, 0,71 mmol) en DMF (3 ml) se

agita a 40ºC durante 1 h. La mezcla se trata con DMTMM (235 mg, 0,71 mmol) y se agita a 40ºC durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 5 min. El precipitado se recoge por filtración y se seca al vacío para producir (2-ciclopropil-5-fluoro-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (35 mg, 13%). MS: 389 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 11,93 (s, NH, 1H), 9,31 (s, 1H), 9,06 (d, 2H), 7,70 (m, 1H), 7,42 (m, 1H), 7,26 (m, 1H), 6,97 (m, 1H), 6,16 (s, 1H), 2,79 (s, 3H), 1,97 (m, 1H), 1,01 (m, 2H), 0,74 (m, 2H).

Ejemplo 218

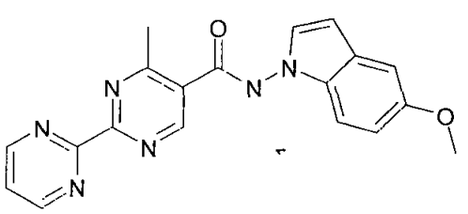
(2-ciclopropil-5-fluoro-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico



Una solución de ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (188 mg, 0,85 mmol) y 2-ciclopropil-5-fluoro-indol-1-ilamina (135 mg, 0,71 mmol) en DMF (3 ml) se agita a 40ºC durante 1 h. La mezcla se trata con DMTMM (235 mg, 0,71 mmol) y se agita a 40ºC durante 1 h. La mezcla se diluye con Na_2CO_3 acuoso saturado (5 ml) y se agita durante 5 min. El precipitado se recoge por filtración y se seca al vacío para producir (2-ciclopropil-5-fluoro-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico (60 mg). MS: 394 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 9,26 (s, 1H), 8,15 (d, 1H), 8,08 (d, 1H), 7,43 (m, 1H), 7,24 (m, 1H), 6,97 (m, 1H), 6,18 (s, 1H), 2,77 (s, 3H), 1,95 (m, 1H), 1,01 (m, 2H), 0,73 (m, 2H).

Ejemplo 219

(5-Metoxil-indol-1-il)-amida del ácido 2-pirimidin-2-il-4-metil-pirimidina-5-carboxílico

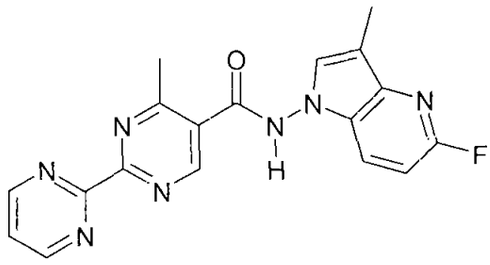


Una solución de ácido 2-pirimidin-2-il-4-metil-pirimidina-5-carboxílico (496 mg, 2,30 mmol) y 5-metoxi-indol-1-ilamina (0,98 mmol) en DMF anhidra (10 ml) se agita a 50ºC

durante 30 min. Se añade DMTMM (555 mg, 2,01 mmol) y la mezcla se agita a 50ºC durante una hora. La DMF se retira por evaporación. El residuo se mezcla con agua (40 ml) y se agita a ta durante 20 minutos. El sólido se recoge por filtración, se lava con agua (3 x 5 ml) y se seca al vacío para producir (5-metoxil-indol-1-il)-amida del ácido 2-pirimidin-2-il-4-metil-pirimidina-5-carboxílico (410 mg) en forma de un sólido. MS: 361 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,93 (s, 3H), 4,84 (s, 3H), 7,04 (t, H), 6,50 (d, H), 6,92 (d, H), 7,14 (s, H), 7,26-7,37 (m, 2H), 7,72 (t, H), 9,09 (d, 2H), 9,27 (s, H).

Ejemplo 220

(5-Fluoro-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico



Etapa 1: Se añade bromo (1,96 g, 12,2 mmol) a una mezcla de 2-fluoro-5-aminopiridina (1,37 g, 12,2 mmol) y acetato sódico (2 mg, 24,4 mmol) en ácido acético (30 ml) y la mezcla se agita a ta durante 4 horas. El ácido acético se retira por evaporación al vacío. El residuo se disuelve en EtOAc (50 ml), se lava con Na_2CO_3 acuoso saturado (10 ml), agua (20 ml) y salmuera (10 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío para producir 2-bromo-3-amino-6-fluoropiridina (2,1 g) en forma de un sólido. MS: 190 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,04 (a, 2H), 6,77 (dd, H), 7,17 (dd, H).

Etapa 2: Se añade gota a gota TFAA (8,31 g, 39,57 mmol) a una solución agitada de 2-bromo-3-amino-6-fluoropiridina (6,30 g, 33,0 mmol) y piridina (3,91 g, 49,46 mmol) en DCM (80 ml) a ta y la mezcla se agita a ta durante una hora. Se añade agua (40 ml). La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío para producir N-(2-bromo-6-fluoropiridin-3-il)-2,2,2-trifluoro-acetamida (9,37 g, >99%) en forma de un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,06 (m, H), 8,40 (a, N-H), 9,75 (dd, H).

Etapa 3: Una solución de N-(2-bromo-6-fluoropiridin-3-il)-2,2,2-trifluoro-acetamida (9,16 g, 31,9 mmol), bromuro de alilo (6,18 g, 47,9 mmol) y carbonato sódico (8,82 g, 63,8 mmol) en CH_3CN (80 ml) se agita a 80ºC durante 2 h. La mezcla de reacción se concentra al vacío y el

residuo se purifica por cromatografía sobre gel de sílice eluyendo con DCM al 0-60% en heptano para producir N-alil-N-(2-bromo-6-fluoro-piridin-3-il)-2,2,2-trifluoro-acetamida (9,05 g) en forma de un aceite. ^{1}H RMN (300 MHz, $CDCl_3$) δ 3,68 (c, H), 5,01 (c, H), 5,17 (d, H), 5,29 (d, H), 6,85 (m, H), 7,00 (dd, H), 7,64 (t, H).

Etapa 4: Una solución de N-alil-N-(2-bromo-6-fluoro-piridin-3-il)-2,2,2-trifluoro-acetamida (3,41 g, 10,43 mmol), acetato de paladio (94 mg, 0,42 mmol), cloruro de tetra(n-butilamonio) (3,19 g, 11,47 mmol) y trietilamina (2,37 g, 23,4 mmol) en DMF anhidra (20 ml) se agita a 100°C en una atmósfera de N_2 durante una hora. La DMF se retira por evaporación y el residuo se mezcla con agua (12 ml) y se agita a ta durante una hora. Se añade EtOAc (15 ml) y se agita a ta durante una noche. La capa orgánica se separa y la capa acuosa se extrae con EtOAc (35 ml). La capa orgánica combinada se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con EtOAc al 10-60% en heptano para producir 5-fluoro-3-metil-1H-pirrolo[3,2-b]piridina (1,5 g) en forma de un sólido. MS: 151 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 2,38 (s, 3H), 6,77 (d, H), 7,28 (s, H), 7,74 (dd, H).

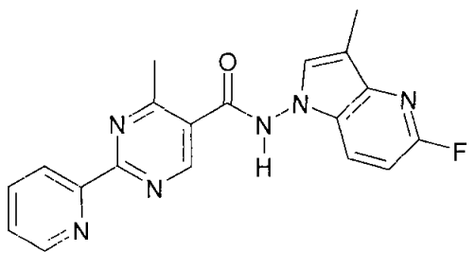
Etapa 5: Una solución de 5-fluoro-3-metil-1H-pirrolo[3,2-b]piridina (10,7 mmol) en DMF anhidra (15 ml) se añade gota a gota a una solución agitada de NaH (al 60%, 160 mmol) en DMF anhidra (25 ml) en una atmósfera de N_2 a 0°C durante 20 min y la mezcla se agita a 0°C en una atmósfera de N_2 durante 30 minutos. Se añade en porciones HOSA (53,5 mmol) durante 30 minutos a 0°C y la mezcla se agita a 0°C durante 1,5 horas. Después de inactivar con hielo-agua (400 ml), la mezcla se extrae con éter (3 x 60 ml). La capa orgánica combinada se lava con agua (2 x 30 ml) y salmuera (20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con EtOAc al 0-60% en heptano para producir 5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-ilamina (570 mg). MS: 166 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$) δ 2,32 (s, 3H), 4,82 (a, 2N-H), 6,76 (d, H), 7,17 (s, H), 7,77 (dd, H).

Etapa 6: Una solución de ácido 2-pirimidin-2-il-4-metil-pirimidina-5-carboxílico (1,41 mmol), 5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-ilamina (1,41 mmol), DIPEA (158 mg, 4,22 mmol) y HATU (1,69 mmol) en DMF anhidra (8 ml) se agita a 90°C durante 16 horas. La DMF se retira por evaporación al vacío. El residuo se disuelve en EtOAc (40 ml), se lava con agua (3 x 10 ml) y salmuera (20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 1-20% en

DCM para producir (5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico (125 mg) en forma de un sólido. MS: 364 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,31 (s, 3H), 2,87 (s, 3H), 6,87 (d, H), 7,50 (s, H), 7,66 (t, H), 7,96 (t, H), 9,04 (d, 2H), 9,27 (s, H).

Ejemplo 221

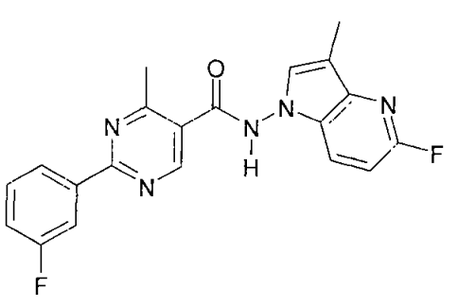
(5-Fluoro-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico



Una solución de ácido 2-piridin-2-il-4-metil-pirimidina-5-carboxílico (1,36 mmol), 5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-ilamina (1,36 mmol), DIPEA (158 mg, 4,07 mmol) y HATU (1,63 mmol) en DMF anhidra (8 ml) se agita a 90ºC durante 15 horas. La DMF se evapora al vacío. El residuo se disuelve en EtOAc (40 ml), se lava con agua (3 x 15 ml) y salmuera (20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se recristaliza en EtOAc para producir (5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 3-metil-2-piridin-2-il-pirimidina-5-carboxílico (285 mg) en forma de un sólido. MS: 363 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,35 (s, 3H), 2,87 (s, 3H), 6,92 (d, H), 7,51 (s, H), 7,60 (t, H), 7,97 (t, H), 8,05 (t, H), 8,65 (d, H), 8,78 (d, H), 9,23 (s, H).

Ejemplo 222

(5-Fluoro-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Una solución de ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (1,34 mmol), 5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-ilamina (1,34 mmol), DIPEA (158 mg, 4,02 mmol) y

metoxi-piridin-3-il)-2,2,2-trifluoro-acetamida (5,68 g) en forma de un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,96 (s,H), 6,80 (s, H), 8,23 (a, N-H), 8,42 (d, H).

Etapa 3: Una mezcla de N-(2-bromo-6-metoxi-piridin-3-il)-2,2,2-trifluoro-acetamida (5,52 g, 18,5 mmol), bromuro de alilo (3,57 g, 27,7 mmol) y carbonato sódico (5,1 g, 11 mmol) en CH_3CN (60 ml) se agita a 80°C durante 3 h. La mezcla se filtra y el filtrado se concentra al vacío. El residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con DCM al 0-60% en heptano para producir N-alil-N-(2-bromo-6-metoxi-piridin-3-il)-2,2,2-trifluoro-acetamida (5,55 g) en forma de un aceite. ^{1}H RMN (300 MHz, $CDCl_3$): δ 3,66 (c, H), 4,00 (s, H), 5,95 (c, H), 5,08-5,30 (c, 2H), 5,75-5,94 (m, H), 6,74 (d, H), 7,38 (d, H).

Etapa 4: Una solución de N-alil-N-(2-bromo-6-metoxi-piridin-3-il)-2,2,2-trifluoro-acetamida (5,54 g, 16,3 mmol), acetato de paladio (147 mg, 0,65 mmol), cloruro de tetra(n-butilamonio) (4,99 g, 17,9 mmol) y trietilamina (3,72 g, 26,8 mmol) en DMF anhidra (35 ml) se agita a 100°C en una atmósfera de N_2 durante una hora. La DMF se retira por evaporación y el residuo se mezcla con agua (20 ml) y se agita a ta durante una noche. Se añade EtOAc (50 ml). La capa orgánica se separa, se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con EtOAc al 30-70% en heptano para producir 5-metoxi-3-metil-1H-pirrolo[3,2-b]piridina (2,62 g) en forma de un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,38 (s, 3H), 4,05 (s, 3H), 6,62 (s, H), 7,12 (s, H), 7,54 (d, H), 7,94 (a, N-H).

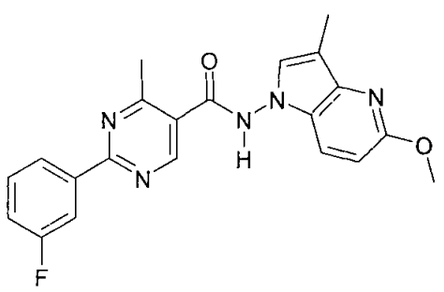
Etapa 5: Una solución de 5-metoxi-3-metil-1H-pirrolo[3,2-b]piridina (17,3 mmol) en DMF anhidra (20 ml) se añade gota a gota a una solución agitada de NaH (al 60%, 260 mmol) en DMF anhidra (35 ml) en una atmósfera de N_2 a 0°C durante 40 min y después se agita a 0°C en una atmósfera de nitrógeno durante 30 minutos. Se añade en porciones HOSA durante 45 minutos a 0°C y después la mezcla se agita a 0°C durante 2 horas. Después de inactivar con hielo-agua (500 ml), la mezcla de reacción se extrae con éter (3 x 40 ml). La capa orgánica combinada se lava con agua (20 ml) y salmuera (20 ml), se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con EtOAc al 5-60% en heptano para producir 5-metoxi-3-metil-pirrolo[3,2-b]piridin-1-ilamina (1,73 g) en forma de un sólido. MS: 178 (M+H); ^{1}H RMN (300 MHz, $CDCl_3$): δ 2,34 (s, 3H), 4,04 (s, 3H), 4,75 (a, 2N-H), 6,63 (d, H), 7,04 (s, H), 7,60 (d, H).

Etapa 6: Una solución de ácido 2-piridin-2-il-4-metil-pirimidina-5-carboxílico (1,69 mmol),

5-metoxi-3-metil-pirrolo[3,2-b]piridin-1-ilamina (1,69 mmol), DIPEA (5,01 mmol) y HATU (2,03 mmol) en DMF anhidra (8 ml) se agita a 90°C durante 16 h. La DMF se evapora al vacío. El residuo se disuelve en EtOAc (40 ml) y se lava con agua (3 x 10 ml) y salmuera (10 ml). La capa orgánica se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con MeOH al 0-15% en DCM para producir (5-metoxi-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico (295 mg) en forma de un sólido. MS: 375 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,40 (s, 3H), 2,84 (s, 3H), 4,02 (s, 3H), 6,70 (d, H), 7,13 (s, H), 7,41 (m, H), 7,50 (d, H), 7,85 (t, H), 8,51 (m, 2H), 8,78 (s,2H), 10,57 (a, N-H).

Ejemplo 224

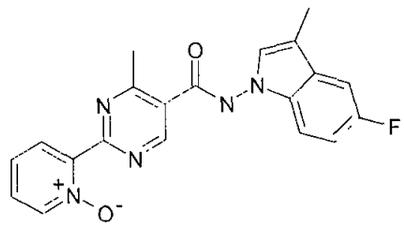
(5-Metoxi-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico



Una solución de ácido 2-(3-fenil)-4-metil-pirimidina-5-carboxílico (1,13 mmol), 5-metoxi-3-metil-pirrolo[3,2-b]piridin-1-ilamina (1,13 mmol), DIPEA (3,39 mmol) y HATU (1,36 mmol) en DMF anhidra (8 ml) se agita a 90°C durante 16 h. La DMF se retira por evaporación al vacío. El residuo se disuelve en EtOAc (45 ml) y se lava con agua (3 x 20 ml) y salmuera (10 ml). La capa orgánica se seca (Na_2SO_4), se filtra y se concentra al vacío. El residuo se tritura con DCM para producir (5-metoxi-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico (265 mg) en forma de un sólido. MS: 392 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ 2,33 (s, 3H), 2,79 (s, 3H), 3,97 (s, 3H), 6,67 (d, H), 7,20-7,60 (m, 2H), 7,53 (m, H), 7,64 (d, H), 8,17 (t, H), 8,34 (t, 2H), 9,05-9,20 (d, H).

Ejemplo 225

(5-Fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-(1-oxi-piridin-2-il)-pirimidin-5-carboxílico



Etapa 1: Una solución de 2-cianopiridina (1,67 g, 16 mmol), H_2O_2 al 30% (3,2 ml) y metiltrioxorrenio (0,2 g, 0,8 mmol) en DCM (6,4 ml) se agita a ta durante una noche. La mezcla de reacción se concentra al vacío y el residuo se purifica por cromatografía sobre gel de sílice eluyendo con MeOH al 3-10% en DCM para producir 1-oxi-piridina-2-carbonitrilo (0,69 g) en forma de un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 7,34 (t, H), 7,49 (t, H), 7,67 (d, H), 8,30 (d, H).

Etapa 2: Una solución de 1-oxi-piridina-2-carbonitrilo (532 mg, 4,43 mmol) y metóxido sódico (0,5 M en MeOH, 0,88 ml) en MeOH (1,8 ml) se agita a ta durante una noche. Se añade cloruro de amonio (261 mg, 4,87 mmol), la mezcla se agita a 56°C durante una hora y después se añade amoniaco 7 N en MeOH (1,5 ml). La mezcla de reacción se cierra herméticamente en un tubo, se agita a 40°C durante una hora y después se enfría a 0°C. Se añade metóxido sódico (0,5 M en MeOH, 8,86 ml). La mezcla se filtra y el filtrado se concentra al vacío. El residuo se recristaliza en etanol para producir 1-oxi-piridina-2-carboxamidina (370 mg) en forma de un sólido. ^{1}H RMN (300 MHz, CD_3OD): δ 7,52-7,68 (m, 2H), 7,96 (dd, H), 8,35 (d, H).

Etapa 3: Una solución de 1-oxi-piridina-2-carboxamidina (366 mg, 2,67 mmol) y acetoacetato de N,N-dimetilaminometileno (495 mg, 2,76 mmol) en etanol (3 ml) y DMF (3 ml) se agita a 90°C durante 16 horas. La mezcla de reacción se concentra al vacío y el residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con MeOH al 2,5% en DCM para producir éster etílico del ácido 4-metil-2-(1-oxi-piridin-2-il)-pirimidina-5-carboxílico (127 mg) en forma de un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1,47 (t, 3H), 2,95 (s, 3H), 4,50 (c, 2H), 7,39 (m, H), 7,70 (c, H), 8,36 (c, H), 9,37 (s, H).

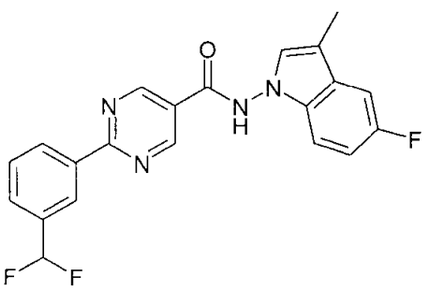
Etapa 4: Una solución de éster etílico del ácido 4-metil-2-(1-oxi-piridin-2-il)-pirimidina-5-carboxílico (123 mg, 0,48 mmol) e hidróxido sódico (123 mg, 3,07 mmol) en una mezcla de MeOH/THF/H_2O (3 ml, 1:1:1) se agita a 65°C durante 5 minutos y después se agita a ta durante una noche (16 horas). Se añade una solución acuosa 1 N de HCl (3,07 ml). La

solución resultante se concentra para producir ácido 4-metil-2-(1-oxi-piridin-2-il)-pirimidina-5-carboxílico y cloruro sódico (313 mg), que se usa en la siguiente etapa sin purificación adicional.

Etapa 5: Una solución de ácido 4-metil-2-(1-oxi-piridin-2-il)-pirimidina-5-carboxílico y cloruro sódico (313 mg), 3-metil-5-fluoro-indol-1-ilamina (78 mg, 0,48 mmol), DIEA (92 mg, 0,71 mmol) y HATU (217 mg, 0,57 mmol) en DMF anhidra (2,4 ml) se agita a 150ºC durante 1 hora. La DMF se retira por evaporación. El residuo se purifica por cromatografía en columna sobre gel de sílice eluyendo con MeOH al 2,5-10% en DCM para producir (5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-(1-oxi-piridin-2-il)-pirimidina-5-carboxílico (169 mg) en forma de un sólido. MS: 378 (M+H); ^{1}H RMN (300 MHz, CD_3OD): δ =1,52 (s, 3H), 2,84 (s, 3H), 7,02(t, H), 7,18 (s, H), 7,25 (d, H), 7,35 (c, H), 7,62-7,80 (m, 2H), 7,85 (dd, H), 8,48 (d, H), 9,21 (s, H). CI_{50} = 851,5 nM.

Ejemplo 226

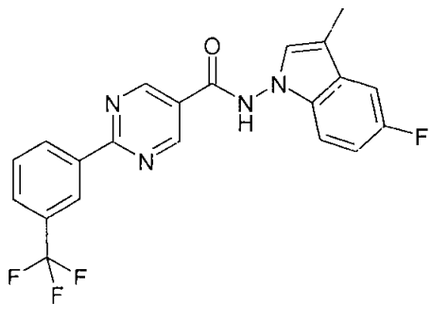
(5-Fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-difluorometil-fenil)-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 158, etapa 4, pero sustituyendo ácido 2-tiazol-2-il-pirimidina-5-carboxílico por ácido 2-(3-difluorometil-fenil)-2-il-pirimidina-5-carboxílico, se prepara (5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-difluorometil-fenil)-pirimidina-5-carboxílico. MS: 397 (M+H); ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,27 (s, 3H), 7,04 (dt, 1H), 7,13 (d, 1H), 7,32 (s, 1H), 7,34-7,44 (m, 2H), 7,73-7,85 (m, 2H), 8,66 (d, 1H), 8,69 (s, 1H), 9,45 (s, 2H). CI_{50} = 17 nM.

Ejemplo 227

(5-Fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-trifluorometil-fenil)-pirimidina-5-carboxílico



Siguiendo procedimientos similares a los del Ejemplo 158, etapa 4, pero sustituyendo ácido 2-tiazol-2-il-pirimidina-5-carboxílico por ácido 2-(3-trifluorometil-fenil)-2-il-pirimidina-5-carboxílico, se prepara (5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-trifluorometil-fenil)-pirimidina-5-carboxílico. MS: 415 (M+H). ^{1}H RMN (300 MHz, DMSO-d_6): δ 2,27 (s, 3H), 7,04 (dt, 1H), 7,33 (s, 1H), 7,34-7,44 (m, 2H), 7,86 (t, 1H), 8,00-8,02 (m, 1H), 8,75-8,79 (m, 2H), 9,47 (s, 2H). CI_{50} = 262 nM.

Siguiendo procedimientos similares a los descritos en los ejemplos anteriores, se preparan los siguientes compuestos:

(4-bencil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

piperazin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

(4-metanosulfonil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

morfolin-4-ilamida del ácido 2-(2-metil-tiazol-4-il)-pirimidina-5-carboxílico,

[4-(1-metil-1H-imidazol-2-carbonil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(1-metil-1H-imidazol-4-carbonil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

éster terc-butílico del ácido 4-[(2-fenil-pirimidina-5-carbonil)-amino]-piperazina-1-carboxílico,

[4-(4-trifluorometil-fenoxi)-piperidin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(4-trifluorometil-fenoxi)-piperidin-1-il]-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

morfolin-4-ilamida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

indol-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

(4-metoxi-piperidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(6-fluoro-2,3-dihidro-benzo[1,4]oxazin-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(6-fluoro-2,3-dihidro-benzo[1,4]oxazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

éster metílico del ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-3-(2-morfolin-4-il-etil)-1H-indolo-6-carboxílico,

[5-fluoro-3-(tetrahidro-piran-4-il)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

N-metil-N-(5-fluoro)-indol-3-ilsulfonil-N`-[2-(3-fluoro)-fenil-pirimidina-5-carbonil]-hidrazida,

[5-fluoro-3-(tetrahidro-piran-4-il)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[3,2-c]piridin-1-ilamida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[3,2-c]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[3,2-c]piridin-1-ilamida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(4-metil-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(2-metil-3-oxo-2,3-dihidro-indazol-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-indol-1-il)amida)amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

6-(4-cloro-tiazol-2-il)-2-metil-N-pirrolo[2,3-c]piridin-1-il-nicotinamida,

(5-metil-4-oxo-4,5-dihidro-pirrolo[3,2-c]piridin-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico.

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico.

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-difluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-difluorometil-indol-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico, y

(3-difluorometil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico.

PROTOCOLOS DE ENSAYO *IN VITRO* PARA IDENTIFICAR INHIBIDORES DE PGD2 SINTASA HEMATOPOYÉTICA

Los compuestos de la presente invención pueden ensayarse con respecto a la actividad inhibidora de enzimas contra la PGD2 Sintasa de acuerdo con uno de los siguientes ensayos.

Ensayo 1: Ensayo de Polarización de Fluorescencia

Como se describe en la publicación PCT WO 2004/016223, Ejemplo II.

Ensayo 2: Método de Inmunoensayo Enzimático (EIA)

I. Soluciones de Ensayo

a. Preparación de tampón K_2HPO_4/KH_2PO_4 0,1 M (pH 7,4)

Preparar KH_2PO_4 0,1 M a partir KH_2PO_4 1 M (Sigma, N° Cat P-8709)

Preparar K_2HPO_4 0,1 M a partir de K_2HPO_4 en polvo (Fisher, BP363-500)

Mezclar K_2HPO_4 0,1 M con KH_2PO_4 0,1 M para ajustar el valor del pH a 7,4.

b. Preparación de γ-globulina al 0,5%

Añadir 0,1 g de γ-globulina (Sigma, N° Cat G-5009) a 20 ml de tampón K_2HPO_4/KH_2PO_4 0,1 M (pH 7,4), preparar alícuotas de 1-ml/vial y almacenar a -80°C.

c. Preparación de GSH 100 mM

Añadir 307 mg de GSH (Sigma, N° Cat G-6529) a 10 ml de tampón K_2HPO_4/ KH_2PO_4 0,1 M (pH 7,4) y almacenar a - 80°C.

d. Preparación de Tampón de Reacción:

198 ml de tampón K_2HPO_4/KH_2PO_4 0,1 M (pH 7,4)

GSH 2 mM – preparado a partir de GSH 100 mM

0,4 g de glicerol

2 ml de γ-globulina al 0,5%

Añadir 0,4 g de glicerol y 2 ml de γ-globulina al 0,5% a 198 ml de tampón K_2HPO_4/ KH_2PO_4 0,1 M (pH 7,4).

Añadir 0,4 ml de GSH 100 mM a 19,6 ml de tampón de reacción antes del ensayo (suficiente para dos placas de 96 pocillos).

e. Preparación de solución de parada de $FeCl_2$/ácido cítrico: (8 mg/ml de $FeCl_2$, ácido cítrico 0,1 M)

Añadir 40 mg de $FeCl_2$ nuevo (IGN, Nº Cat 158046) a 5 ml de ácido cítrico 0,1 M (Sigma, Nº Cat C0759).

f. Preparación de reactivo MOX:

EtOH al 10% - Añadir 1 ml de EtOH a 9 ml de H_2O ultrapura

Disolver 0,1 g de metoxilamina (Cayman, Nº Cat 400036/) en EtOH al 10% (10 ml).

Añadir 0,82 g de acetato sódico (Cayman, Nº Cat 400037) a la solución MOX y disolver.

II. Materiales y Método

Dimetilsulfóxido (DMSO; Sigma; Nº Cat D2650)

Kit EIA de expresión de prostaglandina D2-MOX (Caymen Chemical, Nº de Catálogo 500151)

Antes del ensayo, enfriar 10 ml de acetona en tubos de polipropileno y vaciar placas de 96 pocillos en hielo. Todos los procedimientos excepto la dilución del compuesto se realizan en hielo.

III. Dilución del compuesto

1. Diluir el compuesto en DMSO

Vol de solución madre de DMSO (µl)	DMSO (µl)	Concentración de compuesto (mM)
4 µl de 10 mM	6 µl	4
3 µl de 4 mM	6 µl	1,3333
3 µl de 1,33 mM	6 µl	0,4444
3 µl de 0,44 mM	6 µl	0,1481
3 µl de 0,148 mM	6 µl	0,0494
3 µl de 0,049 mM	6 µl	0,0165
3 µl de 0,016 mM	6 µl	0,0055

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2. Diluir 2 µl de cada una de las concentraciones anteriores de compuesto en 38 µl de tampón de reacción en placas de 96 pocillos y mezclar.

IV. Preparación de solución de enzima y sustrato

1. Preparación de solución enzimática a una concentración de 0,39 ng/µl (0,35 ng/µl al final después de la adición del compuesto).
   Mezclar 4 µl de h-PGDS humana a 4 mg/ml con 396 µl de tampón de reacción (para dar una concentración de enzima de 40 µg/ml). Añadir 46,8 µl de h-PGDS a una concentración de 40 µg/ml a 4,753 ml de tampón de reacción para dar un volumen total de 4,8 ml
2. Preparación de Solución de Sustrato (PGH2): Añadir 0,375 ml de PGH2 a una concentración de 0,1 mg/ml a 1,625 ml de acetona.

V. Reacción enzimática:

1. Añadir 60 µl de solución enzimática al pocillo de compuesto y al control positivo (sin compuesto) en una placa de polipropileno de fondo en U en hielo.
2. Añadir 60 µl de tampón de reacción y 6.6 µl de DMSO al 5% en tampón de reacción en los pocillos de control negativo de la placa.
3. Añadir 6,6 µl de compuesto diluido en tampón de reacción a los pocillos de compuesto y mezclar.
4. Añadir 6,6 µl de DMSO al 5% en tampón de reacción al pocillo de control positivo.
5. Incubar la placa en hielo durante al menos 30 min.
6. Añadir 20 µl de solución de sustrato (PGH2) a los pocillos de compuesto, control negativo y control positivo en la placa de 96 pocillos de fondo en U en hielo.
7. Secar la placa en una sala fría durante aproximadamente 25-28 minutos
8. Introducir con una pipeta 45 µl de solución enzimática (anterior) en una placa de 96 pocillos con PGH2 secada y mezclar 3 veces. Incubar en el hielo durante 1 minuto.
9. Añadir 45 µl de solución de $FeCl_2$ a cada pocillo y mezclar.
10. Añadir 90 µl de solución de MOX y mezclar.
11. incubar durante 30 min a 60 °C
12. Diluir las muestras 2500X con tampón de EIA.

VI. Ensayo EIA

Realizar el ensayo de acuerdo con el procedimiento del kit EIA proporcionado por Cayman. Los niveles totales de PGD2 (pg/ml) se determinaron en las muestras por kits EIA (Caymen Chemical, N° de Catálogo 500151)

Calcular la cantidad de PGD2 como se indica a continuación

Calcular el % de Control positivo de acuerdo con la siguiente ecuación;

% de Control positivo = (Valor de compuesto-Control negativo)/(Valor positivo-Valor de control negativo) · 100,

$$\% \text{ de Control positivo} = \frac{(\text{Valor de compuesto-Control negativo})}{(\text{Valor positivo-Valor de control negativo})} \text{ X } 100$$

Valor de compuesto = niveles de PGD2 (pg/ml) obtenidos a partir de la curva patrón en el ensayo EIA para las muestras con compuesto

Valor de control negativo = niveles de PGD2 (pg/ml) obtenidos a partir de la curva patrón en el ensayo EIA para las muestras sin enzima

Valor de control positivo = niveles de PGD2 (pg/ml) obtenidos a partir de la curva patrón en el ensayo EIA para las muestras con enzima pero sin compuesto

Los valores de CI_{50} se determinan por ajuste excel para conseguir el valor de x cuando y=1/2Ymax usando un modelo logístico de 4 parámetros para las curvas de CI_{50}.

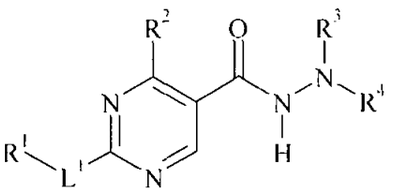
Resultados

Los compuestos dentro del alcance de la invención producen una inhibición de 50% en el Ensayo de Polarización de Fluorescencia o en el ensayo EIA a concentraciones dentro del intervalo de aproximadamente 1 nanomolar a aproximadamente 30 micromolar, particularmente de aproximadamente 1 nanomolar a aproximadamente 1 micromolar, y más particularmente de aproximadamente 1 nanomolar a aproximadamente 100 nanomolar. Los valores de CI_{50} obtenidos por el ensayo EIA para algunos de los ejemplos se muestran al final de cada uno de esos ejemplos.

La presente invención puede llevarse a la práctica en otras formas específicas manteniendo su espíritu o sus atributos esenciales.

REIVINDICACIONES

1. Un compuesto de fórmula (I):



(I)

en la que:

R^1 es alquilo (C_1-C_6) opcionalmente sustituido una o más veces independientemente con halo, hidroxi, alcoxi (C_1-C_6) o haloalcoxi (C_1-C_4) o cicloalquilo (C_3-C_6), arilo o heteroarilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), haloalquilo (C_1-C_4) o haloalcoxi (C_1-C_4);

R^2 es hidrógeno o alquilo (C_1-C_4) opcionalmente sustituido una o más veces con halógeno;

R^3 es hidrógeno, alquilo, arilo o heteroarilo,

R^4 es hidrógeno, cicloalquilo, arilo, heterociclilo, heteroarilo, arilsulfonilo, heteroarilsulfonilo, $-C(=O)-NY^1Y^2$, $-C(=S)-NY^1Y^2$, R^5, $-C(=O)-R^5$ o $-C(=S)-R^5$, donde el resto arilo, heteroarilo o heterociclilo está opcionalmente sustituido una o más veces independientemente con R^6, o

R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman heterociclilo, heterociclenilo, heteroarilo, arilheterociclilo, arilheterociclenilo, heteroarilheterociclilo, heteroarilheterociclenilo, heterociclilheteroarilo o heterociclenilheteroarilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

R^5 es cicloalquilo, cicloalquenilo, arilo, heteroarilo, heterociclilo, heterociclenilo, o alcarilo multicíclico, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

L^1 es un enlace, -O-, -C(=O)-, -NH-C(=O)- o alquileno (C_1-C_2) opcionalmente sustituido una o más veces con halo;

R^6 es ciano, nitro, halo, hidroxi, carboxi, Y^1Y^2N-, Y^1Y^2N-C(=O)-, Y^1Y^2N-SO_2-, acilo, aciloxi, alquilo, alquenilo, alquinilo, alcoxi, alcoxicarbonilo, alquiltio, alquilsulfinilo o alquilsulfonilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con:

aciloxi, halo, alcoxi, haloalcoxi, hidroxi, carboxi, alcoxicarbonilo, Y^1Y^2N-, Y^1Y^2N-C(=O)-, Y^1Y^2N-SO_2-,

arilo, ariloxi, aroílo, heteroarilo, heteroariloxi, heteroaroílo, heterociclilo, heterociclenilo, cicloalquilo, cicloalquenilo o alcarilo multicíclico, cada uno de ellos opcionalmente sustituido una o más veces independientemente con alquilo, halo, haloalquilo, alcoxi, haloalcoxi, hidroxi, amino, alquilamino, dialquilamino, carboxi o alcoxicarbonilo, o

arilo, heteroarilo, aroílo, heteroaroílo, ariloxi, heteroariloxi, heterociclilo, heterociclenilo, cicloalquilo, cicloalquenilo o alcarilo multicíclico, cada uno de ellos opcionalmente sustituido una o más veces independientemente con alquilo, haloalquilo, halo, alcoxi, haloalcoxi, hidroxi, carboxi, alcoxicarbonilo, Y^1Y^2N- o Y^1Y^2N-SO_2-,

donde el resto heterociclilo, heterociclenilo, cicloalquilo, cicloalquenilo o alcarilo multicíclico de R^6 también está opcionalmente sustituido una o más veces independientemente con oxo;

cada uno de Y^1 e Y^2 es independientemente:

hidrógeno, alquilsulfonilo, aroílo, heteroaroílo o

alquilo opcionalmente sustituido una o más veces independientemente con hidroxi, carboxi, halo, amino, alquilamino, dialquilamino, alcoxi, heterociclilo, arilo o heteroarilo, o

Y^1 e Y^2 junto con el átomo de nitrógeno al que están unidos forman un heterociclilo;

o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

2. El compuesto de acuerdo con la reivindicación 1, en el que R^1 es arilo o heteroarilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), haloalquilo (C_1-C_4) o haloalcoxi (C_1-C_4), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

3. El compuesto de acuerdo con la reivindicación 1, en el que R^1 es fenilo o un heteroarilo de cinco o seis miembros, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo, alquilo (C_1-C_6), hidroxi o alcoxi (C_1-C_6), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

4. El compuesto de acuerdo con la reivindicación 1, en el que R^1 es fenilo, pirimidinilo, tiazolilo u oxadiazolilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo, alquilo (C_1-C_6), hidroxi o alcoxi (C_1-C_6), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

5. El compuesto de acuerdo con la reivindicación 1, en el que R^1 es fenilo, piridilo o pirimidinilo, cada uno de ellos opcionalmente sustituido independientemente en la posición orto o meta con halo, alquilo (C_1-C_6), hidroxi o alcoxi (C_1-C_6), o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

6. El compuesto de acuerdo con la reivindicación 1, en el que R^1 es fenilo opcionalmente sustituido independientemente en la posición orto o meta con halo, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

7. El compuesto de acuerdo con la reivindicación 1, en el que R^1 es piridilo, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

8. El compuesto de acuerdo con la reivindicación 1, en el que R^2 es hidrógeno, metilo o trifluorometilo, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

9. El compuesto de acuerdo con la reivindicación 1, en el que R^2 es hidrógeno, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

10. El compuesto de acuerdo con la reivindicación 1, en el que R^2 es metilo, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

11. El compuesto de acuerdo con la reivindicación 1, en el que L^1 es un enlace, -O-, -C(=O)- o -NH-C(=O)- o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

12. El compuesto de acuerdo con la reivindicación 1, en el que L^1 es un enlace, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

13. El compuesto de acuerdo con la reivindicación 1, en el que:

R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman un heterociclilo, heterociclenilo, arilheterociclilo o heteroarilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

R^6 es alcoxi, hidroxilo, cicloalquilo, carboxi, cicloalquilo, halo, ciano, alquilsulfonilo, Y^1Y^2N-, Y^1Y^2N-SO_2-,

alquilo opcionalmente sustituido una o más veces independientemente con aciloxi, hidroxi, alcoxicarbonilo, alcoxi, carboxi, arilo, halo, alquilsulfonilo, ciano, Y^1Y^2N- o Y^1Y^2N-C(=O)-,

acilo o arilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo,

alcoxicarbonilo opcionalmente sustituido una o más veces independientemente con arilo,

heteroaroílo opcionalmente sustituido una o más veces independientemente con alquilo,

heterociclilo opcionalmente sustituido una o más veces con oxo, o

ariloxi opcionalmente sustituido una o más veces independientemente con haloalquilo, y

cada uno de Y^1 e Y^2 es independientemente hidrógeno, alquilsulfonilo, aroílo o alquilo opcionalmente sustituido con morfolinilo o

Y^1 e Y^2 junto con el átomo de nitrógeno al que están unidos forman morfolinilo;

o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

14. El compuesto de acuerdo con la reivindicación 1, en el que:

R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman [1,2,4]triazolilo, pirrolilo, indolilo, pirrolo[2,3-b]piridilo, pirrolo[3,2-b]piridilo o pirrolo[2,3-c]piridilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

R^6 es alcoxi, carboxi, cicloalquilo, halo, ciano, alquilsulfonilo, Y^1Y^2N-SO_2-,

alquilo opcionalmente sustituido una o más veces independientemente con aciloxi, hidroxi, alcoxicarbonilo, alcoxi, carboxi, arilo, halo, heterociclilo, alquilsulfonilo, ciano, heterociclilcarbonilo,

acilo o arilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo,

alcoxicarbonilo opcionalmente sustituido una o más veces independientemente con arilo,

heteroaroílo opcionalmente sustituido una o más veces independientemente con alquilo,

heterociclilo opcionalmente sustituido una o más veces con oxo, o

ariloxi opcionalmente sustituido una o más veces independientemente con haloalquilo, y

cada uno de Y^1 e Y^2 es independientemente hidrógeno o alquilo opcionalmente sustituido con morfolinilo o

Y^1 e Y^2 junto con el átomo de nitrógeno al que están unidos forman morfolinilo;

o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

15. El compuesto de acuerdo con la reivindicación 1, en el que:

R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman imidazolidinilo, [1,2,4]triazinanilo, piperazinilo, morfolinilo, pirrolidinilo, 1,2,3,4-tetrahidro-pirimidinilo, piperidinilo, oxazolidinilo, 2,3-dihidro-indolilo, octahidro-ciclopenta[c]pirrolilo o 3,4-dihidro-benzo[1,4]oxazina, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

R^6 es oxo, alcoxi, carboxi, cicloalquilo, halo, ciano, alquilsulfonilo, $Y^1Y^2N\text{-}SO_2\text{-}$,

alquilo opcionalmente sustituido una o más veces independientemente con hidroxi, alcoxicarbonilo, alcoxi, carboxi, arilo, halo, heterociclilo, alquilsulfonilo, ciano, heterociclilcarbonilo,

acilo o arilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con halo,

alcoxicarbonilo opcionalmente sustituido una o más veces independientemente con arilo,

heteroaroílo opcionalmente sustituido una o más veces independientemente con alquilo,

heterociclilo opcionalmente sustituido una o más veces con oxo, o

ariloxi opcionalmente sustituido una o más veces independientemente con haloalquilo, y

cada uno de Y^1 e Y^2 es independientemente hidrógeno o alquilo opcionalmente sustituido con morfolinilo o

Y^1 e Y^2 junto con el átomo de nitrógeno al que están unidos forman morfolinilo;

o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

16. El compuesto de acuerdo con la reivindicación 1, en el que:

R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman indolilo, opcionalmente sustituido una o más veces independientemente con R^6;

R^6 es $Y^1Y^2N\text{-}SO_2$-, alcoxicarbonilo, carboxialquilo, ciano, halo, alquilsulfonilo, alcoxi o acilo opcionalmente sustituido una o más veces independientemente con halo; y

cada uno de Y^1 e Y^2 es independientemente hidrógeno o alquilo opcionalmente sustituido con morfolinilo, o

Y^1 e Y^2 junto con el átomo de nitrógeno al que están unidos forman morfolinilo;

o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

17. El compuesto de acuerdo con la reivindicación 1, en el que:

R^5 es fenilo, piridilo o benzo[1,3]dioxolilo, cada uno de ellos opcionalmente sustituido una o más veces independientemente con R^6;

R^6 es $Y^1Y^2N\text{-}SO_2$-, hidroxi, alcoxi, halo, alquilo o haloalquilo; y

cada uno de Y^1 e Y^2 es, independientemente, hidrógeno o alquilo;

o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

18. El compuesto de acuerdo con la reivindicación 1, que es

(5-fluoro-2-metil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico,

(5-fluoro-2-metil-indol-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico,

(5-fluoro-2-metil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(5-fluoro-2-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-2-metil-indol-1-il)amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(5-fluoro-2-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-acetil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3,3-dimetil-2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico,

(2,3-dimetil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-cloro-2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-bromo-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

éster bencílico del ácido 3-oxo-4-[(2-fenil-pirimidina-5-carbonil)-amino]-piperazina-1-carboxílico,

(3-dimetilsulfamoil-5-fluoro-indol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,

(3-dimetilsulfamoil-5-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,

[5-fluoro-3-(morfolina-4-sulfonil)indol-1-il]amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,

[5-fluoro-3-(morfolina-4-sulfonil)indol-1-il]amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,

[5-fluoro-3-sulfamoilindol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,

[5-fluoro-3-metilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,

[5-fluoro-3-(2-morfolin-4-iletilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,

[5-fluoro-3-metilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,

{5-fluoro-[(3-tetrahidropiran-4-ilmetil)sulfamoil]indol-1-il}amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,

[5-fluoro-3-(2-morfolin-4-iletilsulfamoil)indol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,

(4-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)pirimidina-5-carboxílico,

(4-fluoroindol-1-il)amida del ácido 2-(3-fluorofenil)-4-metilpirimidina-5-carboxílico,

(4-fluoroindol-1-il)amida del ácido 2-(piridin-2-il)-pirimidina-5-carboxílico,

(4-fluoroindol-1-il)amida del ácido 2-(piridin-2-il)-4-metilpirimidina-5-carboxílico,

[6-(4-fluoro-fenil)-3-oxo-2,5-dihidro-3H-1,2,4-triazin-4-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

[5-fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

[5-fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[5-fluoro-3-(2-hidroxi-2-metil-propil)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-ciano-5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[5-fluoro-3-(1H-tetrazol-5-il)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[1,2,4] triazol-4-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

piperidin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-(2-fluoro-fenil)-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-etil-N'-tolil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

(3-oxo-morfolin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

morfolin-4-ilamida del ácido 2-(5-metil-[1,2,4]oxadiazol-3-il)-pirimidina-5-carboxílico,

morfolin-4-ilamida del ácido 2-benzoil-pirimidina-5-carboxílico,

[4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-benzoil-pirimidina-5-carboxílico,

N'-metil-N'-[5-trifluorometil-piridin-2-il]-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-metil-N'-[4-trifluorometil-piridin-2-il]-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-piridin-2-il-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-(2-cloro-fenil)-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-(2-oxo-piperidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-ciclohexil-N'-metil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-morfolin-4-il-amida del ácido 2-fenoxi-pirimidina-5-carboxílico,

(2,6-dimetil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(6-terc-butil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,

(6-terc-butil-3-oxo-2,5-dihidro-3H-1,2,4-triazina-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

éster metílico del ácido 3-{2,4-dioxo-3-[(2-fenil-pirimidina-5-carbonil)-amino]-1,2,3,4-tetrahidro-pirimidin-5-il}-propiónico,

ácido 3-{2,4-dioxo-3-[(2-fenil-pirimidina-5-carbonil)-amino]-1,2,3,4-tetrahidro-pirimidin-5-il}-propiónico,

(4-metil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

morfolin-4-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(2-hidroxi-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

((S)-2-metoximetil)-pirrolidin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

((R)-2-metoximetil)-pirrolidin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(5-bromo-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(3-isopropil-5-oxo-1,5-dihidro-[1,2,4]triazol-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

pirrol-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

(5-morfolin-4-ilmetil-2-oxo-oxazolidin-3-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(4-ciclopentil-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(2-oxo-oxazolidin-3-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il]-amida del ácido 4-metil-2-fenil-pirimidina-5-carboxílico,

éster etílico del ácido [N'-(2-fenil-pirimidina-5-carbonil)-hidrazino]-acético,

2-[N'-(2-fenil-pirimidina-5-carbonil)-hidrazino]-acetamida,

4-[3-(4-morfolino)propil]-1-(2-fenil-pirimidina-5-carbonil)-3-tiosemicarbazida,

(2,3-dihidro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

éster metílico del ácido {4-[2-fenil-pirimidina-5-carbonil)-amino]-piperazin-1-il}-acético,

(4-cianometil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,
2-{4-[(2-fenil-pirimidina-5-carbonil)-amino]-piperazin-1-il}-etil éster del ácido acético,
(4-acetil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,
[4-(2-oxo-tetrahidro-furan-3-il)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,
[4-(2,2,2-trifluoro-acetil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,
[4-(2-metoxi-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,
[4-(2-morfolin-4-il-2-oxo-etil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,
(2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
piperidin-1-il-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
piperidin-1-il-amida del ácido 2-fenil-pirimidina-5-carboxílico,
(hexahidro-ciclopenta[c]pirrol-2-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,
(2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-fenil-pirimidina-5-carboxílico,
pirrolidin-1-il-amida del ácido 2-fenil-pirimidina-5-carboxílico,
(2,6-dimetil-piperidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,
(4-ciclopentil-piperazin-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
(2-metil-2,3-dihidro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,
(2-metil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
N'-metil-N'-piridin-2-il-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,
(5-fluoro-indol-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,
(2,3-dihidro-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,
indol-1-il-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,
indol-1-il-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
(2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(2-metil-2,3-dihidro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
indol-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(2,3-dihidro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
indol-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(5-metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
(6-metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
(5-metanosulfonil-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,
(5-metanosulfonil-indol-1-il)-amida del ácido 2-piridin-3-il-pirimidina-5-carboxílico,

(5-metanosulfonil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

pirrolo[3,2-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil-4-metil)-pirimidina-5-carboxílico,

pirrolo[3,2-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-indol-1-il)-amida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridina-1-ilamida del ácido 2-piridin-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

pirrolo[3,2-b]piridin-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

pirrolo[3,2-b]piridin-1-ilamida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico,

(5-fluoro-indol-1-il)-amida del ácido 4-metil-2-piridin-3-il-pirimidina-5-carboxílico,

(5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-metoxi-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-ciano-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(4-ciano-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[4-(1H-tetrazol-5-il)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

éster metílico del ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-4-carboxílico,

ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-4-carboxílico,

(3-cianometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-metoxi-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

[3-(1H-tetrazol-5-ilmetil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

2-(2-fenil-pirimidina-5-carbonil)-1-hidrazinacarboxamida,

2-(2-fenil-pirimidina-5-carbonil)-1-hidrazina-1-carbotioamida,

(2,4-dioxo-imidazolidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-fenil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

N'-(2-fenil-pirimidina-5-carbonil)-hidrazida del ácido piridina-2-carboxílico,

4-[N'-(2-fenil-pirimidina-5-carbonil)-hidrazino]-bencenosulfonamida,

N'-(2-fenil-pirimidina-5-carbonil)-hidrazida del ácido 3-hidroxi-benzoico,

N'-(fenil-pirimidina-5-carbonil)-hidrazida del ácido benzo[1,3]dioxo-5-carboxílico,

N'-(fenil-pirimidina-5-carbonil)-hidrazida del ácido 3,4-dimetoxi-benzoico,

N'-metil-N'-fenil-hidrazida del ácido 2-fenil-pirimidina-5-carboxílico,

(5-metoxi-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-metoxi-fenil)-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(2-metoxi-fenil)-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(4-metoxi-fenil)-pirimidina-5-carboxílico

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(3-hidroxi-fenil)-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(2-hidroxi-fenil)-pirimidina-5-carboxílico,

(6-metil-3-oxo-2,5-dihidro-3H-[1,2,4]triazin-4-il)-amida del ácido 2-(4-hidroxi-fenil)-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-tiazol-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido [2,2']bipirimidinil-5-carboxílico,

(3-cloro-5-fluoro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

amida del ácido 5-fluoro-1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indolo-3-carboxílico,

ácido 2-{5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indol-3-il}-2-metil-propiónico,

ácido 2-(5-fluoro-1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-1H-indol-3-il)-2-metil-propiónico,

[5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

[5-fluoro-3-(2-piridin-3-il-etil)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-3-formil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

ácido 5-fluoro-1-[(4-metil-2-piridin-2-il-pirimidina-5-carbonil)-amino]-1H-indolo-3-carboxílico,

(5-fluoro-3-hidroximetil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

[5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[5-fluoro-3-(3-hidroxi-3-metil-butil)-indol-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-etil-5-trifluorometoxi-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(6-trifluorometil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(6-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(6-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(6-trifluorometil-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-etil-5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(5-metoxi-2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

N',N'-difenil-hidrazida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(7-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-metanosulfonil-3-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-etil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-pirrolo[2,3-c] piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-etil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-metil-5-trifluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-nitro-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-amino-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
[5-(dimetanosulfonil)-amino-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-benzoilamino-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
[5-fluoro-3-(1,2,3,6-tetrahidro-piridin-4-il)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-piridin-2-il-4-trifluorometil-pirimidina-5-carboxílico,
(2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(6-fluoro-2,3-dihidro-1,4-benzoxazin-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,
(6-fluoro-2,3-dihidro-1,4-benzoxazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,
(3-etil-5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(3-etil-5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,
(5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-fluoro-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(2-ciclopropil-5-fluoro-indol-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,
(2-ciclopropil-5-fluoro-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,
(5-metoxil-indol-1-il)-amida del ácido 2-pirimidin-2-il-4-metil-pirimidina-5-carboxílico,
(5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,
(5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,
(5-fluoro-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,
(5-metoxi-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(5-metoxi-3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-(1-oxi-piridin-2-il)-pirimidin-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-difluorometil-fenil)-pirimidina-5-carboxílico, o

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(3-trifluorometil-fenil)-pirimidina-5-carboxílico,

o un hidrato, solvato o N-óxido de los mismos, o una sal farmacéuticamente aceptable de los mismos.

19. El compuesto de acuerdo con la reivindicación 1, que es:

(4-bencil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

piperazin-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

(4-metanosulfonil-piperazin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

morfolin-4-ilamida del ácido 2-(2-metil-tiazol-4-il)-pirimidina-5-carboxílico,

[4-(1-metil-1H-imidazol-2-carbonil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(1-metil-1H-imidazol-4-carbonil)-piperazin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

éster terc-butílico del ácido 4-[(2-fenil-pirimidina-5-carbonil)-amino]-piperazina-1-carboxílico,

[4-(4-trifluorometil-fenoxi)-piperidin-1-il]-amida del ácido 2-fenil-pirimidina-5-carboxílico,

[4-(4-trifluorometil-fenoxi)-piperidin-1-il]-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

morfolin-4-ilamida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

indol-1-ilamida del ácido 2-fenil-pirimidina-5-carboxílico,

(4-metoxi-piperidin-1-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

(2-metil-indol-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(6-fluoro-2,3-dihidro-benzo[1,4]oxazin-4-il)-amida del ácido 2-(3-fluoro-fenil)-pirimidina-5-carboxílico,

(6-fluoro-2,3-dihidro-benzo[1,4]oxazin-4-il)-amida del ácido 2-fenil-pirimidina-5-carboxílico,

éster metílico del ácido 1-{[2-(3-fluoro-fenil)-4-metil-pirimidina-5-carbonil]-amino}-3-(2-morfolin-4-il-etil)-1H-indolo-6-carboxílico,

[5-fluoro-3-(tetrahidro-piran-4-il)-indol-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

N-metil-N-(5-fluoro)-indol-3-ilsulfonil-N'-[2-(3-fluoro)-fenil-pirimidina-5-carbonil]-hidrazida,

[5-fluoro-3-(tetrahidro-piran-4-il)-indol-1-il]-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[3,2-c]piridin-1-ilamida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[3,2-c]piridin-1-ilamida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

pirrolo[2,3-b]piridin-1-ilamida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[2,3-c]piridin-1-ilamida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-metil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

pirrolo[3,2-c]piridin-1-ilamida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-isopropil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-cloro-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-3-metil-indol-1-il)-amida del ácido 2-(4-metil-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(2-metil-3-oxo-2,3-dihidro-indazol-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-fluoro-indol-1-il)amida)amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

6-(4-cloro-tiazol-2-il)-2-metil-N-pirrolo[2,3-c]piridin-1-il-nicotinamida,

(5-metil-4-oxo-4,5-dihidro-pirrolo[3,2-c]piridin-1-il)amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-2-(4-metil-tiazol-2-il)-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-2,2-difluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico.

[3-(2,2-difluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(3-difluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[2,3-b]piridin-1-il]-amida del ácido 4-metil-[2,2']bipirimidinil-5-carboxílico,

(5-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(5-difluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[3,2-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-c]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-trifluorometil-pirrolo[2,3-b]piridin-1-il)-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[3-(2,2-difluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-b]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[3,2-c]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

[3-(2,2,2-trifluoro-etil)-pirrolo[2,3-c]piridin-1-il]-amida del ácido 2-(3-fluoro-fenil)-4-metil-pirimidina-5-carboxílico,

(3-difluorometil-indol-1-il)-amida del ácido 4-metil-2-piridin-2-il-pirimidina-5-carboxílico,

(3-difluorometil-indol-1-il)-amida del ácido 2-(4-cloro-tiazol-2-il)-4-metil-pirimidina-5-carboxílico, o

(3-difluorometil-indol-1-il)-amida del ácido 4-metil-2-tiazol-2-il-pirimidina-5-carboxílico,

o un hidrato, solvato o N-óxido de los mismos, o una sal farmacéuticamente aceptable de los mismos.

20. Una composición farmacéutica que comprende el compuesto de acuerdo con la reivindicación 1, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo, y un vehículo farmacéuticamente aceptable.

21. Un método para tratar un trastorno alérgico o inflamatorio en un paciente que lo necesita, que comprende administrar al paciente una cantidad farmacéuticamente eficaz del compuesto de acuerdo con la reivindicación 1, o un hidrato, solvato o N-óxido del mismo, o una sal farmacéuticamente aceptable del mismo.

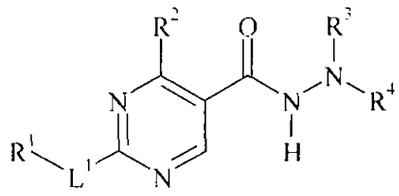
22. El método de acuerdo con la reivindicación 21, en el que el trastorno alérgico o inflamatorio es rinitis alérgica.

23. El método de acuerdo con la reivindicación 21, en el que el trastorno alérgico o inflamatorio es asma.

24. El método de acuerdo con la reivindicación 21, en el que el trastorno alérgico o inflamatorio es enfermedad pulmonar obstructiva crónica.

RESUMEN

Esta invención se refiere a un compuesto de fórmula (I):



(I)

en la que R^1, R^2, R^3, R^3 y L^1 son como se han definido en este documento, a una composición farmacéutica que comprende el compuesto, y al uso del compuesto para tratar trastornos alérgicos y/o inflamatorios, particularmente trastornos tales como rinitis alérgica, asma y/o enfermedad pulmonar obstructiva crónica (COPD).

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/058347

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/28 C07D403/12 C07D403/14 C07D413/12 C07D417/14
A61K31/506 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Week 200724 Derwent Publications Ltd., London, GB; AN 2007-235635 XP002484510 & JP 2007 051121 A (TAIHO PHARM CO LTD) 1 March 2007 (2007-03-01) abstract ----- -/--	1-24

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2008	30/06/2008

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	Lauro, Paola

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/058347

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	OUELLET M ET AL: "Aromatic hydroxamic acids and hydrazides as inhibitors of the peroxidase activity of prostaglandin H2 synthase-2" ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, NEW YORK, US, vol. 431, no. 1, 1 November 2004 (2004-11-01), pages 107-118, XP004581263 ISSN: 0003-9861 the whole document	1-24
X	C. L. JOHNSON: "Quantitative structure-activity studies on monoamine oxidase inhibitors" J. MED. CHEM., vol. 19, no. 5, 1976, pages 600-605, XP002484508 * see Table I, 2nd compound from bottom *	1
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002484509 accession no. 6388585 abstract & BROWN, DESMOND J.; COWDEN, WILLIAM B.: "Unfused heterobicycles as amplifiers of phleomycin. VII. Some triazolyl-, thiadiazolyl- and oxadiazolylpyridines and related pyrimidines" AUST. J. CHEM., vol. 36, no. 7, 1983, pages 1469-1475,	1

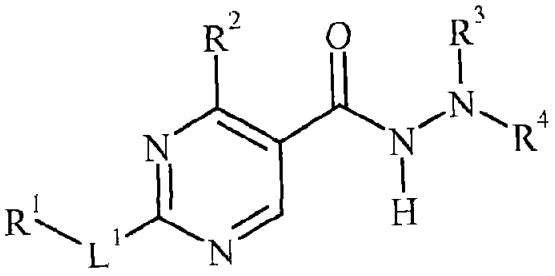
540

INTERNATIONAL SEARCH REPORT

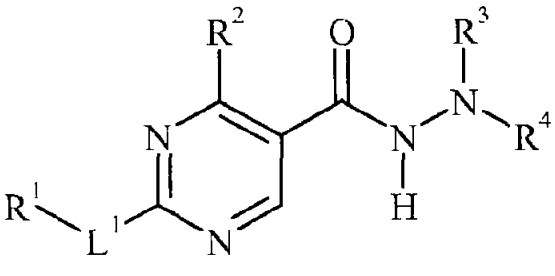
Information on patent family members

International application No
PCT/US2008/058347

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2007051121 A	01-03-2007	NONE	



(I)



(I)

Industrial, los cuales deberán ser interpuestos dentro de los cinco (5) días hábiles siguientes a la fecha de la notificación del presente acto administrativo.

ARTÍCULO CUARTO: Realizar las anotaciones respectivas. Una vez en firme la presente actuación, archivar el expediente.

Notifíquese y Cúmplase
Dado en Bogotá D.C., a los 10 MAR 2010

La Directora de Signos Distintivos (c),

LIGIA MATILDE ATEHORTÚA JIMÉNEZ

Proyectado por: Jagarcia

569

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 8001/6089-2

RECIBO OFICIAL DE CAJA : 09 - 70,589
FECHA : SEPTIEMBRE 21 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-107316- -00000-0000
Fecha 2009-09-30 16 44 17 Dep 2020 NUECREACION
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios 570

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	17854550	21/09/2009	45,108,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	3 PROC. REGISTRO DE MARCAS Y LEMAS	688,000.00
		TOTAL : $	688,000.00

SON: SEISCIENTOS OCHENTA Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 14775-841-102-8

570

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 09 - 68,504
FECHA : SEPTIEMBRE 14 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-107316- -00000-0000
Fecha 2009-09-30 16:44:17 Dep 2020 NUECREACIONI
Tra 11 PATENTEIYII Eve 378 PASENACIONALI
Act 411 PRESENTACION Folios 570

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	17854546	14/09/2009	33,365,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08 PRORROGA DE TERMINOS	31 PRORROGA DE TERMINOS	81,000.00
		TOTAL : $	81,000.00

SON: OCHENTA Y UNO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cojo! 14775-841-102-8

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Claudia M Neira
Firma Responsable

Fe

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-107316- -00000-0000
Fecha 2009-09-30 16:44:17 Dep 2020 NUEVACREACION
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios 570

Carrera 13 No. 27-00 Piso 6, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Industria y Comercio
SUPERINTENDENCIA

Folio 572

2020
Bogotá D.C.,

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
SANOFI - AVENTIS

REFERENCIA	Radicación No.	9 107316
	Solicitud internacional	PCT/US2008/058347
	Fecha inicio fase nacional	30/10/2009
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	9333
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 23 NOV. 2009

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

adpa11