Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 03-23288

54. **TÍTULO** DERIVADOS DE PIRIDINA CON ACTIVIDAD INHIBIDORA DE QUINASA IKB (IKK-BETA)

51. **CLASIFICACIÓN INTERNACIONAL** C07D 401/04, A61K31/44

71. **SOLICITANTE** BAYER AKTIENGESELLSCHAFT

DOMICILIO LEVERKUSEN, ALEMANIA

74 **APODERADO** EMILIO FERRERO
código No. 1002

22. **BOGOTÁ, D. C.,**

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA 03 023288 00

PETITORIO

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03023288 00002000 Folios: 485 Jón
Fecha (ANO): 2003-12-19 17:43:16
Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Observaciones: PARA DIVISION DE NUEVAS SOLICITUDES

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 **S LICITANTE (71)**	Nombre: **BAYER AKTIENGESELLSCHAFT** sociedad constituida y existente bajo las leyes de la República Federal de Alemania. Dirección: 51368 Leverkusen, República Federal de Alemania Domicilio: Leverkusen, República Federal de Alemania.	**IDENTIFICACI N** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número: _____
3 **REPRESENTANTE O APODERADO**	Nombre: EMILIO FERRERO Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 36 11 Fax:: 217 92 11 E-mail: clientes@camyp.com. Domicilio: Bogotá, Colombia.	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número: 438.019 T.P. 31.929

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5 **PCT (86)**

Solicitud Internacional No. PCT/EP01/10405 Fecha: 10 de septiembre de 2001

Publicación Internacional No. WO 02/24679 A1 Fecha : 28 de marzo de 2002

6 **Título (54)** DERIVADOS DE PIRIDINA CON ACTIVIDAD INHIBIDORA DE QUINASA IKB(IKK-BETA).

7 **Clasificación Internacional (51)** C07D 401/04 , A61K 31/44, (C07D 401/04)

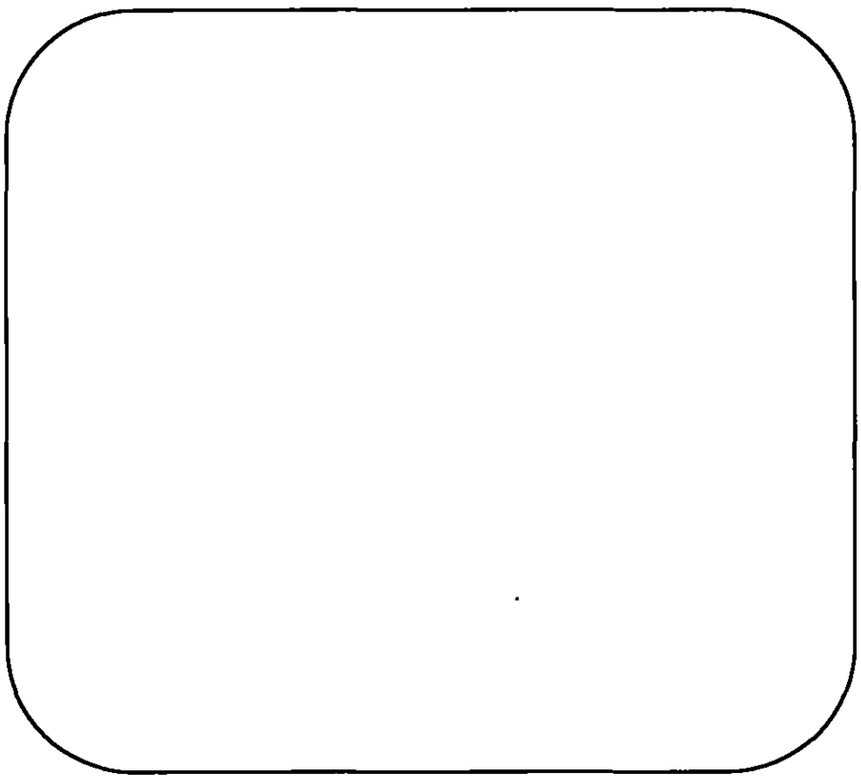
8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	JP.	22 de septiembre de 2000	2000-289173

9 **Comprobante de pago No.:** 03 – 19.443 **Fecha:** 17 de marzo de 2003

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 400.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11 **FIGURA CARACTERISTICA:**



12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA :

C.C. 438.019 de Usaquén T.P. 31.929

MRE/mrm-ld-1263

4

0698
6028

CONSULADO DE COLOMBIA

C E R T I F I C A C I O N

No. 145

Bonn, 8 de agosto de 1996

El suscrito Segundo Secretario Encargado de las Funciones Consulares de Colombia en Bonn, vistos los documentos presentados por los interesados, CERTIFICA: Que el señor Dirk Heiderhoff quien como Notario en Leverkusen autenticó la firma de los signatarios DR. ROLF BRAUN y DR. JOACHIM GREMM del documento precedente, ejercían en la fecha las funciones indicadas y su firma corresponde a la registrada en este Consulado; que la empresa BAYER AKTIENGESELLSCHAFT está constituida de acuerdo con las leyes de la República Federal de Alemania y cumple su objeto conforme a las mismas según el Registro Comercial HRB 1122 del Tribunal de Primera Instancia de Leverkusen; que los señores BRAUN y GREMM, quienes firmaron el documento precedente, son los representantes legales de la empresa arriba mencionada.

El suscrito Segundo Secretario Encargado de las Funciones Consulares no asume responsabilidad alguna por el contenido del documento.

Pagado el impuesto de timbre
y derechos consulares.
Valor US$106,oo = DM$169,60

JUAN PABLO GONZALEZ
Segundo Secretario
Encargado de las Funciones Consulares

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

18 MAR 2003

JUAN MANUEL BOTERO MEDINA
NOTARIO

Resolución No. 509 Minjusticia

NO SE ASUME RESPONSABILIDAD DEL TEXTO

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

1996 AGO 23 A 11:56

COPIA FIRMA ARTICULO EX DOCUMENTO DESCRIPCION LAS FUNCIONES INDICADAS

EXTENDIDOS

N, L, K

5

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

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

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

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

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

of/domiciliado (s) en D-51368 Leverkusen, GERMANY,

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

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

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

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

Given and signed this/Dado y firmado hoy
31st July 1996

in/en Leverkusen
BAYER AKTIENGESELLSCHAFT

Signature/Firma

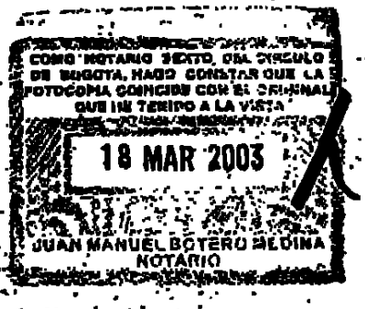
CAVELIER ABOGADOS
WPPODERE-1 (MINUTA Nº 12.1.1.2.5)

LEGALIZACION

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

LEGALIZATION

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



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

URNr. 1799/1996

Ich beglaubige die vor mir vollzogenen Unterschriften der Herren :

1. Dr. Rolf Braun, geschäftsansässig in D 51368 Leverkusen, Bayerwerk,

2. Dr. Joachim Gremm , geschäftsansässig in D 51368 Leverkusen, Bayerwerk,

- persönlich bekannt -.

Ich bescheinige aufgrund Einsicht vom heutigen Tage in das Handelsregister des Amtsgerichts Leverkusen - HRB 1122 -, daß die genannten Herren berechtigt sind, die Bayer Aktiengesellschaft in Leverkusen als Prokuristen gemeinschaftlich zu vertreten.

Leverkusen, den 31. Juli 1996

Notar

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
18 MAR 2003
JUAN MANUEL GUTIERREZ MEDINA NOTARIO

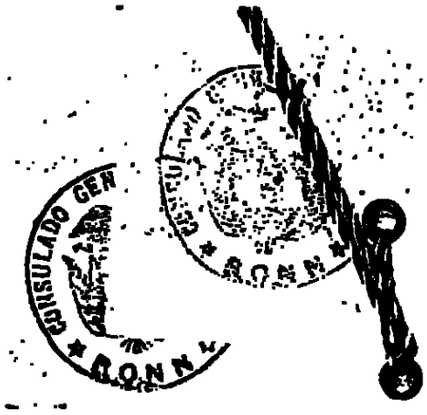
Die Echtheit der vorstehenden Unterschrift des Notars Dirk Schiedlausky in Leverkusen sowie die Echtheit des beigedrückten Dienstsiegels - siegels werden hiermit bestätigt. Zugleich wird bescheinigt, daß der Notar zur Vornahme der Amtshandlung befugt war.

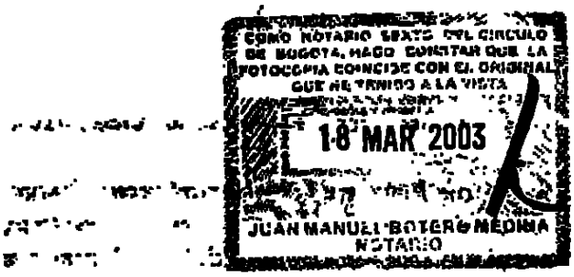
Köln, den 02. Aug. 1996

Der Präsident des Landgerichts

Dr. Wahlrich

DER PRÄSIDENT DES AMTSGERICHTS KÖLN 6


CONSULADO GEN
BONN


COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
18 MAR 2003
JUAN MANUEL BOTERO MEDINA
NOTARIO



7

TRADUCCION OFICIAL No. 5424

de un documento escrito en Alemán, el cual para su identificación se sella con el sello de la traductora, lo mismo que la presente.-

---

(A continuación de la representación y poder conferido a GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO tpa, 31929; y LUZ CLEMENCIA DE PAEZ, tpa 23555, domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia, el 31 de julio de 1996 por los señores Dr. Rolf Braun y Dr. Joachim Gremm, apoderados de la Bayer Aktiengesellschaft, Leverkusen, RFA:)

Protocolo notarial 1799/1996

Certifico la autenticidad de las firmas puestas ante mi por los señores

1. Dr. Rolf Braun, domiciliado en D 51368 Leverkusen, Bayerwerk,

2. Dr. Joachim Gremm, domiciliado en D 51368 Leverkusen, Bayerwerk,

- a quienes conozco en persona-.

COMO NOTARIO SEXTO DE LEVERKUSEN, DOY FE Y TESTIMONIO QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

6 MAR 2003

JUAN MANUEL BOTERO MEDINA
NOTARIO

Certifico por haber tenido a la vista el Registro de Comercio del Juzgado Municipal de Leverkusen - HRB 1122 - que los señores mencionados están facultados, en su calidad de apoderados, para representar conjuntamente a la Bayer Aktiengesellschaft, domiciliada en Leverkusen.

Leverkusen, 31 de julio de 1996

Fdo.: firma ilegible

Notario

(Hilo y oblea notarial en relieve:)

Dirke Heiderhoff - Notario de Leverkusen

(dorso:)

Se certifica la autenticidad de la firma antecedente del notario de Leverkusen, Dirke Heiderhoff, y la del sello oficial que la acompaña. Igualmente se certifica que el mencionado notario estaba facultado para realizar ese acto oficial.

Colonia, 02 de agosto de 1996

El Presidente del Juzgado Municipal

Fdo.: firma ilegible

(Dr. Wohlmich)

(sello redondo en tinata:)

El Presidente del Juzgado Municipal de Colonia

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, DAGO CONSTAR QUE LA FOTOCOPIA CORRESPONDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
MAR 2003
JUAN MANUEL BOTERO MEDINA NOTARIO

EN ESPAÑOL: La legalización de las firmas antecedentes por el Consulado de Colombia en Bonn bajo el No. 145 del 08 de agosto de 1996 y por el Ministerio de Relaciones Exteriores de Colombia bajo el No. 198692 del 23 de agosto de 1996.
Pagados Impuesto de timbre y derechos consulares US$ 106,--

ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los archivos de estas oficinas para su confrontación.

Santafé de Bogotá, 2 de septiembre de 1996

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR QUE LA FIRMA DE
C. C.
COINCIDE CON LA REGISTRADA POR EL (ELLOS)
EN ESTA NOTARIA. 09 SET. 1996

SANTAFE DE BOGOTA, D.C.

Juan Manuel Botero Medina
Notario Sexto de Bogotá

CUYA FIRMA APARECE EN EL DOCUMENTO DESCRITO EN LAS FUNCIONES INDICADAS.

MINISTERIO DE RELACIONES EXTERIORES
2053948

NO SE ASUME RESPONSABILIDAD DEL TEXTO
DEPENDENCIA DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

3

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE SE TUVO A LA VISTA
18 MAR 2003
JUAN MANUEL BOTERO MEDINA
NOTARIO

CAVELIER
ABOGADOS

TELEFAX (57)(1) 2368850
CABLES CAVELEYES
TELEX: 45479

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

CORREO ELECTRONICO MUNDIAL: CAVE
TELEFONO: (57) (1) 2120100

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

Poderdante: BAYER AKTIENGESELLSCHAFT

Poder conferido el: 31-07-96

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

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

Señor Jefe,

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

Acepto:

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

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
18 MAR 2003
JUAN MANUEL [illegible] MEDINA
NOTARIO

2e-780-2

NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

Santafé de Bogotá D. C. 06 SET 1996

Ante Mí JUAN MANUEL BOTERO MEDINA

NOTARIO SEXTO DEL CIRCULO DE BOGOTA

Compareció(eron) personalmente

Carlos Cortés

Guido Leon

quien(es) exhibió(eron) la(s) C. C

41 8019

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

2877904

97852 TT 81929

domiciliado(s) en Bogotá, y declaró(aron) que la(s) firma(s) que aparece(n) en el presente documento es(son) la(s) suya(s) y que el contenido es cierto.

En constancia se firma esta diligencia.

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

18 MAR 2003

JUAN MANUEL BOTERO MEDINA
NOTARIO

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 March 2002 (28.03.2002)

PCT

(10) International Publication Number
WO 02/24679 A1

not. J;

(51) International Patent Classification[7]: C07D 401/04, 213/85, 401/14, 409/14, 401/06, 413/14, 405/14, 471/04, A61P 17/00, 11/06, 29/00, A61K 31/4427, 31/4353, C07D 471/18, 498/04, 213/80, 213/73, 521/00, 513/04

(21) International Application Number: PCT/EP01/10405

(22) International Filing Date:
10 September 2001 (10.09.2001)

(25) Filing Language: English

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(54) Title: PYRIDINE DERIVATIVES WITH IKB-KINASE (IKK-β) INHIBITING ACTIVITY

(57) Abstract: Pyridine compounds of general formula (I) wherein -R^1 represents, or in which R^{11} is hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-12} alkoxy, nitro, amino, C_{1-6} alkylsulfonylamino, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di (C_{1-6} alkyl)amino, C_{1-6} alkanoylamino, phenyl C_{1-6} alkylamino, phenylsulfonylamino, or -O-$(CH_2)_n$-R^{111} ; R^2 represents hydrogen or halogen; R^3 represents hydrogen, -$CR^{31}R^{32}R^{33}$, or -$NR^{34}R^{35}$; R^4 is hydrogen, carbamoyl, CN, carboxyl, etc.; R^5 is amino, C_{1-6} alkylamino, di C_{1-6} alkylamino, etc. or salt thereof. The compound has an excellent anti-inflammatory activity, and other biological activity.

PYRIDINE DERIVATIVES WITH IKB-KINASE (IKK-BETA) INHIBITING ACTIVITY

TECHNICAL FIELD

The present invention relates to novel pyridine derivatives, processes for preparing them and pharmaceutical preparations containing them. The pyridine derivatives of the present invention inhibit IκB kinase β (IKK-β or IKK-beta) activity, thus inhibit nuclear factor kappa B (NF-κB) activity, and can be used for the prophylaxis and treatment of diseases associated with NF-κB activity, in particular for the treatment of inflammatory diseases.

BACKGROUND ART

Nuclear factor kappa B (NF-κB) belongs to a family of closely related homo-and hetero- dimeric transcription factor complexes composed of various combinations of the Rel/NF-κB family of polypeptides. NF-κB and related family members are involved in the regulation of more than 50 genes relating to immune and inflammatory responses ((Barnes PJ, Karin M (1997) N Engl J Med 336, 1066-1071) and (Baeuerle PA, Baichwal VR (1997) Adv Immunol 65, 111-137)). In most cell types, NF-κB is present as a heterodimer comprising a 50 kDa and a 65 kDa subunit (p50/RelA). The heterodimer is sequestered in the cytoplasm in association with inhibitor of NF- B (IκB)-family of proteins to be kept in an inactive state. IκB-family proteins mask the nuclear translocation signal of NF-κB. Upon stimulation of cells with various cytokines (e.g. TNF-α, IL-1), CD40 ligand, lipopolysaccharide (LPS), oxidants, mitogens (e.g. phorbol ester), viruses or many others. IκB proteins are phosphorylated at specific serine residues, poly-ubiquitinated, and then degraded through a proteasome-dependent pathway. Freed from IκB, the active NF-κB is able to translocate to the nucleus where it binds in a selective manner to preferred gene-

specific enhancer sequences. Among the genes being regulated by NF-κB are many coding for pro-inflammatory mediators, cytokines, cell adhesion molecules, and acute phase proteins. Expression of several of these cytokines and mediators in turn can lead to further activation of NF-κB via autocrine and paracrine mechanisms.

Broad evidence is available that suggests a central role of NF-κB in many inflammatory disorders including airway inflammation and asthma ((Yang L et al., J Exp Med 188 (1998), 1739-1750), (Hart LA et al. Am J Respir Crit Care Med 158 (1998), 1585-1592), (Stacey MA et al., Biochem Biophys Res Commun 236 (1997), 522-526) (Barnes P and Adcock IM, Trends Pharmacol Sci 18 (1997), 46-50)).

Further, it has been shown that glucocorticoids, which are by far the most effective treatment for asthma, inhibit airway inflammation by directly interacting with and inhibiting the activity of the transcription factors NF-κB and activating peptide-1 (AP-1) ((Barnes P (1997) Pulmon Pharmacol Therapeut 10, 3-19) and (Dumont A et al. (1998) Trends Biochem Sci 23, 233-235)).

In general, inhibition of NF-κB activation results in strong anti-inflammatory effects similar or superior to those brought upon by steroids. Consequently, NF- B inhibition should improve inflammatory symptoms typical for asthma; allergic rhinitis; atopic dermatitis; hives; conjunctivitis; vernal catarrh; rheumatoid arthritis; systemic lupus erythematosus; psoriasis; diabrotic colitis; systemic inflammatory response syndrome; sepsis; polymyositis; dermatomyositis; Polyaritis nodoa; mixed connective tissue disease; Sjoegren's syndrome; gout, and the like.

Further, several studies imply that NF-κB plays an essential role in neoplastic transformation. For example, NF-κB is associated with cell transformation in vitro and in vivo as a result of gene overexpression, amplification, rearrangement, or translocation (Mercurio, F., and Manning, A.M. (1999) Oncogene, 18:6163-6171). In certain human lymphoid tumor cells, the genes of NF-κB family members are rearranged or amplified. Its possible involvement in cancer pathology is also

disclosed in Mayo, M.W., Baldwin A.S. (2000) Biochmica et Biophysica Acta 1470 M55-M62. Mayo M.W. et al., discloses the inhibition of NF-κB results in the blockage the initiation and/or progression of certain cancer, particularly colorectal cancer.

Finally, NF-κB may also be involved in the regulation of neuronal cell death. It has been shown that NF-κB becomes activated and promotes cell death in focal cerebral ischemia (Nature medicine Vol. 5 No. 5, May 1999).

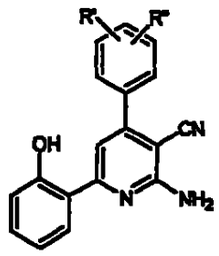
Extensive research during the past years led to the identification of an IκB kinase (IKK) complex as being responsible for the signal-induced IκB phosphorylation ((Mercurio, F., and Manning, A.M. (1999) Current Opinion in Cell Biology, 11:226-232), (Mercurio, F., and Manning, A.M. (1999) Oncogene, 18:6163-6171), (Barnkett, M., and Gilmore T.D. (1999) Oncogene 18, 6910-6924), (Zandi, E., and Karin, M., (1999) 19:4547-4551), (Israel, A., (2000) trends in CELL BIOLOGY 10:129-133), and (Hatada, E.N, et al. (2000) Current Opinion in Immunology, 12:52-58)). This complex is most likely the site of integration of all of the different stimuli leading to NF-κB activation. The IKK-complex (molecular weight 700 – 900 kDa) is composed of various proteins including two homologous IκB kinases, called IKK-α and IKK-β, an upstream kinase, NIK which induces NF-κB, a scaffold protein called IKAP, which tethers together the three kinases, and a regulatory subunit IKK-γ, which preferentially interacts with IKK-β.

IKK-β is a 756 amino acid serine-threonine kinase showing 52 % identity to and the same domain structure as IKK-α ((Mercurio F *et al.* (1997) Science 278, 860-866.), (Woronicz JD *et al.* (1997) Science 278, 866-869.), (Zandi E *et al.* (1997) Cell 91, 243-252.). IKK-β forms homo-dimers and hetero-dimers with IKK-α *in vitro* and in cells, respectively. IKK-β also interacts with IKK-γ, IKAP, NIK and IκBα. Recombinant IKK-β phosphorylates IκBα and IκBβ at specific serine residues with equal efficacy (Li J *et al.* (1998) J Biol Chem 273, 30736-30741.), (Zandi E, Chen

Y, Karin M (1998) Science 281, 1360-1363.). IKK-β shows a higher constitutive kinase activity as compared to IKK-α. This is in agreement with data suggesting that over-expression of IKK-β activates the transcription of a NF-κB-dependent reporter gene with a higher efficacy as compared to IKK-α. IKK-β has been shown to be activated in various cell lines or fresh human cells in response to various stimuli including TNF-α, IL-1β, LPS, anti-CD3/anti-CD28 co-stimulation, protein kinase C and calcineurin, B-cell receptor/CD40 ligand stimulation, and vanadate. IKK-β is activated in fibroblast-like synoviocytes (FLS) isolated from the synovium of patients suffering from rheumatoid arthritis or osteoarthritis (Zandi E *et al.* (1997) Cell 91, 243-252.), (O'Connell MA *et al.* (1998) J Biol Chem 273, 30410-30414.), (Kempiak SJ *et al.* (1999) J Immunol 162, 3176-3187.). Furthermore, IKK-β can be activated by the structurally related upstream kinases MEKK-1 and NIK, most likely through phosphorylation of specific serine residues within the T-loop (activation loop) and by certain protein kinase C isoforms ((Nakano H *et al.* (1998) Proc Natl Acad Sci USA 95, 3537-3542.), (Lee FS *et al.* (1998) Proc Natl Acad Sci USA 95, 9319-9324.), (Nemoto S *et al.* (1998) Mol Cell Biol 18, 7336-7343.), (Lallena MJ *et al.* (1999) Mol Cell Biol 19, 2180-2188.)). A catalytically inactive mutant of IKK-β has been shown to inhibit activation of NF-κB by TNF-α, IL-1β, LPS, anti-CD3/anti-CD28 stimulation ((Mercurio F *et al.* (1997) Science 278, 860-866.), (Woronicz JD *et al.* (1997) Science 278, 866-869.)). The same effects are observed when MEKK1 or NIK are overexpressed. Additionally, IKK-β mutations in the activation loop inhibited IL-1 and TNF-α signaling (Delhase M *et al.* (1999) Science 284, 309-313.). Based on the experimental results described above, there is clear-cut evidence for a pivotal involvement of IKK-β in various pathways leading to NF-κB activation.

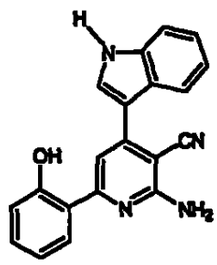
In summary, the specific inhibition of IKK-β should result in a strong anti-inflammatory and immuno-modulatory effect *in vivo* with the potential of improving the underlying causes of asthma and other diseases. In addition, anti-tumor and anti-ischemic effects of an IKK-β inhibitor may be expected.

Manna et al., disclose 4,6-disubstituted 3-cyano-2-aminopyridines represented by general formulas:



wherein (R', R") represent (OCH_3, OCH_3), (Cl, Cl), (H, Cl), (H, Br), (H, CH_3), (H, OCH_3), (H, NO_2), or (H, $N(CH_3)_2$),

or



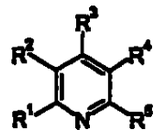
as a general anti-inflammatory, analgesic, and antipyretic agent (Eur J. Med. Chem. 34, 245-254(1999)).

Manna et al. neither disclose pyridine derivatives with aliphatic groups at position 4 of the pyridine ring, nor suggest IKK-β kinase or NF-κB inhibitory activity on the above known pyridine derivatives.

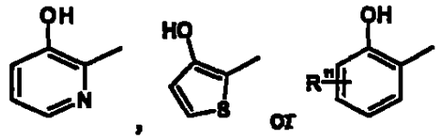
The development of a novel compound having effective anti-inflammatory actions based on a specific and selective inhibitory activity to NF-κB has been desired.

SUMMARY OF THE INVENTION

As the result of extensive studies on chemical modification of pyridine derivatives, the present inventors have found that the compound of novel chemical structure related to the present invention have unexpectedly excellent IKK-β kinase inhibitory activity. This invention is to provide the following general formula (I) and the salts thereof:



wherein $-R^1$ represents



in which R^{11} is hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-12} alkoxy, nitro, amino, C_{1-6} alkylsulfonylamino, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di (C_{1-6} alkyl)amino, C_{1-6} alkanoylamino, phenyl C_{1-6} alkylamino, phenylsulfonylamino, or $-O-(CH_2)_n-R^{111}$,

wherein n represents an integer selected from 0 to 6, and R^{111} is C_{2-6} alkenyl, benzoyl, diphenylmethyl, di (C_{1-6} alkyl)amino, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, or a 3 to 10 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of S, O and N as heteroatoms and is optionally substituted by C_{1-6} alkyl, mono or di halogen, halogen substituted C_{1-6} alkyl, nitro, ciano, C_{1-6} alkoxycarbonyl, phenyl, hydroxy, amino, C_{1-6} alkylamino, di (C_{1-6} alkyl)amino, C_{1-6} alkanoylamino, C_{1-6} alkoxy, or carbamoyl;

R^2 represents hydrogen or halogen;

R^3 represents hydrogen or 1,2,3,6-Tetrahydro-pyridine,

$$-CR^{31}R^{32}R^{33},$$

wherein R^{31} is hydrogen or C_{1-6} alkyl,

R^{32} is hydrogen, α-aminobenzyl, C_{1-6} alkyl optionally substituted by one or two substituents selected from the group consisting of hydroxy, amino, amino substituted phenyl, phenyl, halogen substituted phenyl, and C_{1-6} alkoxy substituted phenyl, or a 5 to 8 membered saturated ring having 0 to 3 atoms selected from the group consisting of S, O and N as heteroatoms and optionally substituted by C_{1-6} alkyl, and

R^{33} is hydrogen, amino, C_{1-6} alkoxycarbonylamino, C_{2-6} alkenyloxycarbonylamino, piperidino-C_{1-6} alkylcarbonylamino, piperidinyl-C_{1-6} alkylcarbonylamino, or

R^{32} and R^{33} may form, together with the adjacent carbon atom, a 5 to 8 membered saturated ring having 0 to 3 heteroatoms selected from the group consisting of N, O and S as heteroatoms, which ring is optionally substituted by phenyl-C_{1-6} alkyl, C_{1-6} alkoxy substituted phenyl- C_{1-6} alkyl, C_{1-6} alkyl, amino, ciano, hydroxy, carbamoyl, carboxy, C_{1-6} alkylamino, C_{1-6} alkoxycarbonyl, di(C_{1-6} alkyl)amino, benzylamino, C_{1-6} alkylsulfonyl, piperidino C_{1-6} alkyl carbonyl, or optionally fused by benzene;

or

$$-NR^{34}R^{35},$$

wherein R^{34} is hydrogen or C_{1-6} alkyl and

R^{35} is hydrogen, a 5 to 8 membered saturated ring having 0 to 3 heteroatoms selected from the group consisting of N, O and S as heteroatoms, or $-(CH_2)_m-NR^{351}R^{352}$ (m represents any of integers from 1 to 6)

wherein R^{351} represents hydrogen, C_{1-6} alkyl,

R^{352} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkyl substituted phenyl, benzoyl, C_{1-6} alkanoyl, phenylaminocarbonyl, phenylsulfonyl, or

R^{34} and R^{35} may form, together with the adjacent N atom, a 5 to 8 membered saturated heterocyclic ring, and said ring may optionally contain NH, S or O atom other than the adjacent N atom and optionally substituted by carbamoyl, amino, or C_{1-6} alkyl;

R^4 represents hydroxycarbonyl, C_{1-6} alkanoyl, carbamoyl, nitro, cyano, carboxyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, C_{1-6} alkylamino, 5 to 10 membered heteroaryl (hydroxy) methyl, 5 to 10 membered heteroaryl-C_{1-6} alkyl, or methyl substituted by hydroxy and a 5 to 7 membered saturated cyclic ring, C_{1-6} alkyl optionally substituted by one selected from the group consisting of hydroxy, C_{1-6} alkoxy, C_{1-6} alkylsulfonylamino, C_{1-6} alkylcarbonylamino, C_{5-10} aryl, C_{5-10} arylsulfonyl, C_{5-10} arylsulfanyl, C_{5-10} aryloxy, imidazolyl, or dioxo substituted pyrolidino-oxy,

$$-(CH_2)_pNHCOR^{41}, -(CH_2)_pNHC(=S)R^{41}$$

wherein p represents any of integer from 1 to 6 and R^{41} represents C_{1-6} alkoxy, amino, phenylamino, C_{1-6} alkyl, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-10} cyclo-alkylamino,

R^3 and R^4 may form, together with the carbon atoms in the pyridine ring, 4 to 10 membered monocycloalkyl or bicycloalkyl optionally interrupted by NH and optionally substituted by benzyl, =NH, or =O;

R^5 represents $NR^{51}R^{52}$,

wherein R^{51} is hydrogen, C_{1-6} alkyl,

R^{52} is hydrogen, C_{1-6} alkyl, phenyl, benzyl, C_{1-6} alkanoyl, or NR51 R52 may form saturated 5-6 membered ring optionally contain NH or O as other heteroatom than the adjacent N atom,

or

R^4 and R^5 may form,

$-R^{40}-CO-NH-$,
$-R^{40}-SO_2-NH-$,
$-R^{40}-C(=S)-NH-$
$-R^{40}-CH_2-NH-$,

wherein said $-R^{40}-$ represents $-CHR^{401}-O-$, $-CH_2-N\ R^{401}-$, $-CO-NR^{401}-$, $-CH_2-CHR^{401}-$, $-CH=CR^{401}-$, (in which R^{401} is C_{1-6} alkanoyl, C_{1-6} alkyl, phenyl, C_{1-6} alkylsulfonyl, C_{3-8} cycloalkylaminocarbonyl, hydrogen, halogen; nitro, amino, ciano, benzoylamino, phenylsulfonyl, carbamoyl, hydroxycarbonyl, C_{1-6} alkoxycarbonyl, C_{1-12} alkylaminocarbonyl, halogen substituted C_{1-6} alkylaminocarbonyl, C_{1-6} alkanoylamino, C_{1-6} alkylamino, di(C_{1-6} alkyl)aminocarbonyl, di(C_{1-6} alkyl)aminoC_{1-6} alkylaminocarbonyl, hydroindenylaminocarbonyl, diphenylmethylaminocarbonyl, pyrrolidinocarbonyl, C_{1-6} alkoxy C_{1-6} alkyl amino carbonyl, morpholinocarbonyl, piperazinocarbonyl, phenylC_{1-6}alkylaminocarbonyl, hydroxycarbonylC_{1-6}alkyl-aminocarbonyl, C_{3-8} cycloalkylaminocarbonyl, C_{3-8} cycloalkylC_{1-6}alkylamino-carbonyl, hydroxyC_{1-6}alkylaminocarbonyl, carboxyethylaminocarbonyl, C_{1-6}alkyl-sulfonylaminocarbonyl)

$-CR^{41}=N-NH-$ (R^{41} is hydrogen, amino, or C_{1-6}alkanoylamino),
$-CR^{42}=N-C=N-$ (R^{42} is hydrogen or amino).

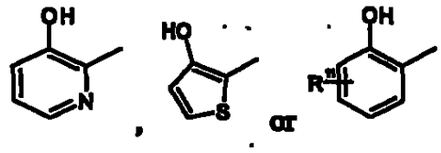
The compounds of the present invention surprisingly show excellent IKK-β kinase inhibitory activity and cytokine inhibitory activity. They are, therefore suitable especially as NF-κB inhibitors and in particular for the production of medicament or medical composition, which may be useful to treat NF-κB dependent diseases.

More specifically, since the pyridine derivatives of the present invention inhibit IKK-β kinase activity, they are useful for treatment and prophylaxis of diseases involving NF-κB activity as follows: inflammatory symptoms including asthma; allergic rhinitis; atopic dermatitis; hives; conjunctivitis; vernal catarrh; chronic arthrorheumatism; systemic lupus erythematosus; psoriasis; diabrotic colitis; systemic inflammatory response syndrome (SIRS); sepsis; polymyositis; dermatomyositis (DM); Polyaritis nodoa (PN); mixed connective tissue disease (MCTD); Sjoegren's syndrome; gout; and the like.

The compounds of the present invention are also useful for treatment and prophylaxis of diseases like ischemia and tumor, since the diseases also relate to IKK-β kinase and NF-κB activity.

Preferred compounds of formula (I) are those wherein:

$-R^1$ represents



in which R^{11} is hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-12} alkoxy, amino, C_{1-6} alkanoylamino, phenyl C_{1-6} alkylamino, phenylsulfonylamino, or $-O-(CH_2)_n-R^{111}$,

wherein n represents an integer selected from 1 to 6, and R^{111} is C_{2-6} alkenyl, benzoyl, diphenylmethyl, di (C_{1-6} alkyl)amino, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, or a 3 to 10 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of S, O and N as heteroatoms and is optionally substituted by C_{1-6} alkyl, mono or di halogen, halogen substituted C_{1-6} alkyl, nitro, ciano, C_{1-6} alkoxycarbonyl, phenyl;

R^2 represents hydrogen;

R^3 represents hydrogen, 1,2,3,6-tetrahydro-pyridine

$$-CR^{31}R^{32}R^{33},$$

wherein R^{31} is hydrogen or C_{1-6} alkyl,

R^{32} is hydrogen, α-aminobenzyl, C_{1-6} alkyl optionally substituted by one or two substituents selected from the group consisting of hydroxy, amino, amino substituted phenyl, phenyl, halogen substituted phenyl, and C_{1-6} alkoxysubstituted phenyl, or a 5 to 8 membered saturated ring having 0 to 3 atoms selected from the group consisting of S, O and N as heteroatoms and optionally substituted by C_{1-6} alkyl, and

R^{33} is hydrogen, amino, C_{1-6} alkoxycarbonylamino, C_{2-6} alkenyloxycarbonylamino, piperidino-C_{1-6} alkylcarbonylamino, or

R^{32} and R^{33} may form, together with the adjacent carbon atom, a 5 to 8 membered saturated ring having 0 to 3 heteroatoms selected from the group consisting of N, O and S as heteroatoms, which ring is optionally substituted by phenyl-C_{1-6} alkyl, C_{1-6} alkoxy substituted phenyl- C_{1-6} alkyl, C_{1-6} alkyl, amino, carboxy, C_{1-6} alkylamino, C_{1-6} alkoxycarbonyl, di(C_{1-6} alkyl)amino, benzylamino, C_{1-6} alkylsulfonyl, piperidino C_{1-6} alkyl carbonyl, or optionally fused by benzene;

or

$-NR^{34}R^{35}$,

wherein R^{34} is hydrogen and

R^{35} is hydrogen, a 5 to 8 membered saturated ring having 0 to 3 heteroatoms selected from the group consisting of N, O and S as heteroatoms, or $-(CH_2)_m-NR^{351}R^{352}$(m represents any of integers from 1 to 6)

wherein R^{351} represents hydrogen, C_{1-6} alkyl,

R^{352} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsubstituted phenyl, benzoyl, C_{1-6} alkanoyl, phenylaminocarbonyl, phenylsulfonyl, or

R^{34} and R^{35} may form, together with the adjacent N atom, a 5 to 8 membered saturated heterocyclic ring, and said ring may optionally contain NH, S or O atom other than the adjacent N atom and optionally substituted by carbamoyl, amino, or C_{1-6} alkyl;

R^4 represents hydroxycarbonyl, C_{1-6} alkanoyl, carbamoyl, cyano, carboxyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, C_{1-6} alkylamino, 5 to 10 membered heteroaryl (hydroxy) methyl, 5 to 10 membered heteroaryl-C_{1-6} alkyl, or methyl substituted by hydroxy and a 5 to 7 membered saturated cyclic ring, C_{1-6} alkyl optionally substituted by one selected from the group consisting of hydroxy, C_{1-6} alkoxy, C_{1-6} alkylsulfonylamino, C_{1-6} alkylcarbonylamino, C_{5-10} aryl, C_{5-10} arylsulfanyl, C_{5-10} arylsulfenyl, C_{5-10} aryloxy, imidazolyl, or dioxo substituted pyrolidino-oxy,

$-(CH_2)_pNHCOR^{41}$, $-(CH_2)_pNHC(=S)R^{41}$

wherein p represents any of integer from 1 to 6

and R^{41} represents C_{1-6} alkoxy, amino, phenylamino, C_{1-6} alkyl, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-10} cycloalkylamino,

R^3 and R^4 may form, together with the carbon atoms in the pyridine ring, 4 to 10 membered monocycloalkyl or bicycloalkyl optionally interrupted by NH and optionally substituted by benzyl, =NH, or =O;

R^5 represents $NR^{51}R^{52}$,

wherein R^{51} is hydrogen, C_{1-6} alkyl,

R^{52} is hydrogen, C_{1-6} alkyl, phenyl, benzyl, C_{1-6} alkanoyl, or NR^{51} R^{52} may form piperidino,

or

R^4 and R^5 may form,

$-R^{40}-CO-NH-$, $-R^{40}-SO_2-NH-$,
$-R^{40}-C(=S)-NH-$ or
$-R^{40}-CH_2-NH-$,

wherein said $-R^{40}-$ represents $-CHR^{401}-O-$, $-CH_2-N\ R^{401}-$, $-CO-NR^{401}-$, (in which R^{401} is hydrogen, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkyl, phenyl, C_{1-6} alkylsulfonyl, C_{3-8} cycloalkylaminocarbonyl, C_{1-6} alkylaminocarbonyl, carbamoyl, di (C_{1-6} alkyl)aminocarbonyl), $-CH_2-CHR^{402}-$, $-CH=CR^{402}-$, (in which R^{402} is hydrogen, halogen, nitro, amino, ciano, benzoylamino, phenylsulfonyl, carbamoyl, hydroxycarbonyl, C_{1-6} alkoxycarbonyl, C_{1-12} alkylaminocarbonyl, halogen substituted C_{1-6} alkylaminocarbonyl, C_{1-6} alkanoylamino, C_{1-6} alkylamino, di(C_{1-6} alkyl)aminocarbonyl, di(C_{1-6} alkyl)aminoC_{1-6} alkylaminocarbonyl,

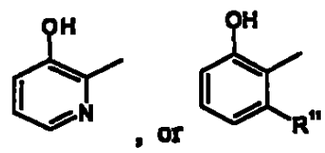
hydroindenylaminocarbonyl, diphenylmethylaminocarbonyl, pyrrolidinocarbonyl, C_{1-6} alkoxy C_{1-6} alkyl amino carbonyl, morpholinocarbonyl, piperazinocarbonyl, phenylC_{1-6}alkylaminocarbonyl, C_{3-8} cycloalkylaminocarbonyl, hydroxycarbonylC_{1-6}alkylaminocarbonyl, C_{3-8} cycloalkylC_{1-6}alkylaminocarbonyl, hydroxyC_{1-6}alkylaminocarbonyl, carboxyethylaminocarbonyl, methylsulfonylaminocarbonyl,)

$-CR^{41}=N-NH-$ (R^{41} is hydroxy, amino, C_{1-6}alkanoylamino) or
$-CR^{42}=N-C=N-$ (R^{42} is amino)

or a salt thereof.

More preferred compound of formula (I) are those wherein:

$-R^1$ represents



in which R^{11} is hydrogen, C_{1-12} alkoxy, or $-O-(CH_2)_n-R^{111}$,

wherein n represents an integer selected from 1 to 6, and R^{111} is phenyl, C_{3-8} cycloalkyl;

R^2 represents hydrogen;

R^3 represents 1,2,3,6-tetrahydro-pyridine,

$-CR^{31}R^{32}R^{33}$,

wherein R^{31} is hydrogen,

and

R^{32} and R^{33} form, together with the adjacent carbon atom, a 5 to 8 membered saturated ring interrupted by NH, which ring is optionally substituted by phenyl-C_{1-6} alkyl, C_{1-6} alkoxy substituted phenyl- C_{1-6} alkyl, C_{1-6} alkyl, amino, carboxy, C_{1-6} alkylamino, C_{1-6} alkoxycarbonyl, di(C_{1-6} alkyl)amino, benzylamino, C_{1-6} alkylsulfonyl, piperidino C_{1-6} alkyl carbonyl, or optionally fused by benzene;

or

$-NR^{34}R^{35}$,

wherein R^{34} is hydrogen and

R^{35} is $-(CH_2)_m-NR^{351}R^{352}$(m represents any of integers from 1 to 6)

wherein R^{351} represents hydrogen, C_{1-6} alkyl,

R^{352} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsubstituted phenyl, benzoyl, C_{1-6} alkanoyl, phenylaminocarbonyl, phenylsulfonyl; and

R^4 represents cyano, C_{1-6} alkyl optionally substituted by hydroxy or C_{1-6} alkoxy, or

$-(CH_2)_pNHCOR^{41}$, $-(CH_2)_pNHC(=S)R^{41}$

wherein p represents any of integer from 1 to 6 and R^{41} represents C_{1-6} alkoxy, amino, phenylamino, C_{1-6} alkyl, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-10} cycloalkylamino;

R^5 represents amino,

or

R^4 and R^5 may form,

$-R^{40}-CO-NH-$, $-R^{40}-SO_2-NH-$,
$-R^{40}-C(=S)-NH-$ or
$-R^{40}-CH_2-NH-$,

wherein said $-R^{40}-$ represents $-CHR^{401}-O-$, $-CH_2-N\ R^{401}-$, $-CO-NR^{401}-$, (in which R^{401} is hydrogen, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkyl, phenyl, C_{1-6} alkylsulfonyl, C_{3-8} cycloalkylaminocarbonyl, C_{1-6} alkylaminocarbonyl, carbamoyl, di(C_{1-6} alkyl)aminocarbonyl), $-CH_2-CHR^{402}-$, $-CH=CR^{402}-$, (in which R^{402} is hydrogen, halogen, nitro, amino, ciano, benzoylamino, phenylsulfonyl, carbamoyl, hydroxycarbonyl, C_{1-6} alkoxycarbonyl, C_{1-12} alkylaminocarbonyl, halogen substituted C_{1-6} alkylaminocarbonyl, C_{1-6} alkanoylamino, C_{1-6} alkylamino, di(C_{1-6} alkyl)aminocarbonyl, di(C_{1-6} alkyl)aminoC_{1-6} alkylaminocarbonyl, hydroindenylaminocarbonyl, diphenylmethylaminocarbonyl, pyrrolidinocarbonyl, C_{1-6} alkoxy C_{1-6} alkyl amino carbonyl, morpholinocarbonyl, piperazinocarbonyl, phenylC_{1-6}alkylaminocarbonyl, C_{3-8} cycloalkylaminocarbonyl, hydroxycarbonylC_{1-6}alkylaminocarbonyl, C_{3-8} cycloalkylC_{1-6}alkylaminocarbonyl, hydroxyC_{1-6}alkylaminocarbonyl, carboxyethylaminocarbonyl, methylsulfonylaminocarbonyl,)

$-CR^{41}=N-NH-$ (R^{41} is hydroxy, amino, C_{1-6}alkanoylamino) or
$-CR^{42}=N-C=N-$ (R^{42} is amino)

or a salt thereof.

The preferable compounds of the present invention are as follows or the salt thereof:

7-(2-hydroxyphenyl)-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one;

2-amino-6-[2-(benzyloxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinonitrile;
2-amino-6-(2-hydroxy-6-propoxyphenyl)-4-(3-piperidinyl)nicotinonitrile;
2-[6-amino-5-(hydroxymethyl)-4-(3-piperidinyl)-2-pyridinyl]-3-(benzyloxy)phenol;
7-[2-(benzyloxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3d][1,3]oxazin-2-one;
2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinonitrile trifluoroacetate;
7-(2-hydroxyphenyl)-5-(3-piperidinyl)-3,4-dihydro-1,8-naphthyridin-2(1H)-one;
2-amino-6-[2-(cyclobutylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinonitrile;
2-[6-amino-5-(hydroxymethyl)-4-(3-piperidinyl)-2-pyridinyl]-3-propoxyphenol;
7-(2-hydroxy-6-propoxyphenyl)-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3d][1,3]-oxazin-2-one;
ethyl 7-(2-hydroxy-6-propoxyphenyl)-2-oxo-5-(3-piperidinyl)-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate;
7-(2-hydroxy-6-propoxyphenyl)-5-(3-piperidinyl)-3,4-dihydro-1,8-naphthyridin-2(1H)-one;
2-[6-amino-5-(hydroxymethyl)-4-(3-piperidinyl)-2-pyridinyl]-3-(cyclopropyl-methoxy)phenol;
2-[6-amino-5-(hydroxymethyl)-4-(4-piperidinyl)-2-pyridinyl]-3-(cyclopropyl-methoxy)phenol;
7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-3,4-dihydro-1,8-naphthyridin-2(1H)-one;
ethyl 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate;
7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(4-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one;
6'-amino-5'-(hydroxymethyl)-4'-(3-piperidinyl)-2,2'-bipyridin-3-ol;
7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(4-piperidinyl)-3,4-dihydro-1,8-naphthyridin-2(1H)-one;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-fluoro-5-(3-piperidinyl)-1,8-naphthyridin-2(1H)-one;

7-(2-hydroxy-6-propoxyphenyl)-5-(4-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one;

3-(cyclopropylmethoxy)-2-[5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-7-yl]phenol;

2-[6-amino-5-(hydroxymethyl)-4-(3-piperidinyl)-2-pyridinyl]-3-(neopentyloxy)phenol;

2-[6'-amino-5'-(hydroxymethyl)-1,2,5,6-tetrahydro-3,4'-bipyridin-2'-yl]phenol;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-1,8-naphthyridin-2(1H)-one;

N-{[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methyl}acetamide;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,2-dihydro-1,8-naphthyridine-3-carboxamide;

3-acetyl-7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-one;

2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(4-piperidinyl)nicotinonitrile;

2-amino-4-[(2-aminoethyl)amino]-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]nicotinonitrile;

N-{[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methyl}-N'-propylurea;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-one;

ethyl [2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methylcarbamate;

2-amino-6-{2-hydroxy-6-[(4-methylpentyl)oxy]phenyl}-4-(4-piperidinyl)nicotinonitrile;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxamide;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-N-isopropyl-2-oxo-5-(3-piperidinyl)-1,2-dihydro-1,8-naphthyridine-3-carboxamide;

ethyl 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxylate;

N-{[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methyl}urea;

2-amino-6-(2-hydroxy-6-propoxyphenyl)-4-(4-piperidinyl)nicotinonitrile;

N-cyclohexyl-7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxamide;

2-amino-6-[2-(cyclobutylmethoxy)-6-hydroxyphenyl]-4-(4-piperidinyl)nicotinonitrile;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-N,N-dimethyl-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxamide;

2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(1-methyl-3-piperidinyl)nicotinonitrile;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydro-pyrido[2,3-d]pyrimidine-3(2H)-carboxamide;

isopropyl [2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methylcarbamate;

isopropyl 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxylate;

isobutyl 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxylate;

neopentyl 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxylate;

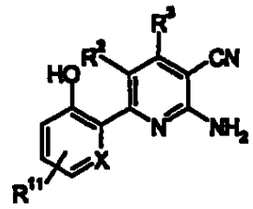
neopentyl [2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methylcarbamate;

2-amino-6-[2-(hexyloxy)-6-hydroxyphenyl]-4-(4-piperidinyl)nicotinonitrile; and

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-N-ethyl-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxamide

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by combining various known methods. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis (2nd Edition)" by Greene and Wuts.

The compound (I-a)

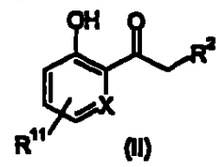


(I-a)

wherein X is CH or N, R^{11}, R^2, and R^3 are the same as defined,

or a salt thereof, can be prepared, for example, by the following reaction A.

The compound of the formula (II)

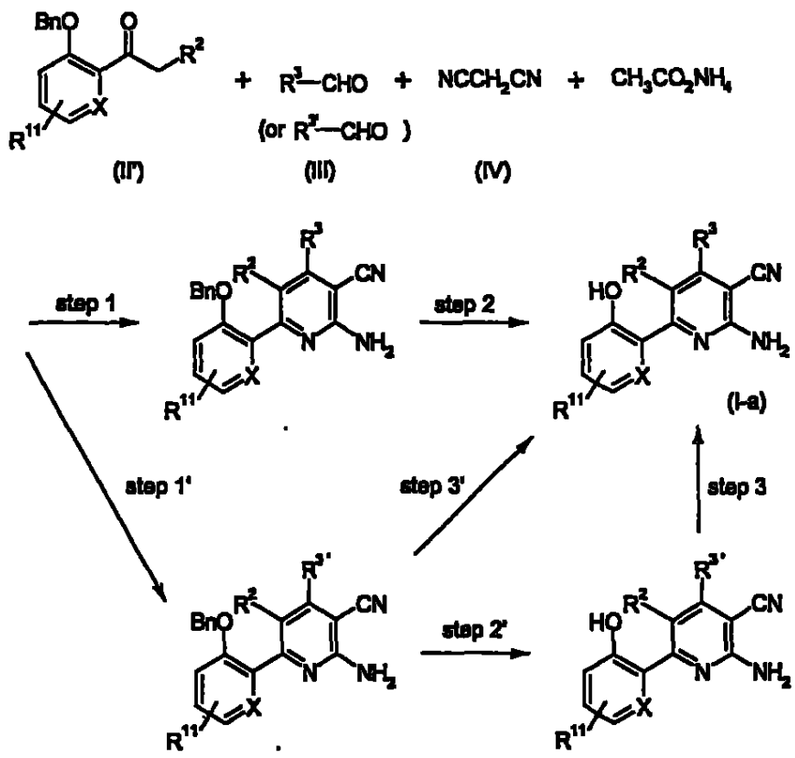


(II)

in which R^{11} and R^2 are the same as defined above,

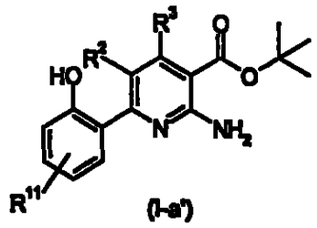
are reacted with an aldehyde of the formula R^3-CHO(III), a nitrile of the formula $NCCH_2CN$ (IV), and an ammonium salt such as ammonium acetate. R^3 is the same

as defined above. $R^{3'}$-CHO(III') can be advantageously used instead of R^3-CHO(III) in some instances. $R^{3'}$ can represent esterified R^3 by ethyl, tertiary butyl or the like: or other esters or other substituents which can be easily converted to R^3 by conventional methods. Hydroxyl group of the compound of the formula (II) is protected by an appropriate protecting group (e.g., benzyl, methoxybenzy, and silyl) during the reaction, and deprotected afterward. $R^{3'}$ can also be treated by acids to obtain R^3.



Reaction A

In the sketch above, CN at position C-3 can be replaced by carboxylates derived from tertiary alcohol, such as COOtBu with the use of $NCCH_2$-COOtBu (IV') instead of $NCCH_2CN$ (IV). In this case the following compound (I-a') can be obtained.



(I-a')

The step 1 and step 1' of the reaction A can be carried out without a solvent or in a solvent including, for instance, ethers, such as dioxane, and tetrahydrofuran; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as dimethylformamide (DMF) and dimethylacetamide; sulfoxides such as dimethyl sulfoxide, and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 50°C to 200°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

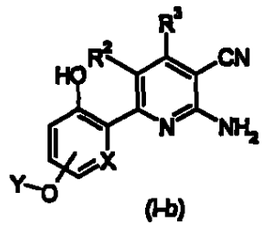
The compounds of the general formula (II), (III), (III') can be commercially available, or can be prepared by the use of known techniques.

Step 2 and step 2' of the reaction A can be carried out for example, under the hydrogen atmosphere with hydrogeneous catalysis, such as Pd-C in a solvent including, for instance, esters, such as ethyl acetate, ethers, such as dioxane, and tetrahydrofuran; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as dimethylformamide (DMF) and dimethylacetamide; sulfoxides such as dimethyl sulfoxide, and others.

The reaction temperature can be, but not limited to, about 50°C to 200°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

Step 3 and Step 3' of the reaction A can be any kind of conventional reaction starting from ester to obtain R^3, e.g., acid treatment, alkali treatment, amidation, and hydrogenation: or other reaction such as alkylation or the like to obtain R^3.

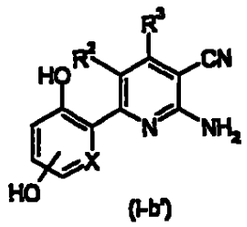
Alternatively, the compound (I-b)



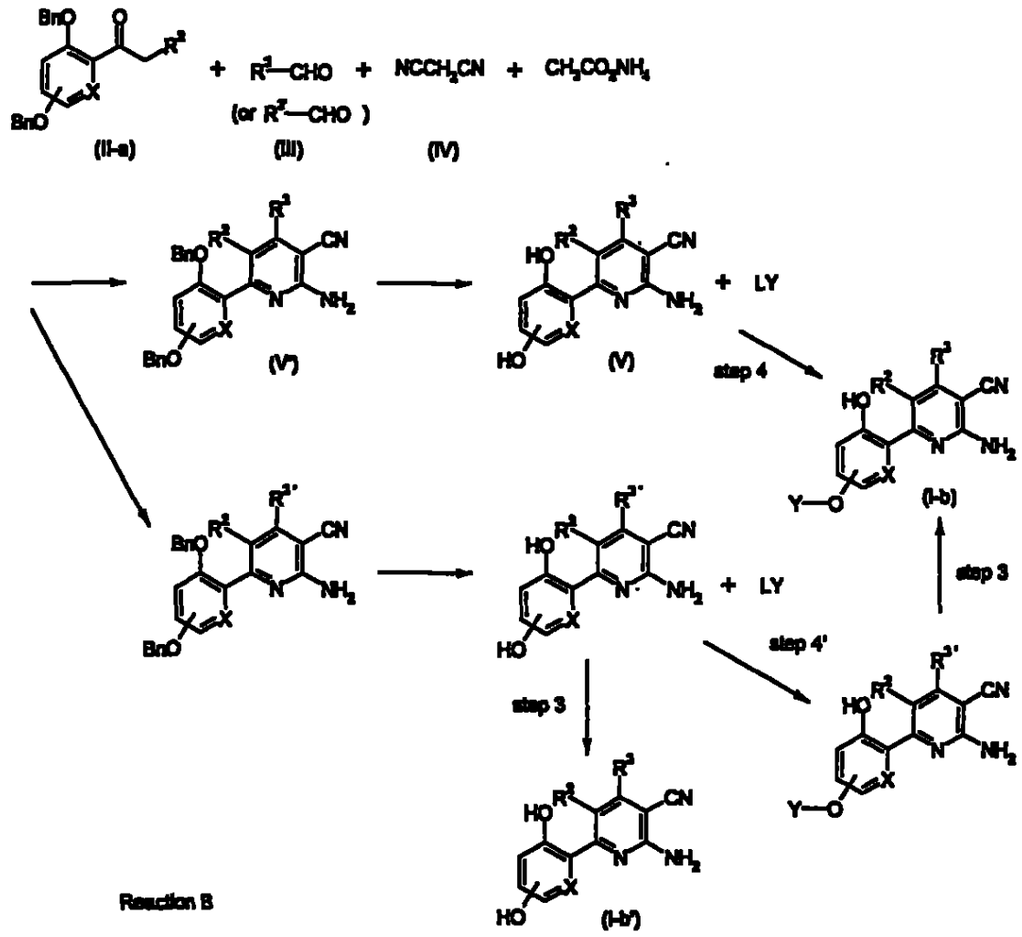
(I-b)

wherein X, R^2, and R^3 are the same as defined above and Y is C_{1-12} alkyl or R^{111}-$(CH_2)_n$-, in which R^{111} and n are the same as defined above, or a salt thereof can be obtained by the following reaction B.

The compound (I-b') can be also obtained in the reaction B.



(I-b')



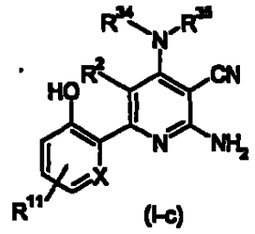
In reaction B, the compound of the formula (II-a) is reacted with an aldehyde (III), a nitrile (IV) and ammonium acetate under the same condition as the reaction A to obtain the compound of the formula (V'). The benzyl protecting groups in the compound of the general formula (II-a) can be replaced with any of appropriate protecting group. The protecting group is then removed after the reaction. In the step 4 of the reaction B, the compound (V) is reacted with L-Y, wherein L represents a leaving group, such as halogen atom e.g., chlorine, bromine or iodine atom; C_6-C_{10} arylsulfonyloxy group e.g. benzenesulfonyloxy, polysulfonyloxy, or p-toluene-sulfonyloxy; and C_1-C_4 alkylsulfonyloxy group, e.g. methanesulfonyloxy and the like. Y represents C_1-C_6 alkyl, or $-(CH_2)_n-R^{111}$ (wherein R^{111} is the same as defined above). The reaction with the compound (V) and L-Y can be carried out in a solvent including, for instance, alcohols such as methanol and ethanol; ethers, such as

dioxane, and tetrahydrofuran (THF); nitriles such as acetonitrile; amides such as dimethylformamide (DMF) and dimethylacetamide; sulfoxides such as dimethyl sulfoxide, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature of the reaction between compound (V) and L-Y can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about -10°C to 200°C and preferably about 10°C to 80°C. The reaction may be carried out for, usually, 30 minutes to 48 hrs and preferably 1 to 24 hrs. The reaction can be advantageously conducted in the presence of a base. Examples of the base include an alkali metal hydride such as sodium hydride or potassium hydride; alkali metal alkoxide such as sodium methoxide or sodium ethoxide; alkali metal hydroxide such as sodium hydroxide or potassium hydroxide; carbonates such as sodium carbonate or potassium carbonate, and hydrogen carbonates such as sodium hydrogen carbonate and potassium hydrogen carbonate; organic amines such as triethylamine.

The step 3 of the reaction B is the same as that of reaction A.

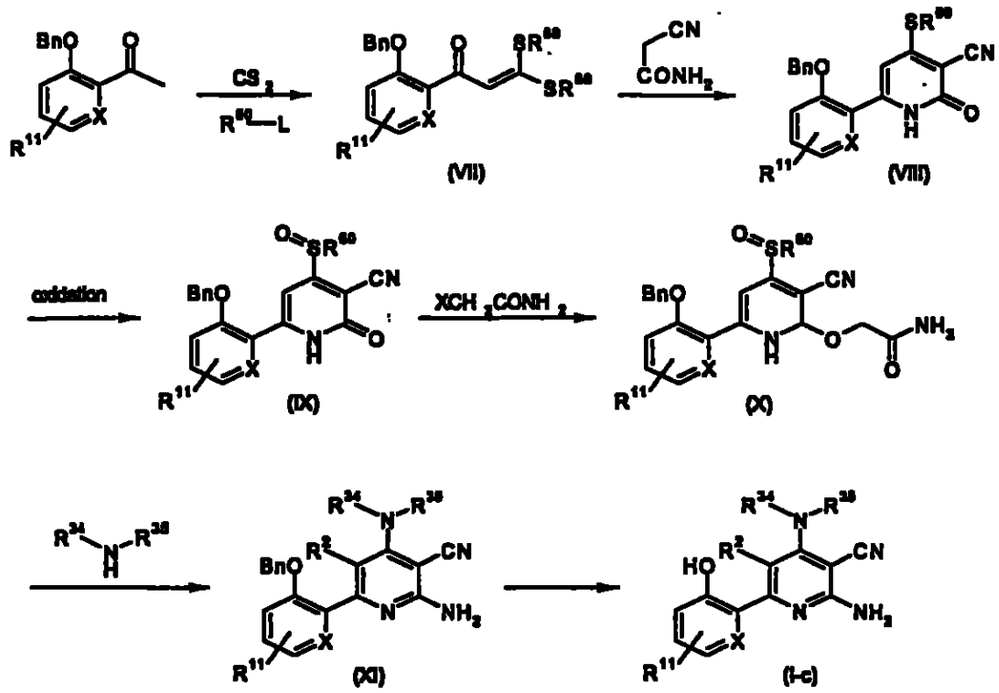
Alternatively, the compound of the formula (I-c) below:



(I-c)

wherein X, R^{11}, R^2, R^{34} and R^{35} are the same as defined above, can be advantageously prepared by the following reaction C.

Reaction C:



First, the compound of the formula (VI) may be reacted with carbon disulfide and R^{60}–L (wherein R^{60} represents C_{1-6} alkyl and L represents a leaving group as defined above) to obtain the compound of the formula (VII). Benzyl protecting group in the compound of the formula (VI) can be replaced with any of an appropriate protecting group. This reaction may be advantageously conducted in the presence of base, such as the combination of sodium hydride and dimethyl acetamide.

The resulting compound (VII) may be reacted with cyanoacetamide in the presence of a solvent and a base. Then the compound (VIII) may be oxidized to yield the compound (IX). The compound (IX) is then reacted with halogenoacetoamide such as chloroacetamide in the presence of a base in a solvent. The resulting compound (X) is reacted with $NHR^{34}R^{35}$ (R^{34} and R^{35} are the same as defined above). Finally, the generated product is reacted with a base and is deprotected to obtain the compound (I-c).

The solvents used in each process of the reaction include, for instance, ethers, such as

dioxane and tetrahydrofuran; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as dimethylformaide (DMF) and dimethylacetamide; sulfoxides such as dimethyl sulfoxide, and others. The above solvent may be used alone or in combination.

Examples of the base used in the reaction include an alkali metal hydride such as sodium hydride or potassium hydride; alkali metal alkoxide such as sodium methoxide or sodium ethoxide; alkali metal hydroxide such as sodium hydroxide or potassium hydroxide; carbonates such as sodium carbonate or potassium carbonate, and hydrogen carbonates such as sodium hydrogen carbonate and potassium hydrogen carbonate; organic amines such as triethylamine.

The reaction temperature can be optionally set depending on the compound to be reacted. The reaction temperature, unless otherwise stated above, is about 10°C to 200°C. Each process of the reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

Amino group at position 2 of the pyridine ring is, if necessary, modified according to conventional method to prepare other groups such as alkylamino, alkanoylamino, etc.

When R^{11} is C_{1-6} alkylsulfonylamino, C_{1-6} alkylamino, di (C_{1-6}-alkyl)amino, C_{1-6} alkanoylamino, phenyl C_{1-6} alkylamino, or phenylsulfonylamino, it is derived from $-NH_2$ with the use of conventional methods during the course of reaction A.

The compounds of the formulas (I-a), (I-b) and (I-c) can be further reacted to modify the substituents at position 2 and position 3 of the pyridine ring to synthesize the desired compounds in the scope of the present invention. Also, in the course of reaction A, B, and C above, the substituents at position 2 and position 3 of the pyridine ring can be modified.

The amino moiety at position 2 can be modified by the conventional methods as follows:



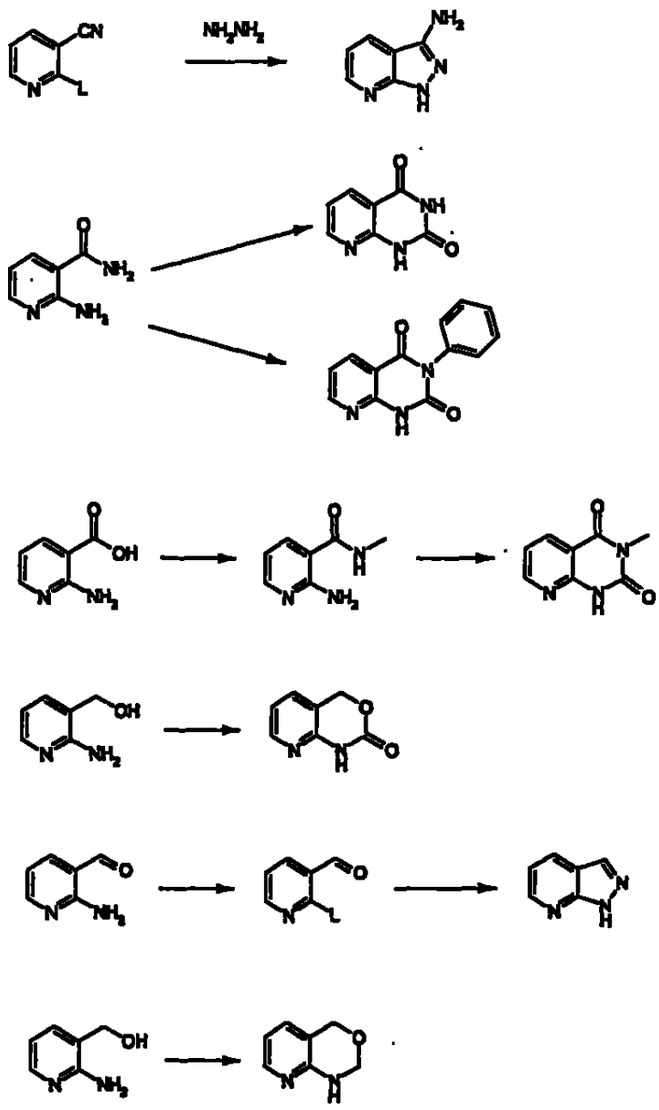
wherein L is the leaving group and the same as defined above, Z is benzyl, C_{1-6} alkyl, or phenyl, or NHZ may form saturated 5-6 membered ring optionally contain NH or O as other heteroatom than the adjacent N atom.

In another embodiment, the amino moiety at position 2 can be converted to amide with the use of acid chloride.

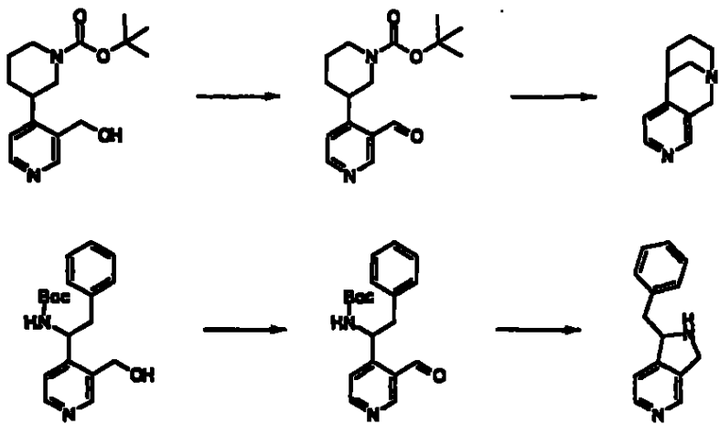
The cyano moiety at position 3 can be converted to carbamoyl by the conventional alkaline hydrolysis.

The tertiary butoxy carbonyl at position 3 can be easily modified, by the conventional reactions of ester, to alcohol, carboxyl, and the like. Alcohol or carboxy may be further converted to another substituents by the conventional methods.

In some embodiment, the substituents of the positions 2 and 3 together form ring optionally having substituents. Any conventional method or combination of any conventional methods can be used to form the rings. The examples of forming the rings are shown below.



Yet, in another embodiment, the substituents of the positions 3 and 4 together form ring optionally having substituents. Any conventional method or combination of any conventional methods can be used to form the rings. The examples of forming the rings are shown below.



When the compound shown by the formula (I) or a salt thereof has tautomeric isomers and/or stereoisomers (e.g, geometrical isomers and conformational isomers), each of their separated isomer and mixtures are also included in the scope of the present invention.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal

hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring

agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet, another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically acceptable excipients therefor. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xantham gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, acacia, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid, which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in suitable oil.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01 mg /kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven

advantageous to administer quantities of about 0.001 to 100 mg /kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

The effect of the present compounds was examined by the following assays and pharmacological tests.

[IKK-β kinase inhibitory assay]

(1) Preparation of IKK-β kinase protein.

A cDNA fragment encoding human IKK-β open reading frame was generated by PCR with the use of a pair of primers designed from the published sequence (Woronicz JD et al. (1997) Science 278, 866-869). A template was obtained from Quickclone cDNA (Clontech) using Elongase™ Amplification kit (Life Technologies). The DNA fragments generated by PCR were gel-purified and subcloned into pBluescript. The cDNA fragment cloned in pBluescript was inserted into pcDNA3.1/His C KpnI/NotI, and transferred into pVL1393 SmaI/XbaI (Pharmingen) to construct a baculovirus transfer vector. Then the vector, together with the linearized baculovirus (BaculoGold™, Pharmingen) was used to transfect Sf21 cells (Invitrogen, San Diego, CA). Generated recombinant baculovirus was cloned and amplified in Sf21 cells, grown in TNM-FH insect cell medium (Life Technologies, Inc.) supplemented with 10% FCS, 50 g/ml Gentamycin, 0.1% Pluronic F-68 (Life Technologies, Inc.) as suspension culture (200 ml in 1 L Erlenmeyer flask; 27°C; 130 rpm). Sf21 cells were infected with this amplified virus with a multiplicity of infection of 5 following standard protocols (Crossen R, Gruenwald S (1997) Baculovirus Expression Vector System Instruction Manual, Pharmingen Corporation) and harvested 48 hrs

later. The cells were lysed to obtain the produced chimeric protein of IKK-β kinase fused by histidine (His-tagged IKK-beta).

(2) The preparation of purified GST-IκBα fusion proteins

An expression vector containing the nucleotide sequence encoding fusion protein of GST with amino acid residues 1 to 54 of IκBα under the control of an IPTG-inducible promoter was constructed. The expression vector was introduced in E. coli and the transformant was cultured and lysed to obtain a GST-IκBα fusion protein. Then the resulting GST-IκBα fusion protein was purified and biotinated for kinase assay.

(3) The measurement of IKK-β kinase activity

The 96-well format kinase assay of IKK-β were performed to test the inhibitory activity of the compounds of the present invention. First, 5 μl of a test compound was put in the presence of 2.5% dimethyl sulfoxide (DMSO) in each well in a U-bottomed 96-well plate (Falcon). For control wells of background (BG) and total phosphorylation (TP), 5 μl of 2.5% DMSO was put. Recombinant IKK-β (final 0.6 μg/ml) and bio-GST-IκBα (1-54) (final 0.2 μM) were diluted in 25 μl of 2 x kinase buffer β (40 mM Tris-HCl, pH 7.6, 40 mM $MgCl_2$, 40 mM β-glycerophosphate, 40 mM p-nitro-phenylphosphate, 2 mM EDTA, 40 mM creatine phosphate, 2 mM DTT, 2 mM Na_3VO_4, 0.2 mg/ml BSA and 0.8 mM phenylmethylsulfonyl fluoride) and transferred to the 96-well plate. Bio-GST-IκBα (1-54) in 25 μl of 2 x kinase buffer β without IKK-β was transferred to BG wells. Then 20 μl of 12.5 μM ATP, 62.5 μCi/ml [γ-^{33}P] ATP (Amersham Pharmacia Biotech) was added and the resulting mixture was incubated for 2 hrs at room temperature. The kinase reactions were terminated by the addition of 150 μl of termination buffer (100 mM EDTA, 1 mg/ml BSA, 0.2 mg NaN_3). One hundred and fifty μl of the sample were transferred to a streptavidin-coated, white MTP (Steffens Biotechniche Analysen GmbH #08114E14.FWD) to capture the biotinylated substrates. After 1 hr of incubation, non-bound radioactivity was

eliminated by washing the wells five times with 300 µl of washing buffer including 0.9 % NaCl and 0.1% (w/v) Tween-20 with the use of a MW-96 plate washer (BioTec). The bound radioactivity was determined after the addition of 170 µl MicroScint-PS scintillation cocktail (Packard) using a TopCount scintillation counter.

[Syk tyrosine kinase inhibitory assay for selectivity]

(1) Preparation of Syk protein

A cDNA fragment encoding human Syk openreading frame was cloned from total RNA of human Burkitt's lymphoma B cell lines, Raji (American Type Culture Collection), with the use of RT-PCR method. The cDNA fragment was inserted into pAcG2T (Pharmingen, San Diego, CA) to construct a baculovirus transfer vector. Then the vector, together with the linearized baculovirus (BaculoGoldTM, Pharmingen), was used to transfect Sf21 cells (Invitrogen, San Diego, CA).

Generated recombinant baculovirus was cloned and amplified in Sf21 cells. Sf21 cells were infected with this amplified high titer virus to produce a chimeric protein of Syk kinase fused by glutathione-S-transferase (GST).

The resulting GST-Syk was purified with the use of glutathione column (Amersham Pharmacia Biotech AB, Uppsala, Sweden) according to the manufacturer's instruction. The purity of the protein was confirmed to be more than 90% by SDS-PAGE.

(2) Synthesize of a peptide

Next, a peptide fragment of 30 residues including two tyrosine residues, KISDFGLSKALRADENYYKAQTHGKWPVKW, was synthesized by a peptide synthesizer. The N-terminal of the fragment was then biotinylated to obtain biotinylated activation loop peptide (AL).

(3) The measurement of Syk tyrosine kinase activity

All reagents were diluted with the Syk kinase assay buffer (50 mM Tris-HCl (pH 8.0), 10 mM $MgCl_2$, 0.1 mM Na_3VO_4, 0.1% BSA, 1 mM DTT). First, a mixture (35 µl) including 3.2 µg of GST-Syk and 0.5 µg of AL was put in each well in 96-well plates. Then 5µl of a test compound in the presence of 2.5% dimethyl sulfoxide (DMSO) was added to each well. To this mixture was added 300 µM ATP (10 µl) to initiate the kinase reaction. The final reaction mixture (50 µl) consists of 0.65 nM GST-Syk, 3 µM AL, 30 µM ATP, a test compound, 0.25% DMSO, and a Syk kinase assay buffer.

The mixture was incubated for 1 hr at room temperature (RT), and the reaction was terminated by the addition of 120 µl of termination buffer (50 mM Tris-HCl (pH 8.0), 10 mM EDTA, 500 mM NaCl, 0.1% BSA). The mixture was transferred to streptavidin-coated plates and incubated for 30 min. at room temperature to combine biotin-AL to the plates. After washing the plates with Tris-buffered saline (TBS) (50 mM Tris-HCl (pH 8.0), 138 mM NaCl, 2.7 mM KCl) containing 0.05% Tween-20 for 3 times, 100 µl of antibody solution consisting of 50 mM Tris-HCl (pH 8.0), 138 mM NaCl, 2.7 mM KCl, 1% BSA, 60 ng/ml anti-phosphotyrosine monoclonal antibody, 4G10 (Upstate Biotechnology), which was labeled with europium by Amersham Pharmacia's kit in advance, was added and incubated at room temperature for 60 minutes. After washing, 100 µl of enhancement solution (Amersham Pharmacia Biotech) was added and then time-resolved fluorescence was measured by multi-label counter ARVO (Wallac Oy, Finland) at 340 nm for excitation and 615 nm for emission with 400 msec of delay and 400 msec of window.

[The measurement of RANTES production in response to TNF-α from A549 cells]

(1) Preparation of A549 cells

The A549 human lung epithelium cell line (ATCC #CCL-885) was maintained in Dulbecco's modified Eagle's medium (D-MEM, Nikken

Biomedical Institute) supplemented with 10% FCS (Gibco), 100 U/ml penicillin, 100 μg/ml streptomycin, and 2 mM glutamine (culture medium). Forty thousand (4×10^4) cells (80 μl/well) were seeded in each well of 96 well flat-bottom tissue culture plate (Falcon #3072). The plate was allowed to stand for 2 hrs, thus the cells were adhered to the bottom of each well. To the each well was added 10 μl vehicle (1% DMSO), serial dilutions of test compounds in 1% DMSO, or 5 nM Dexamethasone in 1% DMSO as a reference. The mixture (90 μl/well) was incubated for 1 hr at 37°C. After 1 hr, 1 μg/ml TNF-α (10 μl) in culture medium was added to the mixture to obtain 100 μl of reaction mixture. The reaction mixture was cultured for 24 hrs to stimulate the cells with 100 ng/ml TNF-α. Cells with vehicle without TNF-α stimulation were also prepared.

(2) Measurement of RANTES production

Then the concentration of RANTES released from the cells in the supernatants of each well was determined using a quantitative sandwich enzyme immunoassay technique. First, 2μg/ml mouse anti-huRANTES mAb (R&D Systems, #mAb678) in PBS buffer (pH 7.4, 100μl) was put in each well of 96-well NUNC fluoro plate (Nalge Nunc, New York USA) (Final 200ng/well) and the plate was allowed to stand for overnight at 4°C to be coated by the antibody. Each well of the plate was then washed with 350 μl wash buffer (0.05% Tween-20, 0.85% NaCl, and 25 mM Tris/HCl pH7.4) for three times. Blocking buffer containing 1% BSA (Sigma 99% pure, 100 g), 5% sucrose (Nacalai tesque, 99% pure, 500 g), and 0.02% azide (Nacalai tesque, 100%, 500 g) were added (200 μl) to each well and then the plate was allowed to stand for 4 hours to stabilize the coated antibody. Next, 50 μl supernatants of cell culture prepared in (1) above were put in each well of the 96-well NUNC fluoro plate with coated antibody. Recombinant Human RANTES (Pepro Tech, Inc. #300-06) was used as the standard for the determination of RANTES production (linear range between 1 and 10 ng/ml). Eu-labelled mouse anti-huRANES mAb (60 ng/ml: R&D Systems,

#mAb278) in PBS supplemented by 1% BSA and 0.05% Tween 20 was added (50 µl) to each well. The reaction mixtures were incubated at room temperature for 4 hrs. After washing with wash buffer (0.05% Tween-20, 0.85% NaCl, and 25 mM Tris/HCl pH7.4, 350 µl/well) for 5 times with the use of a Sera Washer (Bio-Tech, #MW-96R), the enhancement solution (DELFIA, #1244-405, 100 µl/well) was added to each well. The plate was incubated for 10 minutes at room temperature with moderate shaking. Fluorescent intensity was measured using a DELFIA fluorimeter (Wallac). Excitation was performed at 340 nm and emission was measured at 615 nm.

[The measurement of TNF-α production in response to LPS from Peripheral blood mononuclear cells (PBMC)]

(1) Preparation of PBMC

Human PBMC were prepared by first obtaining blood from healthy donors and isolating the cells from the blood. The isolation was done by Ficoll gradient-centrifugation method using Ficoll Pacque (Pharmacia #17-1440-02). Within three hours from donation, the isolated PBMC was used. After three times washing with PBS, PBMC were resuspended with RPMI 1640 (Nikken BioMedical Institute) supplemented with 10% FCS (Gibco), 100 U/ml penicillin, 100 µg/ml streptomycin, and 2 mM glutamine (culture medium). The cells (1×10^5 in 150 µl/well) were seeded in each well of 96 well flat-bottom tissue culture plate (Falcon #3072). To the each well was added 20 µl vehicle (1% DMSO), serial dilutions of test compounds in 1% DMSO, or 250 nM Dexamethasone in 1% DMSO as a reference. The mixture (170 µl/well) was incubated for 1 hr at 37°C. After 1 hr, 20 ng/ml LPS (30 µl) in culture medium was added to the mixture to obtain 200 µl of reaction mixture. The reaction mixture was cultured for 7 hrs to stimulate the cells with 3 ng/ml LPS. Cells with vehicle without LPS stimulation were also prepared. The supernatants of the reaction mixture were then collected.

(2) Measurement of TNF-α production

The TNF-α concentration in the supernatants was determined using a DuoSet™ ELISA Development Kit (GenzymeTechne, Minneapolis, USA) following the manufacturer's recommendations. First, 4 µg/ml of mouse anti-human TNF-α Ab in PBS buffer (100 µl) was put in each well of 96-well plate (NUNC, Maxisorp ™) and the plate was allowed to stand for overnight at 4°C to be coated with the antibody. Each well of the plate was then washed 5 times with 350 µl of wash buffer containing PBS, 0.05% Tween 20 (Nakalai tesque) using Sera Washer (Bio-Tech, #MW-96R). To each well was added 300 µl of 1% BSA (Sigma), 5% sucrose in PBS. After 2 hrs incubation at room temperature, the buffer was discarded, and 50 µl of culture medium was added. Next, 50 µl supernatant of stimulated cell culture prepared (1) above was put in each well of the 96-well plate. Recombinant human TNF-α (Genzyme Techne) was used as the standard for the determination of TNF-α production (linear range between 30 and 2,000 pg/ml). The reaction mixtures were incubated for 1 hr at room temperature. After 5 times washing, 100 µl biotinylated goat anti-human TNF-α antibody (Genzyme Techne, 300 ng/ml) in 0.1% BSA, 0.05% Tween in PBS (Reagent diluent) was added to each well, and incubated at room temperature for 1 hr. After 5 times washing, 100 µl of Streptavidin-conjugated horseradishperoxidase (Genzyme Techne, 1/100 in Reagent diluent) was added to each well. After 20 min, each well of the plate was washed 5 times with wash buffer (350 µl/well). The substrate of hourseradishperoxidase and H_2O_2 (TMBZ peroxidase detection kit, SUMILON #ML-1120T) were added to the mixture and the mixture was allowed to stand at room temperature. The reaction was terminated after 10 min by adding 2N H_2SO_4. Optical density at 450 nm was measured with the use of a microplate reader (Labosystems, Multiscan Multisoft). Quantification of TNF-α production in each sample was performed by comparison of optical densities between each sample and the standard curve.

[The measurement of IL-2 production in Jurkat T cells in response to antibody stimulation]

IL-2 production was measured in Jurkat T cells (E6-1 clone; ATCC # TIB-152) in response to stimulation with anti-CD3/anti-CD28 antibodies.

(1) Preparation of immobilized antibodies

First, anti-CD3 antibodies (400 ng/well Nichirei, NU-T3 4 μg/ml in 100 μl Dulbecco's PBS) were put in each well of 96-well plate (Falcon #3072) and the plate was allowed to stand for 2 hrs at room temperature to be coated with the antibody. Each well of the plate was then washed with 250 μl PBS 3 times.

(2) Preparation of Jurkat cell culture

Jurkat T cells were cultured in RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum, 2 mM L-glutamine, 100 U/ml penicillin G, and 100 μg/ml streptomycin (culture medium). Two hundred thousand ($2x10^5$) cells (190 μl/well) were seeded in each well of 96-well U-bottom tissue culture plates (Falcon #3077). To each well was added 10 μl vehicle (0.2% DMSO), serial dilution of compounds in 0.2% DMSO, or 25 nM cyclosporin A as a reference in 0.2% DMSO. The mixture (200 μl) was incubated for one hour at 37°C in a humidified 5% CO_2 environment.

(3) Stimulation of the cell

The reaction mixture obtained in (2) (100 μl) was put in the each well of the antibody-immobilized plate prepared in (1). To this well was added anti-CD28 antibodies (Nichirei, KOLT-2, 6 μg/ml in cell culture medium, 50 μl/well) and 2.5 μg/ml goat anti-mouse kappa chain antibodies (Bethyl Laboratories, (Cat#A90-119A) 10 μg/ml in culture medium, 50 μl/well). The reaction mixture in each well was incubated for 24 hrs at 37°C to stimulate cells with immobilized anti-CD3 antibodies (400 ng/well) and anti-CD28

antibodies (1.5 μg/ml), and then to cross-link receptors on the cells with anti-mouse kappa chain antibodies (2.5 μg/ml).

(4) Measurement of IL-2 production

The supernatants of the reaction mixture were then collected. The IL-2 concentration in the supernatants was determined using a DuoSet™ ELISA Development Kit (GenzymeTechne, Minneapolis, USA) following the manufacturer's recommendations. First, 2 μg/ml of mouse anti-huIL-2 Ab in PBS buffer (100 μl) was put in each well of 96-well plate (NUNC, Maxisorp ™) and the plate was allowed to stand for overnight at 4°C to be coated with the antibody. Each well of the plate was then washed 5 times with 350 μl of wash buffer containing PBS, 0.05% Tween 20 (Nakalai tesque) using Sera Washer (Bio-Tech, #MW-96R). To each well was added 250 μl of 1% BSA (Sigma) in PBS, 0.05% Tween 20 (dilution buffer). After 2 hrs incubation at room temperature, the buffer was discarded, and 50 μl of culture medium was added. Next, 50 μl supernatant of stimulated cell culture prepared (3) above was put in each well of the 96-well plate with coated mouse anti-huIL-2 antibody. Recombinant Human IL-2 (Genzyme Techne) was used as the standard for the determination of IL-2 production (linear range between 200 and 5,400 pg/ml). The reaction mixtures were incubated for 1 hr at room temperature. After 5 times washing, 100 μl biotinylated rabbit anti-huIL-2 antibody (Genzyme Techne, 1.25 μg/ml) in dilution buffer was added to each well, and incubated at room temperature for 1 hr. After 5 times washing, 100 μl of Streptavidin-conjugated horseradishperoxidase (Genzyme Techne, 1/1000 in dilution buffer) was added to each well. After 20 min, each well of the plate was washed 5 times with wash buffer (350 μl/well). Substrate and H_2O_2 (TMBZ peroxidase detection kit, SUMILON #ML-1120T) were added to the mixture and the mixture was allowed to stand at room temperature. The reaction was terminated after 10 min by adding 2N H_2SO_4. Optical density at 450 nm was measured with the use of a microplate reader (Labosystems, Multiscan Multisoft). Quantification of IL-2 production in

each sample was performed by comparison of optical densities between each sample and the standard curve.

[Mouse LPS-induced TNF-α production]

Eight weeks old BALB/c female mice were placed into two groups, a control group and a treated group. A solution containing 200 μg/mouse of LPS in 0.9% physiological salt was administered by intraperitoneal (ip) injection into the control mice. Mice in the treated group were first injected ip with compounds of the present invention 30 minutes prior to the LPS injection. Under anesthesia with pentobarbital (80 mg/kg, i.p.), blood was collected from the posterior venous cavity of the treated and control mice at 90 min post-LPS injection into 96-well plate containing 2% EDTA solution. The plasma was separated by centrifugation at 1800 rpm for 10 minutes at 4°C and then diluted with four times volumes of phosphate buffer saline (pH 7.4) containing 1% bovine serum albumin. TNF-α concentration in the sample was determined using an ELISA kit (Pharmingen, San Diego, CA.)

The mean TNF-α level in 5 mice from each group was determined and the percent reduction in TNF-α levels was calculated. The treated mice showed significant decrease in the level of TNF-α as compared to the control mice. The result indicates that the compounds of the present invention can restrain LPS-induced cytokine activity.

Results in vitro test and Cellular assay result (A549) are shown in Examples and tables of the Examples below. The data corresponds to the compounds as yielded by solid phase synthesis and thus to levels of purity of about 40 to 90%. For practical reasons, the compounds are grouped in four classes of activity as follows:

In vitro IC_{50} = A (= or <) 0.5μM < B (= or <) 2 μM < C (= or <) 10 μM < D

Cellular IC_{50} = A (= or <) 1μM < B (= or <) 10 μM < C

The compounds of the present invention also show excellent selectivity and strong activity in other cellular activity and in vivo assays.

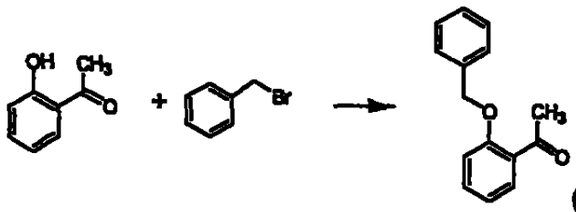
EXAMPLES

The present invention will be described in detail below in the form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight. Proton nuclear magnetic resonance (1H NMR) spectra were recorded at either 300 or 500 MHz by Bruker DRX-300

500 Bruker UltraShield™ and chemical shifts are reported in parts per million relative to tetramethylsilane (TMS). Mass spectra were obtained using electrospray (ES) ionization techniques (micromass Platform LC).

[Starting compound 1A]

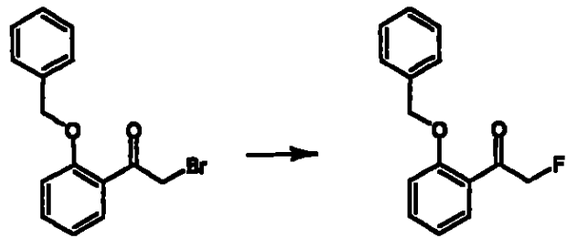


(Starting compound 1A)

A mixture of 2'-hydroxyacetophenone (68.1 g, 0.500 mol), benzylbromide (94.1 g, 0.550 mol) and K_2CO_3 (103 g, 0.750 mol) in acetone (1.0 L) was heated at reflux, and the stirring was continued overnight. After cooled to room temperature, the mixture was concentrated under reduced preasure. The residue was diluted with water, and extracted with ethyl acetate. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by distillation under reduced pressure to give 1-[2-(benzyloxy)phenyl]ethanone as a colorless oil. (100 g, yield; 88%)

[Starting compound 1B]

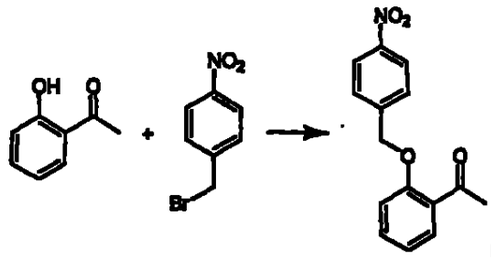
To a solution of 2' hydroxyacetophenone (6.79 g, 30 mmol) in ether (200 mL) was added a solution of bromine (5.00 g, 31 mmol) in ether (20 mL). After being stirred at room temperature for 30 min, the mixture was diluted with ether (100 mL), and then washed with saturated aqueous $NaHCO_3$ (100 mL) and with brine (100 mL), successively. The combined organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was washed with ether and hexane successively, and dried under reduced pressure to give 1-[2-(benzyloxy) phenyl]-2-bromoethanone. (8.42 g, yield; 92%)



(Starting compound 1B)

To a solution of 1-[2-(benzyloxy) phenyl]-2-bromoethanone (2.59 g, 8.5 mmol) and pyridine (1.37 mL, 17 mmol) in THF was added tetrabutylammonium hydrogen difluoride (4.78 g, 17 mmol). The reaction mixture was stirred under reflux for 22 hrs. The mixture was diluted with ether (250 mL), then washed with 1N aqueous hydrochloric acid (100 mL) and brine (100 mL), successively. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 4:1) to give 1-[2-(benzyloxy)phenyl]-2-fluoroethanone (688 mg, yield; 33%).

[Starting compound 1C]

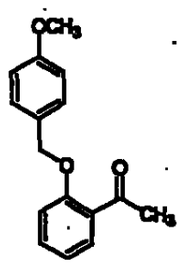


(Starting compound 1C)

To a stirred solution of 2'-hydroxyacetophenone (5.000 g, 36.724 mmol) in acetonitrile (200 mL) was added potassium carbonate (7.613 g, 55.086 mmol). The mixture was stirred at 50 °C for 30 min. 4-Nitrobenzyl bromide (8.727 g, 40.396 mmol) was added to the mixture, and the stirring was continued at 50 °C for 12 hrs. Potassium carbonate (0.508 g, 3.672 mmol) and 4-nitrobenzyl bromide (0.793 g, 3.672 mmol) were added to the mixture and the resulting mixture was stirred at 50 °C for 12 hrs. After cooled to room temperature, the reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate. The organic phase was washed with water, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was washed with hexane to give 1-{2-[(4-nitrobenzyl)oxy]phenyl}ethanoneas a white solid. (8.900 g, yield; 89%)

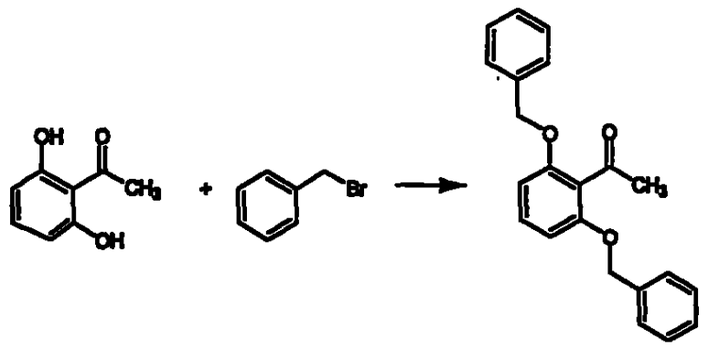
[Starting compound 1D]

In a same manner as the method to prepare starting compound 1A, except that benzylbromide was replaced with methoxybenzylchloride, methoxybenzyl-acetophenone was prepared.



(Starting compound 1D)

[Starting compound 1E]

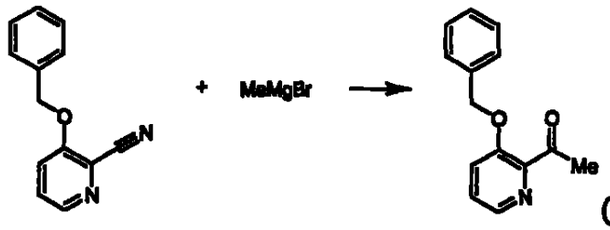


(Starting compound 1E)

A suspension of (2',6'-dihydroxy)acetophenone (25.0 g, 164 mmol), benzyl bromide (40 mL, 337 mmol), potassium carbonate (136 g, 986 mmol) and sodium iodide (2.5 g, 16 mmol) in acetone (500 mL) was stirred at reflux overnight. The mixture was concentrated under reduced pressure, and diluted with ethyl acetate (500 mL) and water (250 mL). The separated aqueous phase was extracted with ethyl acetate (200 mL x 2). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with hexane, collected by filtration, washed with hexane and dried under reduced pressure to give 1-[2,6-bis(benzyloxy)phenyl]ethanone (24.9 g, yield; 46%).

[Starting compound 1F]

A suspension of 3-hydroxypicolinonitrile (3.00 g, 25.0 mmol), which was prepared according to "Synthesis" 316 (1983) and " J. Org. Chem." 48 1375 (1983), potassium carbonate (5.40 g, 39.1 mmol) and benzyl bromide (5.10 g, 29.8 mmol) in acetone (150 mL) was stirred at room temperature for 20 hrs. The reaction mixture was filtrated and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate/n-hexane = 1/3 to 1/2) followed by recrystallization from ethyl acetate/n-hexane = 1/4 to give 3-benzyloxypicolinonitrile as a colorless solid (4.354 g, yield; 83%).



(Starting compound 1F)

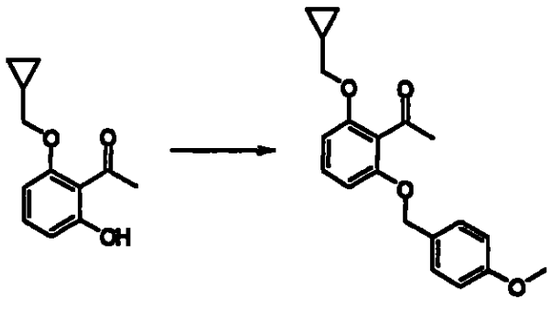
To a cold (0 °C) solution of 3-benzyloxypicolinonitrile (2.50 g, 11.9 mmmol) in tetrahydrofuran (100 mL) was added dropwise 0.92M methyl magnesium bromide in tetrahydrofuran (150 mL, 138 mmol). The mixture was stirred at 0 °C for 30 minutes and then at room temperature for 4 hrs. The reaction mixture was poured into water (2000 mL) and acidified with 10% sulfuric acid (500 mL). After being stirred for 30 min, the reaction mixture was poured into saturate aqueous $NaHCO_3$ solution slowly and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtrated, and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate/n-hexane = 1/3) to give 1-(2-benzyloxy-phenyl)-ethanone as a colorless oil (2.49 g, yield; 92%).

[Starting compound 1G]

To a stirred solution of 1-(2,6-dihydroxyphenyl)ethanone

(50.0 g, 328 mmol) in acetone (1000 mL) was added potassium carbonate (227 g, 1643 mmol) and (bromomethyl)cyclopropane (35.1 mL, 361 mmol). The mixture was stirred at 50 °C for 2 days. The reaction mixture was filtrated on Celite®, and then the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The separated organic phase was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was suspended in hexane. Then the suspension was stirred at 80 °C for 30 min. The solution was filtered and the filtrate was allowed to cool to room temperature. The resulting white solid was collected by filtration, washed with

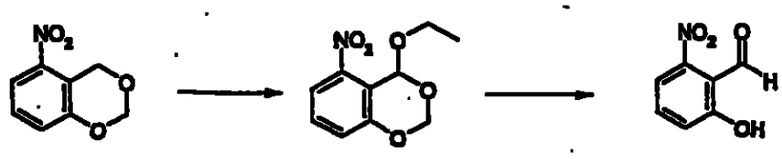
hexane, and dried under reduced pressure to give 1-{2-[(cyclopropylmethyl)oxy] –6-hydroxyphenyl}ethanone as a pale yellow solid (56.3 g, yield; 83%).



(Starting compound 1G)

To a stirred solution of 1-{2-[(cyclopropylmethyl)oxy]-6-hydroxyphenyl} ethanone (56.3 g, 272 mmol) in acetone (1000 mL) was added potassium carbonate (188 g, 1364 mmol), 4-methoxybenzyl chloride (40.9 mL, 300 mmol) and tetrabutyl-ammonium iodide (20.2 g, 54.6 mmol). The mixture was stirred at reflux overnight. The reaction mixture was allowed to cool to room temperature, filtered on Celite®, and then the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Then the resulting white solid was recrystallized from ethanol, collected by filtration, washed with ethanol, and dried under reduced pressure to give 1-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy] phenyl}ethanone as a white solid (79.2 g, yield; 89%).

[Starting compound 1H]



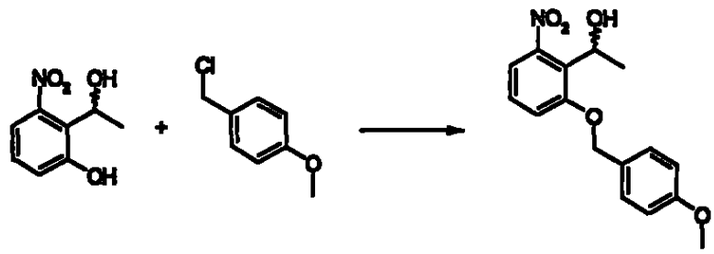
To a stirred solution of 5-nitro-4H-1,3-benzodioxine (10.0 g, 55.203 mmol) in carbon tetrachloride (70 mL) were added N-bromosuccinimide (10.808 g, 60.723 mmol) and

2, 2'-azobisisobutyronitrile (0.906 g, 5.520 mmol). The mixture was stirred at 100 °C for 2 hrs. After cooled to room temperature, a solution of sodium ethoxide (4.884 g, 71.764 mmol) in ethanol (70 mL) was added to the mixture, and the stirring was continued at room temperature for 3 hrs. The reaction was quenched with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 9/1) to give 4-ethoxy-5-nitro-4H-1,3-benzodioxine as a pale yellow oil (10.8 g, yield; 87%).

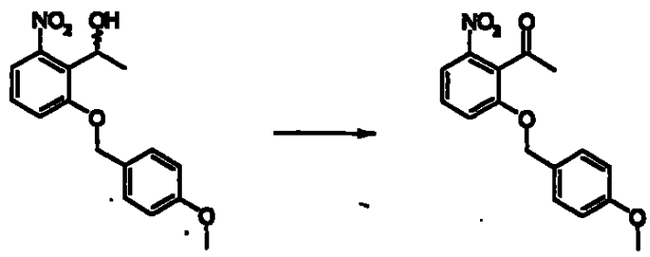
To a stirred solution of 4-ethoxy-5-nitro-4H-1,3-benzodioxine (5.80 g, 25.755 mmol) in ethanol (15 mL) and THF (10 mL) was added 4N HCl in 1, 4-dioxane (20 mL). The mixture was stirred at 60 °C for 6 hrs and 90 °C for 6 hrs. After cooled to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 9/1) to give 2-hydroxy-6-nitrobenzaldehyde as a pale yellow oil (4.450 g, yield; quant.).



To a stirred solution of 2-hydroxy-6-nitrobenzaldehyde (4.5 g, 26.926 mmol) was added dropwise trimethylaluminum (2M in toluene, 27 mL) under an argon atmosphere. The mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into a cold (0 °C) aqueous 1N hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine and dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 9/1) to give 2-(1-hydroxyethyl)-3-nitrophenol as an orange oil (4.660 g, yield; 95%).

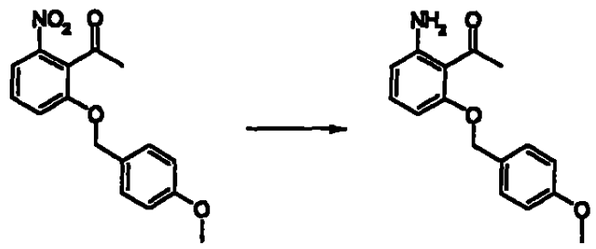


To a stirred solution of 2-(1-hydroxyethyl)-3-nitrophenol (0.300 g, 1.638 mmol) in acetone (5 mL) was added potassium carbonate (0.25 g, 1.802 mmol). The mixture was stirred at room temperature for 15 min, and 4-methoxybenzyl chloride (0.22 mL, 1.638 mmol) was added to the mixture. The mixture was stirred at room temperature for 2 hrs and at 60 °C for 3 hrs. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 4/1). The purified compound was washed with diisopropyl ether to give 1-{2-[(4-methoxybenzyl)oxy]-6-nitrophenyl}ethanol as a white solid (0.201 g, yield; 41%).



To a cooled (0 °C), stirred solution of 1-{2-[(4-methoxybenzyl)oxy]-6-nitrophenyl}ethanol (0.20 g, 0.659 mmol) in dichloromethane (20 mL) were added molecular sieves 4A (1 g), N-methylmorpholine N-oxide (0.15 g, 1.319 mmol) and tetra-n-propylammonium perruthenate (0.01 g). The mixture was stirred at room temperature for 12 hrs. The reaction mixture was filtered on Celite®, and the filtrate was diluted with ethyl acetate. The organic phase was washed with saturated aqueous ammonium chloride solution and dried over Na_2SO_4, filtered and

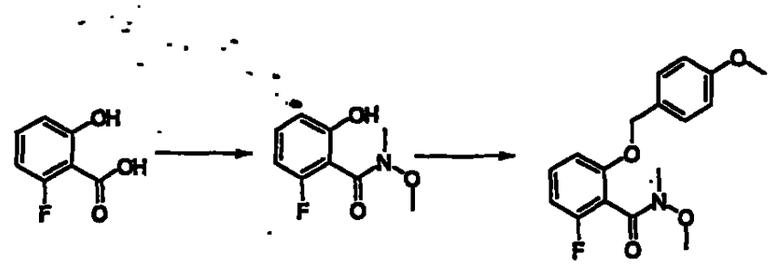
concentrated under reduced pressure to give 1-{2-[(4-methoxybenzyl)oxy]-6-nitrophenyl}ethanone as a white solid (0.159 g, yield; 80%). The residue was used for the next step without further purification.



(Starting compound 1H)

To a stirred suspension of 1-{2-[(4-methoxybenzyl)oxy]-6-nitrophenyl}ethanone (0.50 g, 1.659 mmol) in ethanol was added a solution of ammonium chloride (0.10 g, 1.825 mmol) in water (5 mL) followed by iron powder (0.75 g). The mixture was stirred at 100 °C for 1 hr. The reaction mixture was filtrated on Celite®. The filtrate was diluted with ethyl acetate and washed with water. The separated organic phase was washed with brine and dried over Na_2SO_4, filtrated and concentrated under reduced pressure to give 1-{2-amino-6-[(4-methoxybenzyl)oxy]phenyl}ethanone as a yellow solid (0.790 g, yield; 108%). The residue was used for the next step without further purification.

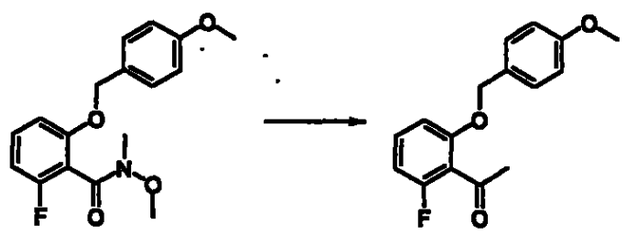
[Starting compound 1I]



To a cold (0 °C) solution of 2-fluoro-6-hydroxybenzoic acid (5.00 g, 32.029 mmol) in dimethyl formamide (200 mL) were added N,O-dimethylhydroxylamine hydrochloride (6.25 g, 64.057 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (9.82 g, 48.043 mmol), 1-hydroxybenzotriazole (5.19 g, 38.435 mmol), and triethylamine (8.93 mL, 64.057 mmol). The mixture was stirred at room temperature for 15 hrs. The reaction mixture was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (ethyl acetate / hexane = 2/1) to give 2-fluoro-6-hydroxy-N-methoxy-N-methylbenzamide as an orange solid (4.320 g, yield; 68%).

To a stirred solution of 2-fluoro-6-hydroxy-N-methoxy-N-methylbenzamide (4.320 g, 21.689 mmol) in acetone (50 mL) were added 4-methoxy benzylchloride (3.74 g, 23.858 mmol), potassium carbonate (4.50 g, 32.534 mmol), and potassium iodide (360 mg, 2.169 mmol). The mixture was stirred at reflux for 15 hrs. After cooled to room temperature, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 2/1) to give 2-fluoro-N-methoxy-6-[(4-methoxybenzyl)oxy]-N-methylbenzamide as a pale yellow oil (6.926 g, yield; quant.).

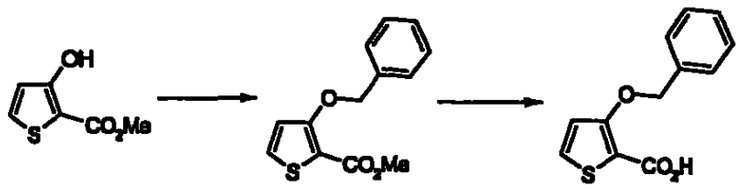


(Starting compound 1I)

To a cold (0 °C) solution of 2-fluoro-N-methoxy-6-[(4-methoxybenzyl)oxy]-N-methylbenzamide (6.926 g, 21.70 mmol) in tetrahydrofuran (10 mL) was added 1N methyl magnesium bromide in tetrahydrofuran (43.40 mL, 43.40 mmol). The reaction mixture was stirred at reflux for 4 hrs. After cooled to room temperature,

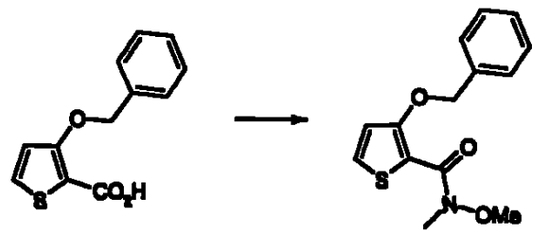
the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, and extracted with ethyl acetate. The separated organic phase was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (hexane : ethyl acetate, 3/1) to give 1-{2-fluoro-6-[(4-methoxybenzyl)oxy]phenyl}ethanone as a pale yellow solid (1.21 g, yield; 20%).

[Starting compound 1J]

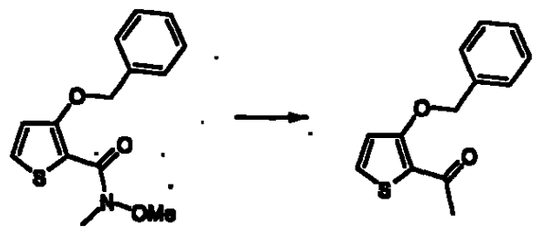


A mixture of methyl 3-hydroxy-2-thiophenecarboxylate (5.00 g, 31.61 mmol), benzyl bromide (3.76 mL, 31.61 mmol), and K_2CO_3 (4.81 g, 34.77 g) in acetone (50 mL) was stirred at reflux for 1.5 hrs. After cooled to room temperature, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate = 15/1 to 9/1) to give methyl 3-(benzyloxy)-2-thiophenecarboxylate as a pale yellow oil (7.91 g, yield: quant.).

To a solution of methyl 3-(benzyloxy)-2-thiophenecarboxylate (7.85 g, 31.61 mmol) in MeOH (32 mL) and THF (16 mL) was added 2 N NaOH (21 mL), and the mixture was stirred at reflux for 10 hrs, and then concentrated under reduced pressure. The residue was diluted with water, washed with ether. The separated aqueous phase was acidified with 5N HCl. The precipitated solid was collected by filtration, washed with hexane, and dried under reduced pressure at 60 °C to give 3-(benzyloxy)-2-thiophenecarboxylic acid as a yellow solid (6.76 g, yield; 91%).



To a solution of 3-(benzyloxy)-2-thiophenecarboxylic acid (3.00 g, 12.81 mmol) in CH_2Cl_2 (30 mL) were added oxalyl chloride (1.34 mL, 15.4 mmol) and DMF (0.05 mL). The mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (10 mL). Then the solution was added to a mixture of N,O-dimethylhydroxyamine hydrochloride (1.50 g, 15.37 mmol) and K_2CO_3 (3.54 g, 25.62 mmol) in ethyl acetate (30 mL) and water (30 mL) at 0 °C. The mixture was vigorously stirred at 0 °C for 0.5 hrs, and at room temperature for 1.5 hrs. The organic phase was separated, washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel (n-hexane/ethyl acetate = 2/1) to give 3-(benzyloxy)-N-methoxy-N-methyl-2-thiophenecarboxamide as a pale yellow solid (3.473 g, yield; 98%).

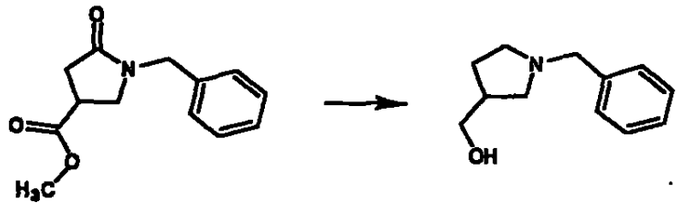


(Starting compound 1J)

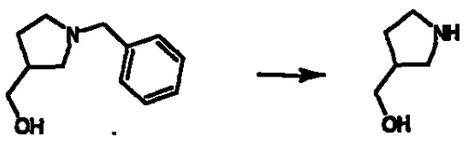
To a cold (0 °C) solution of 3-(benzyloxy)-N-methoxy-N-methyl-2-thiophene-carboxamide (3.47 g, 12.50 mmol) in THF (50 mL) was added a solution of methyl-magnesium bromide in THF (1 M, 35 mL). After being stirred at 0 °C for 1 hr, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, diluted with water, and extracted with ethyl acetate. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by

column chromatography on silica gel (hexane/ethyl acetate/CH_2Cl_2 = 3/1/1) followed by recrystallization from n-hexane/ethyl acetate to give 1-[3-(benzyloxy)-2-thienyl]ethanone as a white solid (2.592 g, yield; 89%).

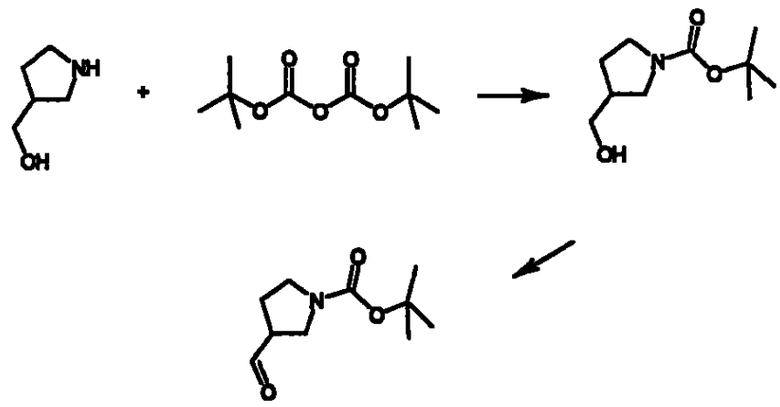
[Starting compound 2A]



To a cold (0 °C) suspension of lithium aluminum hydride (2.44 g, 64 mmol) in THF (40 mL) was added methyl 1-benzyl-5-oxo-3-pyrrolidinecarboxylate (5.00 g, 21 mmol). The reaction mixture was stirred at room temperature for 5 hrs. To the reaction mixture were added water (2.5 mL), 15% aqueous sodium hydroxide solution (2.5 mL), and water (7.5 mL), successively. The mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure to give (1-benzyl-3-pyrrolidinyl)methanol. (4.16 g, yield; quant.)



To a suspension of $Pd(OH)_2$ (0.4 g) in methanol (30 mL) was added (1-benzyl-3-pyrrolidinyl)methanol (4.16 g, 21 mmol). The reaction mixture was stirred under a hydrogen atmosphere for 24 hours. The reaction mixture was diluted with ethyl acetate (200 mL), then filtered through a Celite®. The filtrate was concentrated under reduced pressure to give 3-pyrrolidinylmethanol (2.33 g, yield; quant.).



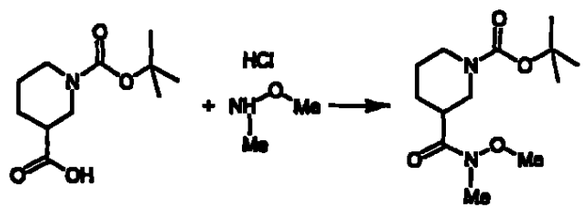
(Starting compound 2A)

To a solution of 3-pyrrolidinylmethanol (2.33 g, 21 mmol) and triethylamine (4.8 mL, 35 mmol) in dichloromethane (60 mL) was added di(tert-butyl) dicarbonate (5.3 g, 24 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 26 hrs. The mixture was diluted with ethyl acetate (200 mL), and washed with 1N HCl (100 mL), with a saturated aqueous $NaHCO_3$ solution (100 mL) and with brine (100 mL), successively. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give tert-butyl 3-(hydroxymethyl)-1-pyrrolidinecarboxylate (4.06 g, yield; 96%).

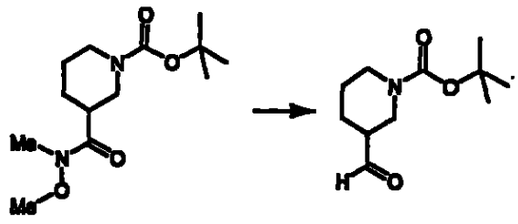
To a cold (0 °C) mixture of tert-butyl 3-(hydroxymethyl)-1-pyrrolidinecarboxylate (4.0 g, 20 mmol), dichloromethane (100 mL), dimethyl sulfoxide (20 mL) and triethylamine (16.9 mL, 121 mmol) under an argon atmosphere was added sulfur trioxide-pyridine complex (9.63 g, 60 mmol). The reaction mixture was allowed to warm to room temperature, and the stirring was continued for 1 hr. The mixture was extracted with ether (200 mL) and a saturated aqueous $NaHCO_3$ solution (100 mL). The separated aqueous phase was further extracted with ether (100 mL x 2). The combined organic phase was washed with a 1N aqueous HCl solution (100 mL), a saturated aqueous $NaHCO_3$ solution (100 mL), and brine (100 mL), successively. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure (5.32 g, yield; quant.).

[Starting compound 2B]

To a cooled (0 °C), stirred solution of 3-piperidinecarboxylic acid (100.000 g, 774.233 mmol) in dioxane (400 mL) were added 2N NaOH (400 mL, 800 mmol) and di-tert-butyl dicarbonate (168.978 g, 774.233 mmol). The mixture was allowed to warm to room temperature, and the stirring was continued for 12 hrs. The mixture was concentrated under reduced pressure. The residue was diluted with water and acidified (pH 3-4) with aqueous 1N HCl solution. The resulting solid was collected by filtration. The white solid was dissolved in ethyl acetate and washed with water. The separated organic phase was dried over Na_2SO_4, filtered, and concentrated. The resulting solid was suspended in hexane and collected by filtration, and dried under reduced pressure to give 1-(tert-butoxycarbonyl)-3-piperidine carboxylic acid as a white solid. (156 g, yield; 88%)



To a cold (0 °C) solution of 1-(tert-butoxycarbonyl)-3-piperidine carboxylic acid (7.000 g, 30.531 mmol) in dichloromethane (200 mL) including triethylamine (4.681 mL, 33.584 mmol) were added benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (15.885 g, 30.531 mmol), N,O-dimethylhydroxyamine (3.276 g, 33.584 mmol) and triethylamine (4.255 mL, 30.531 mmol) successively. The mixture was allowed to warm to room temperature, and the stirring was continued for 12 hrs. The reaction mixture was diluted with dichloromethane and washed with an aqueous 1N HCl solution, saturated aqueous $NaHCO_3$ solution, and brine, successively. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel (chloroform/ethyl acetate = 10/1-9/1) to give 3-{[methoxy(methyl)amino]carbonyl}-1-piperidine-carboxylic acid tert-butyl ester as a white solid. (8.050 g, yield;96%)

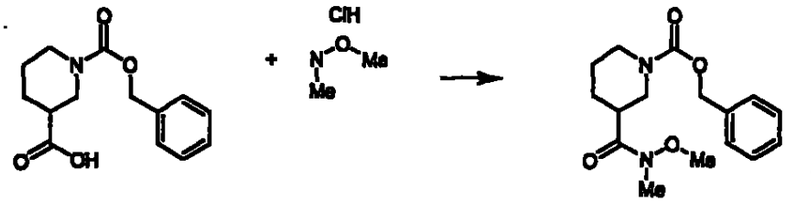


(Starting compound 2B)

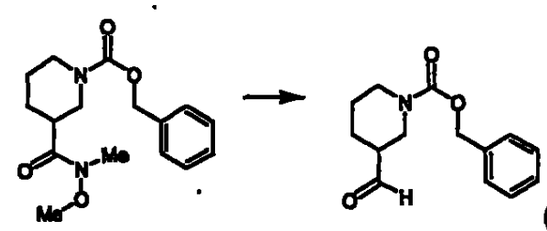
To a cooled (-15 °C), stirred suspension of lithium aluminum hydride (4.355 g, 114.743 mmol) in diethyl ether (500 mL) was added dropwise a solution of 3-{[methoxy(methyl)amino]carbonyl}-1-piperidine-carboxylic acid tert-butyl ester (25.000 g, 91.795 mmol) in THF (150 mL) over 30 min. The reaction mixture was quenched with aqueous 1N potassium hydrogen sulfate (300 mL), and extracted with a 1:1 mixture of diethyl ether and ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 3-formyl-piperidine-1-carboxylic acid tert-butyl ester, which was used for the next steps without further purification. (22.56 g, yield; quant.)

[Starting compound 2C]

To a cooled (0 °C) and stirred solution of nipecotinic acid (3.0 g, 23.3 mmol) in 1,4-dioxane (12 mL) was added 2N NaOH solution (24.0 mL, 48.0 mmol) followed by a solution of benzyl chloroformate (3.96 g, 23.2 mmol) in 1,4-dioxane (12 mL). The reaction mixture was allowed to warm to room temperature, and the stirring was continued for 3hrs. The mixture was concentrated under reduced pressure. The residue was diluted with water and acidified with 1H HCl (pH 3-4). The mixture was extracted with ethyl acetate, and the separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The resulting white solid was suspended in hexane, collected by filtration, washed with hexane, and dried under reduced pressure to give 1-[(benzyloxy)carbonyl]-3-piperidinecarboxylic acid as a white solid (4.4 g, yield; 71%).



To a cooled (-15 °C to –20 °C) and stirred solution of 1-[(benzyloxy)carbonyl]-3-piperidinecarboxylic acid (4.0 g, 15.2 mmol) in dry THF (50 mL) including methylmorpholine (2 mL) was added dropwise a solution of isobutyl chloroformate (2.28 g, 16.7 mmol) in THF (10 mL). After the mixture was stirred at the same temperature for 20 min, a solution of N,O-dimethylhydroxylamine hydrochloride (1.63 g, 16.7 mmol) in THF (20 mL) including methylmorpholine (2 mL) was added. The reaction mixture was allowed to warm to room temperature, and then stirred for 16 hrs. The reaction mixture was concentrated under reduced pressure and partitioned between ethyl acetate and water. The separated organic phase was washed with 1N HCl, saturated $NaHCO_3$, and brine, successively. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give benzyl 3-{[methoxy(methyl)amino]carbonyl}-1-piperidinecarboxylate as a colorless oil (4.7 g, yield; quant.).

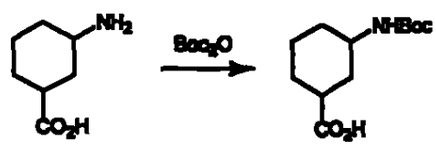


(Starting compound 2C)

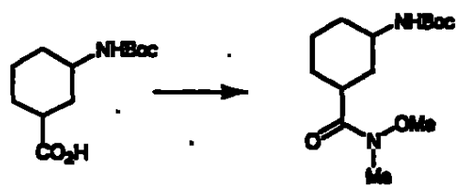
To a cooled (-78 °C) suspension of lithium aluminum hydride (0.70 g, 18.4 mmol) in dry THF (100 mL) under an argon atmosphere was added dropwise a solution of benzyl 3-{[methoxy(methyl)amino]carbonyl}-1-piperidinecarboxylate (4.5 g, 14.7 mmol) in THF (30 mL), and the stirring was continued at –78 °C for 45 min. The reaction mixture was quenched with 0.5N $KHSO_4$ (130 mL), and then extracted with ether. The separated organic phase was dried over $MgSO_4$, filtered, and concentrated

under reduced pressure to give benzyl 3-formyl-1-piperidinecarboxylate as a colorless oil (0.54 g, yield; 82%).

[Starting compound 2D]

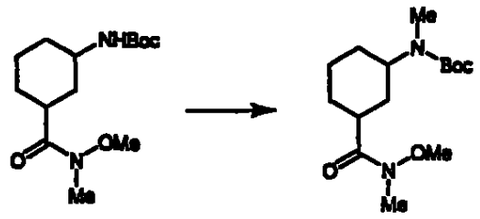


To a cold (0 °C) mixture of 3-aminocyclohexane-carboxylic acid (10.0 g, 69.8 mmol) in 1,4-dioxane (100 mL) and 2N NaOH (100 mL) was added di(tert-butyl) dicarbonate (15.2 g, 69.8 mmol). The mixture was stirred at room temperature for 1.5 hrs, and then neutralized with 2N HCl. The resulting mixture was concentrated under reduced pressure. The residue was acidified with 2N HCl and extracted with ethyl acetate. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered and evaporated. The residual solid was triturated with hexane, collected by filtration, and dried under reduced pressure to give 3-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylic acid as a white solid (8.00 g, yield; 47%).

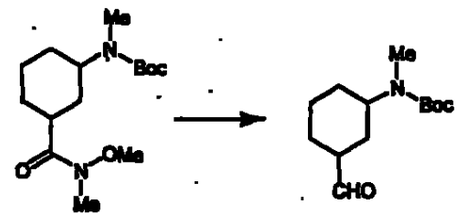


To a cold (0 °C) solution of 3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylic acid (5.00 g, 20.6 mmol) in CH_2Cl_2 (50 mL) including triethylamine (3.1 mL, 22.2 mmol) were added benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (10.7 g, 20.6 mmol), N,O-dimethylhydroxyamine hydrochloride (2.21 g, 20.6 mmol) and Et_3N (3.2 mL, 23.0 mmol) successively. The resulting mixture was allowed to warm to room temperature, and the stirring was continued for 18hrs. The reaction mixture was diluted with CH_2Cl_2 and washed with 1N HCl,

saturated aqueous $NaHCO_3$ solution, and brine, successively. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1:1) to give tert-butyl 3-{[methoxy(methyl)amino]carbonyl}cyclohexylcarbamate as a colorless oil (5.39 g, yield; 92%).



To a suspension of NaH (60%, 340 mg, 8.38 mmol) in THF (10 mL) was added dropwise a solution of tert-butyl 3-{[methoxy(methyl)amino]carbonyl}cyclohexylcarbamate (2.00 g, 6.98 mmol) in THF (10 mL)followed by methyl iodide (1.09 g, 7.68 mmol). The mixture was stirred at 60 °C for 0.5 hr. After cooled to room temperature, the mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1/1) to give tert-butyl N-[3-(N-methoxy-N-methylcarbamoyl)cyclohexyl]-N-methylcarbamate as a colorless oil (1.94 g, yield; 93%).



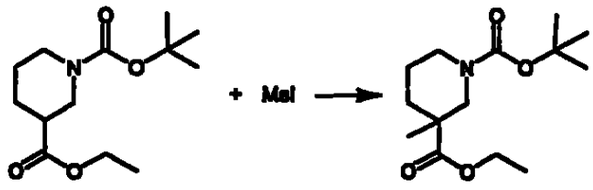
(Starting compound 2D)

To a cold (0 °C) suspension of $LiAlH_4$ (380 mg, 9.9 mmol) in Et_2O (40 mL) was added dropwise a solution of tert-butyl N-[3-(N-methoxy-N-methylcarbamoyl)cyclohexyl]-N-methylcarbamate (2.38 g, 7.92 mmol) in Et_2O (40 mL) over 10 min. The

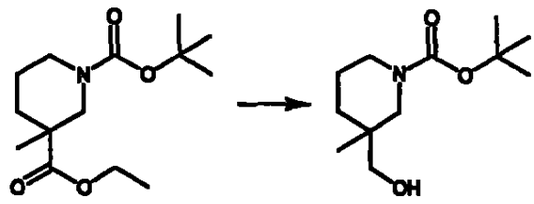
reaction mixture was stirred at 0 °C for 0.5 hr, and quenched with 1N $KHSO_4$ (100 mL). The organic phase was separated, dried over $MgSO_4$ and evaporated to give tert-butyl 3-formylcyclohexyl(methyl)carbamate as a colorless oil, which was used for next step without purification (1.66 g, yield;87%).

[Starting compound 2E]

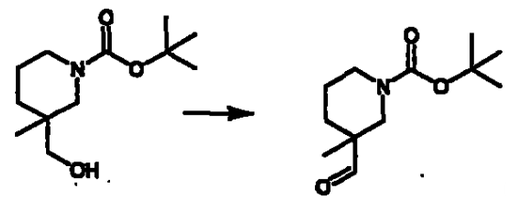
To a cold (0 °C) solution of ethyl nipecotate (7.86 g, 50 mmol) in CH_2Cl_2 (120 mL) was added di-tert-butyl dicarbonate (11.46 g, 52.5 mmol). The resulting mixture was stirred at room temperature for 4 hrs. The reaction mixture was diluted with a 5% aqueous $NaHCO_3$ solution. The organic phase was separated, dried over $MgSO_4$, filtered and evaporated under reduced pressure to give 1-tert-butyl 3-ethyl 1,3-piperidinedicarboxylate (12.8 g, yield; quant.).



To a cold (-78 °C) solution of lithium diisopropylamide (LDA) (23.3 mmol) in THF (10 mL) under an argon atmosphere was added dropwise a solution of 1-tert-butyl 3-ethyl 1,3-piperidinedicarboxylate (3.0 g, 11.6 mmol) in THF (5 mL), then stirred at -50 °C for 2 hrs. To the resulting mixture was added a solution of MeI (1.98 g, 14 mmol) in THF at –50 °C. The reaction mixture was allowed to warm to room temperature, and quenched with saturated aqueous NH_4Cl solution. The mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane:ethyl acetate, 9:1) to give 1-tert-butyl 3-ethyl 3-methyl-1,3-piperidinedicarboxylate as a pale yellow oil (2.27 g, yield; 72%).



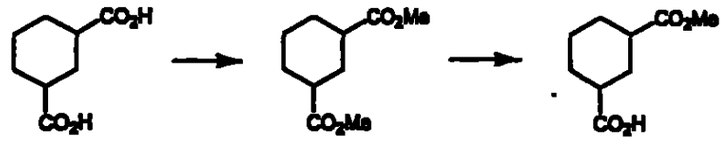
To a cold (-20 °C) solution of 1-tert-butyl 3-ethyl 3-methyl-1,3-piperidinedicarboxylate (2.3 g, 8.48 mmol) in dry THF was added $LiBH_4$ (2M in THF, 10.6 mmol), and the stirring was continued overnight. The reaction mixture was allowed to warm to room temperature. The reaction mixture was cooled by ice water and acidified (pH 5-6) with aqueous 1N HCl. The mixture was concentrated under reduced pressure, then extracted with ethyl acetate. The organic phase was separated, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on silica gel (hexane: ethyl acetate, 4:1-3:1) to give tert-butyl 3-(hydroxymethyl)-3-methyl-1-piperidinecarboxylate as a colorless oil form (1.5 g, yield; 78%).



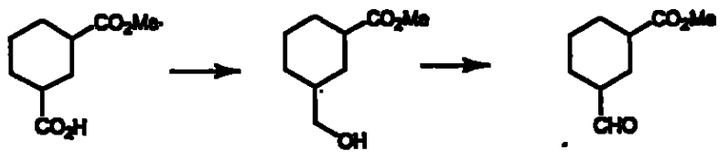
(Starting compound 2E)

To an ice water cooled solution of tert-butyl 3-(hydroxymethyl)-3-methyl-1-piperidinecarboxylate (1.5 g, 6.6 mmol) in CH_2Cl_2 were added DMSO (7.1 g, 91.6 mmol), Et_3N (5.5 mL, 39.8 mmol), and sulfur trioxide-Pyridine complex (3.1 g, 19.9 mmol) successively. The mixture was stirred at room temperature for 1hr. The reaction mixture was diluted with ether, purified by column chromatography on silica gel (hexane:ethyl acetate, 5:1 – 4:1) to give tert-butyl 3-formyl-3-methyl-1-piperidinecarboxylate as a colorless oil form (1.3 g, yield; 86%).

[Starting compound 2F]



To a solution of 1,3-cyclohexanedicarboxylic acid (10 g, 58 mmol) in MeOH (50 mL) was added conc. H_2SO_4 (2 mL). Then the mixture was stirred at room temperature for 4 hrs. The mixture was concentrated under reduced pressure, and then partitioned between ethyl acetate and a saturated aqueous $NaHCO_3$ solution. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated to give dimethyl 1,3-cyclohexanedicarboxylate as a colorless oil (11.6 g, yield; quant.). To a solution of dimethyl 1,3-cyclohexanedicarboxylate (11.6 g, 57.9 mmol) in MeOH (58 mL) was added a 1N NaOH solution (58 mL) dropwise over 1 hr at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 hrs, and at room temperature for 2 hrs. The mixture was concentrated under reduced pressure, and the residual solution was partitioned between ethyl acetate and water. The aqueous phase was separated, acidified with conc. HCl (15 mL), saturated with NaCl, and then extracted with ethyl acetate. The extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 3-(methoxycarbonyl)cyclohexanecarboxylic acid as a colorless oil (6.16 g, yield; 57%).

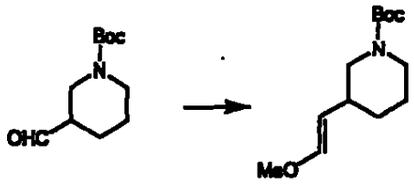


(Starting compound 2F)

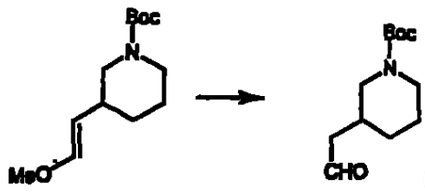
To a cold (-78 °C) solution of 3-(methoxycarbonyl)cyclohexanecarboxylic acid (1.25 g, 6.71 mmol) in THF (20 mL) was added $BH_3 \cdot Me_2S$ (0.7 mL, 7.38 mmol). The resulting mixture was stirred at –78 °C to room temperature overnight. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution and

extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (n-hexane/ethyl acetate = 2/1) to give methyl 3-(hydroxymethyl)cyclohexanecarboxylate as a colorless oil (845 mg, yield; 73%). To a solution of methyl 3-(hydroxymethyl)cyclohexanecarboxylate (840 mg, 4.88 mmol) in Et_3N (4.4 mL, 32 mmol) and DMSO (10 mL) was added sulfur trioxide-pyridine complex (2.56 g, 16.1 mmol). The mixture was stirred at room temperature for 1 hr. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel (n-hexane/ethyl acetate = 2/1) to give methyl 3-formylcyclohexanecarboxylate as a pale yellow oil (795 mg, yield; 96%).

[Starting compound 2G]



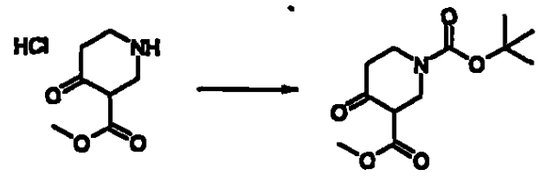
To a suspension of methoxymethylphosphonium chloride (5.14 g, 15 mmol) in THF (18 mL) was added potassium tert-butoxide (1.98 g, 15 mmol) at 0 °C, and the mixture was stirred at 0 °C for 0.5 hr. A solution of tert-butyl 3-formyl-1-piperidinecarboxylate (2.13 g, 10 mmol) in THF (8 mL) was added dropwise at -20 °C, and the resulting mixture was stirred at 0 °C to room temperature overnight. The mixture was partitioned between toluene and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 5/1) gave tert-butyl 3-(2-methoxyethenyl)-1-piperidinecarboxylate as a colorless oil (1.16 g, yield; 48%).



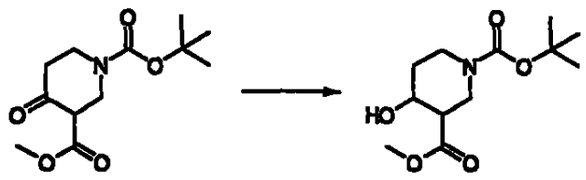
(Starting compound 2G)

tert-Butyl 3-(2-methoxyethenyl)-1-piperidinecarboxylate (1.16 g, 4.81 mmol) was dissolved in 90% formic acid (2 mL). The mixture was stirred at room temperature for 40 min. The mixture was then partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered and evaporated. Purification by column chromatography (hexane/ethyl acetate = 4/1) gave tert-butyl 3-(2-oxoethyl)-1-piperidinecarboxylate as a colorless oil (652 mg, yield; 60%).

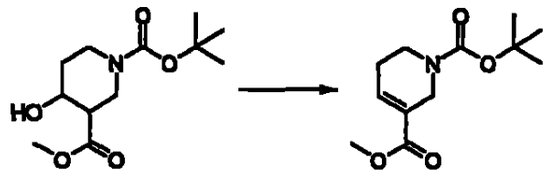
[Starting compound 2H]



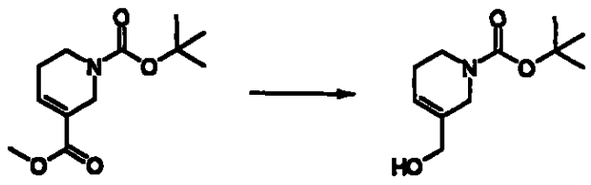
To a cold (0 °C) mixture of 3-methoxycarbonyl 4-piperidone HCl (10 g, 51.6 mmol) and triethylamine (10.8 mL, 77.5 mmol) in dichloromethane (100 mL) was added a solution of di-tert-butyl dicarbonate (11.8 g, 54.2 mmol) in dichloromethane (100 mL). The mixture was stirred at room temperature for 2 hrs and concentrated under reduced pressure. The residue was quenched with water, extracted with ether, dried over $MgSO_4$, filtered, and evaporated to give 1-tert-butyl-3-methyl 4-oxo-1,3-piperidinedicarboxylate, which was used for the next reaction without further purification. (14.9 g, yield; quant.)



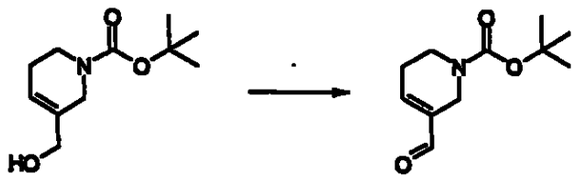
To a cold (0 °C) solution of 1-tert-butyl 3-methyl 4-oxo-1,3-piperidinedicarboxylate (134.0 g, 520.8 mmol) in methanol (800 mL) was added $NaBH_4$ (9.85 g, 260.4 mmol) portionwise. The resulting mixture was stirred overnight to be allowed to warm to room temperature. The solvent was removed under reduced pressure, the residue was dissolved into ethyl acetate, washed with brine, dried over $MgSO_4$, filterd, and concentrated under reduced pressure to give 1-tert-butyl 3-methyl 4-hydroxy-1,3-piperidinedicarboxylate, which was used for the next reaction without further purification. (120.8 g, yield 90%)



To a cold (0 °C) solution of 1-tert-butyl 3-methyl 4-hydroxy-1,3-piperidine-dicarboxylate (1,64 g, 6.32 mmol), 4-dimethylaminopyridine (16.0 mg, 0.13 mmol), and triethylamine (2.64 mL, 19.0 mmol) in dichloromethane (25 mL) was added dropwise trifluoroacetic anhydride (1.12 mL, 7.91 mmol). The reaction mixture was stirred at room temperature for 40 hrs. The reaction was quenched with 10% K_2CO_3 solurtion, extracted with $CHCl_3$. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane: ethyl acetate = 5:1) to give 1-tert-butyl 3-methyl 5,6-dihydro-1,3(2H)-pyridinedicarboxylate as a pale yellow oil. (707.4 mg, yield 46%)



To a cold (-20 °C) solution of 1-tert-butyl 3-methyl 5,6-dihydro-1,3(2H)-pyridinedicarboxylate (700.0 mg, 2.90 mmol) in dry toluene (40 mL) was added a solution of diisobutylaluminum hydride in toluene (1.5M, 4.83 mL, 7.25 mmol) dropwise under an argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and then stirred at room temperature. The reaction was quenched by an addition of water and the stirring was continued for additional 1hr. The precipitated aluminum salts were filtered off. The filtrate was diluted with saturated NH_4Cl solution, extracted with ethyl acetate. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated to give tert-butyl 5-(hydroxymethyl)-3,6-dihydro-1(2H)-pyridinecarboxylate, which was used for the next reaction without further purification. (580.0 mg, yield 94%)

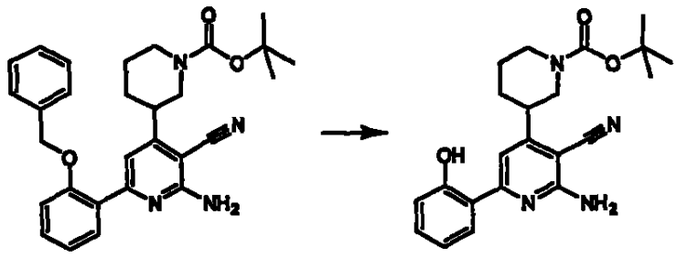


(Starting compound 2H)

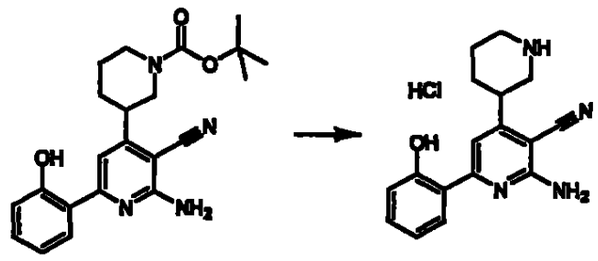
To a solution of tert-butyl 5-(hydroxymethyl)-3,6-dihydro-1(2H)-pyridinecarboxylate (14.65 g, 68.69 mmol) in dichloromethane was added MnO_2 (89.58 g, 1030.36 mmol), then stirred overnight at room temperature. The reaction mixture was filtered through Celite®, the filtrate was concentrated under reduced pressure to give tert-butyl 5-formyl-3,6-dihydro-1(2H)-pyridinecarboxylate, which was pure enough to be used for the next reaction. (13.55 g, yield 94%)

Example 1-1

(1) A mixture of 2'-benzyloxyacetophenone (starting compound 1A) (10.00 g, 44.19 mmol), tert-butyl 3-formyl-1-piperidine carboxylate (starting compound 2B) (10.37 g, 44.61 mmol), malononitrile (3.21 g, 48.61 mmol), and ammonium acetate (17.03 g, 220.97 mmol) in toluene (50 mL) was stirred at 150 °C for 2 hrs. After cooled to room temperature, the reaction mixture was diluted with ethyl acetate. The organic phase was washed with water and saturated brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1). The purified compound (yellow oil) was recrystallized from ethanol to give tert-butyl 3-{2-amino-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate as a white solid. (5.83 g, yield; 27%).



(2) A mixture of tert-butyl 3-{2-amino-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate (2.160 g, 4.457 mmol) and 10% Pd-C (0.720 g) in ethyl acetate (30 mL) was stirred at room temperature for 2 days under a hydrogen atmosphere (3 atm). The mixture was filtrated with Celite® and the filtrate was concentrated under reduced pressure. The residue was recrystallized from diethyl ether to give tert-butyl 3-[2-amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate as a white solid. (0.180 g, yield; 10%)



(3) To a stirred solution of tert-butyl 3-[2-amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.170 g, 0.431 mmol) in dioxane (30 mL) was added 4N HCl in dioxane (3 mL). The mixture was stirred at room temperature for 12 hrs. The resulting precipitates were collected by filtration and the filtrate was washed with dioxane to give 2-amino-6-(2-hydroxyphenyl)-4-(3-piperidinyl)-nicotinonitrile hydrochloride(0.075 g, yield; 53%).

Molecular weight: 330.82

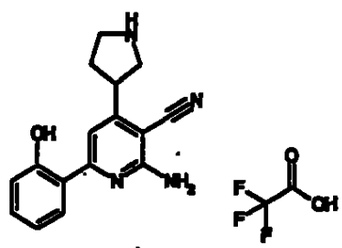
Mass spectrometry: 295 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A/(Jurkat)-A

^{1}H-NMR(300 MHz, DMSO-d6): 1.81 – 1.89 (4H, m), 2.88 – 2.92 (1H, m), 3.31 – 3.40 (4H, m), 6.89 – 6.94 (2H, m), 7.32 – 7.38 (1H, m), 7.43 (1H, s), 8.05 (1H, d, J = 7.4 Hz), 8.83 – 8.85 (1H, br s), 9.45 – 9.47 (1H, br s).

Example 1-2



With the use of starting compound 2A instead of 2B, 2-amino-6-(2-hydroxyphenyl)-4-(3-pirrolidinyl)nicotinonitrile trifluoroacetate was prepared in a similar manner as described in Example 1-1.

Molecular weight: 394.36

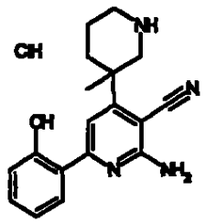
Mass spectrometry: 281 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A594)-A/(Jurkat)-B

^{1}H-NMR(500 MHz, DMSO-d6): 2.10 (1H, m), 3.60 – 3.70 (2H, m), 6.91 (2H, m), 7.36 – 7.44 (4H, m), 8.05 (1H, d, J = 8.2 Hz), 9.00 (2H, br), 13.35 (1H, s).

Example 1-3



With the use of starting compound 2E instead of 2B, 2-amino-6-(2-hydroxyphenyl)-4-(3-methylpiperidin-3-yl)-nicotinonitrile hydrochloride was prepared in a similar manner as described in Example 1-1.

Molecular weight: 344.85

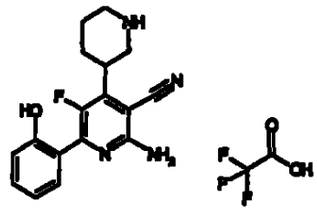
Mass spectrometry: 309 $(M+H)^+$

In vitro activity grade: B

Cellular activity grade: (A594)-B

^{1}H-NMR(500 MHz, DMSO-d6): 1.52 (3H, s), 1.78 (2H, br d, J = 38.1 Hz), 1.97 – 2.04 (1H, m), 2.37 – 2.44 (1H, m), 2.99 (2H, br d, J = 31.7 Hz), 3.34 (1H, dd, J = 5.5, 12.5 Hz), 3.75 (1H, dd, J = 5.5, 12.5 Hz), 6.92 – 6.96 (2H, m), 7.22 (1H, s), 7.33 – 7.39 (2H, m), 8.05 – 8.08 (1H, m), 9.02 (1H, br s), 9.42 (1H, br s).

Example 1-4



With the use of the starting compound 1B instead of 1A, 2-amino-5-fluoro-6-(2-hydroxyphenyl)-4-(3-piperidinyl)-nicotinonitrile trifluoroacetate was prepared in a similar manner as described in Example 1-1.

Molecular weight: 426.37

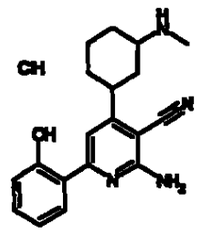
Mass spectrometry: 313 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A594)-B/(Jurkat)-B

^{1}H-NMR(500 MHz, DMSO-d6): 1.77 (2H, m), 1.95 (3H, m), 2.94 (1H, t, J = 10.7 Hz), 3.25 – 3.37 (2H, m), 3.50 (1H, d, J = 12.0 Hz), 6.90 (1H, dt, J = 1.0, 8.2 Hz), 6.93 (1H, d, J = 8.2 Hz), 7.03 (2H, br), 7.32 (1H, dt, J = 1.6, 8.5 Hz), 7.47 (1H, dd, J = 1.6, 7.9 Hz), 8.73 (2H, br), 10.72 (1H, s).

Example 1-5



With the use of the starting compound 2D instead of 2B, 2-amino-6-(2-hydroxyphenyl)-4-[3-methylamino]cyclohexyl]nicotinonitrile hydrochloride was prepared in a same manner as described in Example 1-1.

Molecular weight: 358.87

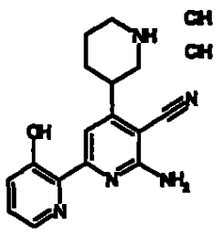
Mass spectrometry: 323 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A594)-B

^{1}H-NMR(300 MHz, DMSO-d6): 1.34 – 1.86 (5H, m), 1.86 – 2.04 (1H, m), 2.04 – 2.30 (2H, m), 2.50 – 2.60 (3H, m), 2.76 – 2.95 (1H, m), 3.17 (1H, br s), 6.85 – 6.96 (2H, m), 7.20 – 7.40 (3H, m), 7.99 (1H, d, J = 8.1 Hz), 9.11 (2H, br s).

Example 1-6



With the use of starting compound 1F instead of 1A, 6-amino-3'-hydroxy-4-(3-piperidinyl)-2,2'-bipyridine-5-carbonitrile hydrochloride was prepared in a same manner as described in Example 1-1.

Molecular weight: 368.27

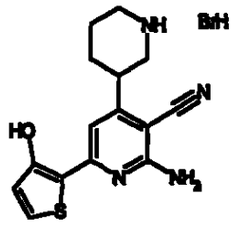
Mass spectrometry: 337 $(M+H)^+$

In vitro activity grade:A

Cellular activity grade: (A594)-A

^{1}H-NMR (500 MHz, DMSO-d6): 1.78 – 1.82 (2H, m), 1.93 – 1.95 (2H, m), 3.03 – 3.07 (1H, m), 3.27 – 3.37 (3H, m), 3.56 (1H, m), 7.39 (1H, dd, J = 1.6, 8.5 Hz), 7.43 (1H, dd, J = 4.1, 8.5 Hz), 7.56 (1H, br), 7.76 (1H, s), 8.23 (1H, dd, J = 1.6, 4.1 Hz), 8.78 (1H, br), 9.18 (1H, br).

Example 1-7



With the use of the starting compound 1J instead of 1A, 2-amino-6-(3-hydroxy-2-thienyl)-4-(3-piperidinyl)nicotinonitrile hydrobromide was prepared in a same manner as described in Example 1-1.

Molecular weight: 381.30

Mass spectrometry: 301 $(M+H)^+$

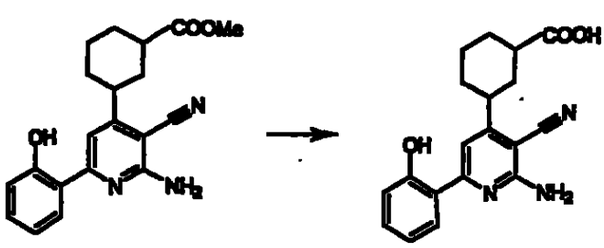
In vitro activity grade:A

Cellular activity grade: (A594)-A

^{1}H-NMR (500 MHz, DMSO-d6): 1.69 – 1.84 (2H, m), 1.84 – 2.00 (2H, m), 2.94 – 3.06 (1H, m), 3.12 – 3.28 (2H, m), 3.28 – 3.40 (2H, m), 6.82 (2H, d, J = 5.4 Hz), 6.83 (1H, s), 7.63 (2H, d, J = 5.4 Hz), 8.55 – 8.70 (1H, m), 8.85 – 9.00 (1H, m).

Example 1-8

With the use of the starting compound 2F instead of 2B, methyl 3-[2-amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]-cyclohexanecarboxylate was prepared in a similar manner as described in Example 1-1.



A suspension of methyl 3-[2-amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]cyclohexanecarboxylate (151 mg, 0.43 mmol) in 2N NaOH (1 mL) and THF (2 mL) was stirred at 60 °C for 4 hrs. The reaction mixture was neutralized with 1N HCl (2 mL), and then diluted with water. The resulting precipitates were collected by filtration, washed with EtOH, and dried (60 °C, 2 hrs, under reduced pressure) to give 3-[2-amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]cyclohexanecarboxylic acid as a yellow solid (105 mg, yield; 72%).

Molecular weight: 337.38

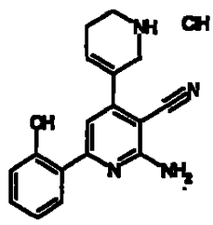
Mass spectrometry: 338 $(M+H)^+$

In vitro activity grade: B

Cellular activity grade: (A594)-C

^{1}H-NMR (300 MHz, DMSO-d6): 1.30 – 2.14 (8H, m), 2.30 – 2.59 (1H, m), 2.70 – 2.89 (1H, m), 6.83 – 6.93 (2H, m), 7.24 – 7.38 (4H, m), 8.00 – 8.10 (1H, m), 12.41 (1H, s), 13.47 (1H, s).

Examples 1-9



With the use of the starting compound 1D instead of 1A and the starting compound 2H instead of 2B, 2'-amino-6'-(2-hydroxyphenyl)-1,2,5,6-tetrahydro-3,4'-bipyridine-3'-carbonitrile hydrochloride was prepared in a same manner as described in Example 1-1.

Molecular weight: 328.80

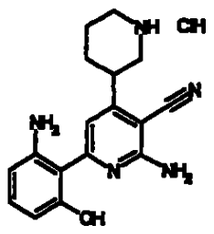
Mass spectrometry: 293 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A594)-A

^{1}H-NMR (500 MHz, DMSO-d6): 2.52 (2H, br s), 3.24 (2H, br s), 4.05(2H, br s), 6.45 (1H, s), 6.90 – 6.93 (2H, m), 7.35 – 7.46 (4H, m), 8.01 – 8.02 (1H, m), 9.37 (1H, br s).

Examples 1-10



With the use of starting compound 1H instead of 1A, 2-amino-6-(2-amino-6-hydroxyphenyl)-4-(3-piperidinyl) nicotinonitrile hydrochloride was prepared in a same manner as described in Example 1-1.

Molecular weight: 345.83

Mass spectrometry: 310 $(M+H)^+$

In vitro activity grade: C

Cellular activity grade: (A594)-C

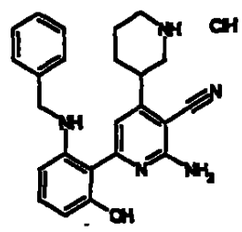
^{1}H-NMR (500 MHz, DMSO-d6): 1.81 – 1.92 (3H, m), 2.89 – 2.93 (1H, m), 3.28 – 3.32 (3H, m), 6.97 (2H, dd, j = 11.7, 8.2 Hz), 7.30 (2H, t, J = 8.2 Hz), 9.01 (1H, m), 9.59 (1H, m).

Examples 1-11

(1) With the use of the starting compound 1H instead of 1A, tert-butyl 3-(2-amino-6-{2-amino-6-[(4-methoxybenzyl) oxy]phenyl}-3-cyano-4-pyridinyl)-1-piperidinecarboxylate was prepared in a same manner as described in the step (1) of Example 1-1.

(2) To a cooled (0 °C), stirred solution of tert-butyl 3-(2-amino-6-{2-amino-6-[(4-methoxybenzyl)oxy]phenyl}-3-cyano-4-pyridinyl)-1-piperidinecarboxylate (0.30 g, 0.566 mmol) in methanol (10 mL) including acetic acid (0.03 g, 0.566 mmol) was added benzaldehyde (0.08 mL, 1.133 mmol) followed by sodium cyanoborohydride (0.04 g, 0.566 mmol), and the stirring was continued at 0 °C for 3 hrs. The reaction was quenched with water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / ethyl acetate = 4/1) to give tert-butyl 3-(2-amino-6-{2-(benzylamino)-6-[(4-methoxybenzyl)oxy]-phenyl}-3-cyano-4-pyridinyl)-1-piperidinecarboxylate as a yellow amorphous (0.299 g, yield; 85%).

(3) Then the yellow amorphous was treated under acidic conditions in the similar manner as that of the step (3) in Example 1-1 to give 2-amino-6-[2-(benzylamino)-6-hydroxyphenyl]-4-(3-piperidinyl) nicotinonitrile hydrochloride.



Molecular weight: 435.96

Mass spectrometry: 400 $(M+H)^+$

In vitro activity grade: B

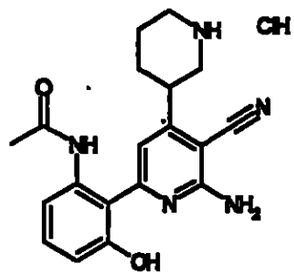
Cellular activity grade: (A594) C

^{1}H-NMR (500 MHz, DMSO-d6): 1.69 – 1.83 (2H, m), 1.90 – 1.92 (2H, m), 2.89 – 2.92 (1H, m), 3.15 – 3.18 (1H, m), 3.28 – 3.33 (3H. m), 4.28 (2H, s), 6.17 (1H, d, J = 8.2 Hz), 6.32 (1H, d, J = 8.2 Hz), 7.00 (1H, t, J = 8.2 Hz), 7.09 (1H, s), 7.20 – 7.23 (1H, m), 7.28 – 7.33 (4H, m), 8.97 (1H, m), 9.47 (1H, m).

Example 1-12

To a cooled (0 °C), stirred solution of tert-butyl 3-(2-amino-6-{2-amino-6-[(4-methoxybenzyl)oxy]phenyl}-3-cyano-4-pyridinyl)-1-piperidinecarboxylate (0.10 g, 0.189 mmol) obtained in the step (1) of Example 1-11 in dichloromethane (10 mL) including triethylamine (0.02 g, 0.227 mmol) was added acetic anhydride (0.08 g, 0.889 mmol).The stirring was continued at 0 °C for 5 hrs. The mixture was allowed to warm to room temperature, and the stirring was continued for 30 min. The reaction was quenched with water and extracted with ethyl acetate. The organic phase was washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / ethyl acetate = 2/1 – 1/1 – 1/2) to give tert-butyl 3-(6-{2-(acetylamino)-6-[(4-methoxybenzyl)oxy]phenyl}-2-amino-3-cyano-4-pyridinyl)-1-piperidine-carboxylate as a pale yellow oil (0.102 g, yield; 94.5%).

Then the yellow oil was treated with acids in the same manner as in the step (2) in Example 1-1 to give *N*-{2-[6-amino-5-cyano-4-(3-piperidinyl)-2-pyridinyl]-3-hydroxyphenyl}acetamide hydrochloride.



Molecular weight: 387.87

Mass spectrometry: 352 $(M+H)^+$

In vitro activity grade: C

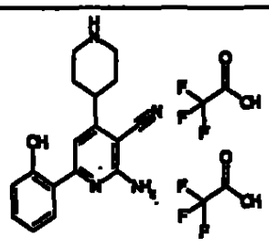
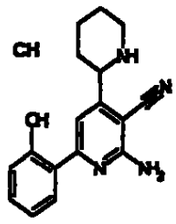
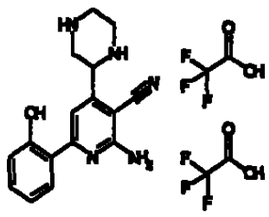
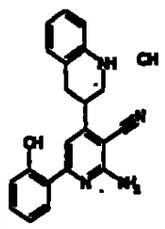
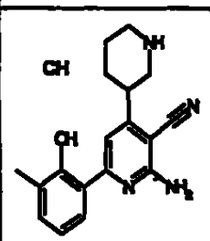
Cellular activity grade: (A594) C

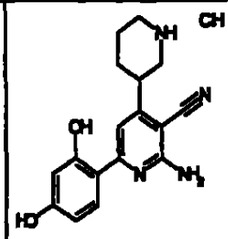
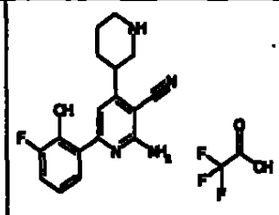
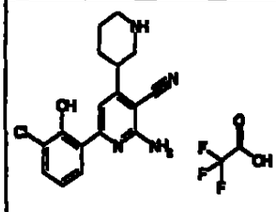
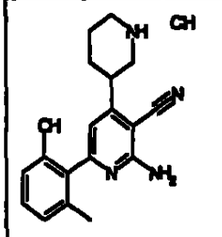
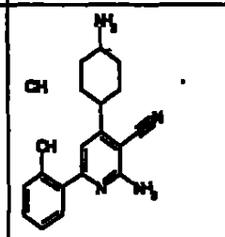
^{1}H-NMR (500 MHz, DMSO-d6): 1.60 – 1.86 (4H, m), 1.90 (3H, s), 2.88 – 2.95 (1H, m), 3.12 – 3.26 (4H, m), 6.78 (1H, d, J = 8.2 Hz), 7.02 (1H, s), 7.23 (1H, t, J = 8.2 Hz), 7.28 – 7.30 (1H, m), 8.90 – 8.92 (1H, m), 9.40 – 9.42 (1H, m), 9.90 (1H, br s).

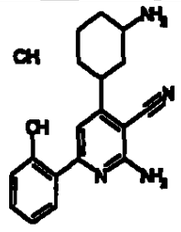
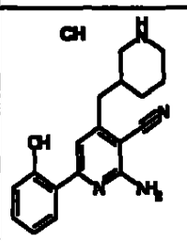
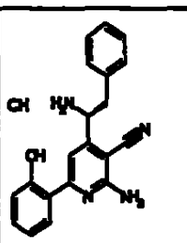
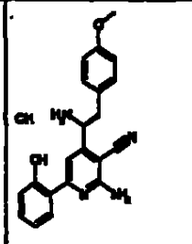
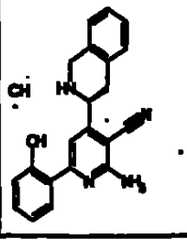
Examples 1-13 to 1-44

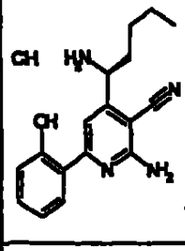
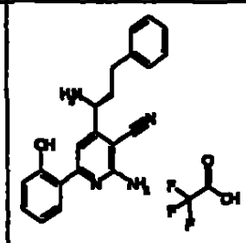
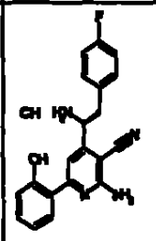
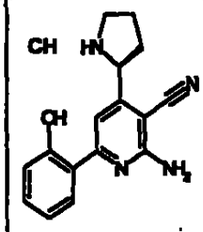
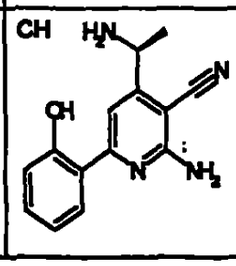
In similar manners as described in Example 1-1 to Example 1-12 above, compounds in Examples 1-13 to 1-44 as shown in Table 1 were synthesized.

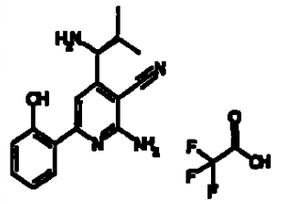
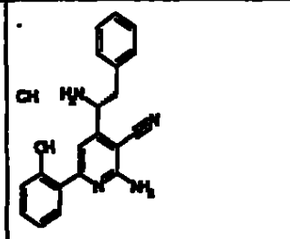
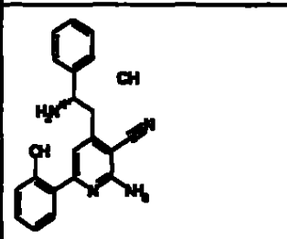
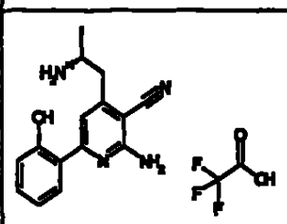
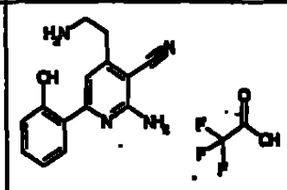
Table 1

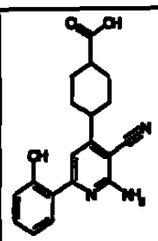
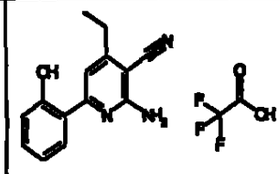
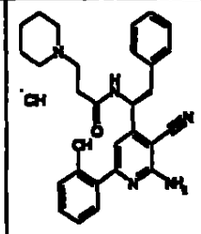
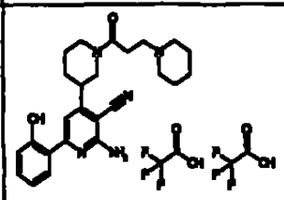
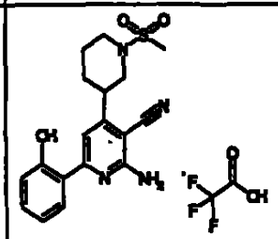
Ex. No	Structure	Mol weight	Mass	In vitro	A549	NMR
1-13		522.41	295	A	A	(300 MHz, DMSO-d6): 1.99 (4H, m), 3.11 (3H, m), 3.43 (2H, d, J = 13.2 Hz), 6.91 (2H, m), 7.20 (1H, s), 7.35 (3H, m), 7.94 (1H, d, J = 8.5 Hz), 8.46 (1H, br), 8.76 (1H, br), 13.20 (1H, br).
1-14		330.82	295	B	B	(300 MHz, DMSO-d6): 1.67 - 2.05 (6H, m), 3.19 - 3.28 (1H, m), 3.42 - 3.51 (1H, m), 4.30 - 4.33 (1H, m), 6.91 - 6.95 (2H, m), 7.35 - 7.40 (1H, m), 7.65 (1H, br s), 8.07 (1H, s), 8.18 (1H, d, J = 7.3 Hz),8.41 - 9.45 (1H, m), 10.27 - 10.30 (1H, m).
1-15		523.40	296	B	B	(300 MHz, DMSO-d6): 3.00 (3H, m), 3.69 (3H, m), 4.06 (1H, m), 4.55 (1H, d, J = 3.7 Hz), 5.14 (1H, dd, J = 4.0, 11.7 Hz), 6.95 (2H, m), 7.38 (1H, t, J = 8.3 Hz), 7.81 (3H, m), 7.98 (1H, d, J = 8.3 Hz), 8.40 (3H, br), 13.5 Hz, (1H,s).
1-16		378.86	343	D		(500 MHz, DMSO-d6): 2.88 (1H, d, J = 14.8 Hz), 2.92 - 3.19 (2H, m), 3.38 - 3.41 (2H, m), 6.54 (1H, m), 6.59 (1H, d, J = 7.9 Hz), 6.84 - 6.90 (2H, m), 6.94 - 6.97 (2H, m), 7.30 - 7.37 (4H, m), 7.96 (1H, d, J = 8.2 Hz), 13.45 (1H, br).
1-17		344.85	309	B	B	(300 MHz, DMSO-d6): 1.76 - 1.98 (4H, m), 2.20 (3H, s), 2.87 - 2.93(1H, m), 3.23 - 3.43 (4H, m), 6.32 (0.7H, br s), 6.82 (1H, t, J = 7.5 Hz), 7.23 (1H, d, J = 7.2 Hz), 7.42 (3H, br s), 7.91 (1H, d, J = 8.3 Hz), 13.88 (1H, br s).

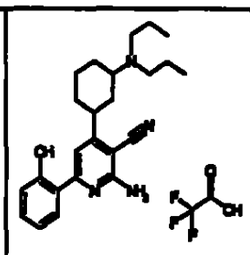
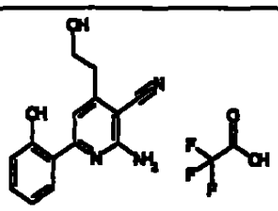
1-18		346.82	311	B	B	(300 MHz, DMSO-d6): 1.76 - 1.95 (4 H, m), 2.89 (1H, m), 3.22 (1H, m), 3.31 - 3.39 (3H, m), 6.26 (1H, d, J = 2.3 Hz), 6.36 (1H, dd, J = 2.3, 8.7 Hz), 7.24 (1H, s), 7.31 (1H, br s), 7.87 (1H, d, J = 8.7 Hz), 8.77 (1H, br s), 9.38 (1H, br s).
1-19		426.37	313	A	A	(500 MHz, DMSO-d6): 1.76 - 1.97 (4H, m), 2.88 - 2.90 (1H, m), 3.22 - 3.27 (4H, m), 6.88 - 6.94 (1H, m), 7.30 - 7.35 (1H, m), 7.44 (1H, s), 7.55 (2H, br s), 7.88 (1H, d, J = 8.5 Hz), 8.60 (1H, br s), 8.99 (1H, br s), 13.83 (1H, br s).
1-20		442.83	329	A	A	(500 MHz, DMSO-d6): 1.74 - 1.97 (4H, m), 2.86 - 2.92 (1H, m), 3.23 - 3.45 (4H, m), 6.94 (1H, t, J = 7.8 Hz), 7.47 (1H, br s), 7.55 (1H, dd, J = 7.8, 1.4 Hz), 7.59 (2H, br s), 8.07 (1H, dd, J = 8.5, 1.4 Hz), 8.60 (1H, br s), 8.99 (1H, br s), 14.58 (1H, br s).
1-21		344.85	309	C	B	(500 MHz, DMSO-d6): 1.79 - 1.85 (4H, m), 2.20 (3H, s), 2.90 (1H, dd, J = 10.4, 11.3 Hz), 3.23 - 3.42 (4H, m), 6.82 (1H, t, J = 7.6 Hz), 7.26 (1H, d, J = 7.6 Hz), 7.43 (2H, br s), 7.43 (1H, s), 7.91 (1H, d, J = 7.6 Hz), 8.66 (1H, br), 9.51 (1H, br), 13.91 (1H, br).
1-22		344.85	309	A	A	(300 MHz, DMSO-d6): 1.40 - 2.20 (6H, m), 2.60 - 2.88 (1H, m), 3.10 and 3.48(1H, br s), 6.75 - 6.85 (2H, m), 7.00 - 7.85 (3H, m), 7.85 - 8.25 (1H, m), 8.14 (1H, br s), 8.37 (1H, br s).

1-23		344.85	309	A	A	(300 MHz, DMSO-d6): 1.27 - 2.17 (9H, m), 2.75 - 3.00 (1H, m), 3.19 (1H, br s), 6.70 - 7.00 (2H, m), 7.00 - 7.80 (3H, m), 7.80 - 8.40 (3H, m).
1-24		344.85	309	A	B	(500 MHz, DMSO-d6): 1.25 - 1.38 (1H, m), 1.58 - 1.70 (1H, m), 1.72 - 1.84 (2H, m), 2.15 - 2.25 (1H, m), 2.60 - 2.85 (4H, m), 3.10 - 3.22 (2H, m), 6.88 - 6.94 (2H, m), 7.34 (1H, t, J = 7.7 Hz), 7.38 (1H, s), 7.45 (2H, br), 7.95 (1H, d, J = 8.5 Hz), 8.70 (1H, br), 9.05 (1H, br).
1-25		368.85	331	A	B	(300 MHz, DMSO-d6): 3.20(1H, dd, J = 9.5, 13.2 Hz), 3.22 (1H, dd, J = 5.7, 13.2 Hz), 4.54 (1H, br), 6.90 - 6.95 (2H, m), 7.10 - 7.13 (2H, m), 7.22 - 7.51 (7H, m), 8.09 (1H, s), 8.12 (1H, d, J = 7.9 Hz), 9.00 (3H, br).
1-26		398.88	361	A	B	(500 MHz, DMSO-d6): 3.11 - 3.24 (1H, m), 3.27 - 3.45 (1H, m), 3.66 (3H, s), 5.24 (1H, br s), 6.79 (2H, d, J = 8.8 Hz), 6.88 - 6.99 (2H, m), 7.08 (2H, d, J = 8.8 Hz), 7.33 - 7.41 (3H, m), 7.83 (1H, s), 8.00 (1H, dd, J = 1.3, 8.2 Hz), 10.14 (1H, s).
1-27		378.86	343	C		(300 MHz, DMSO-d6): 2.77 - 2.88 (1H, m), 4.82 (1H, d, J = 17.4 Hz), 5.08 (1H, dd, J = 4.2, 11.9 Hz), 5.20 (1H, d, J = 17.4 Hz), 6.93 - 7.00 (2H, m), 7.28 - 7.51 (4H, m)7.83 (1H, s), 7.94 (1H, br s), 8.07 (1H, dd, J = 7.2, 14.9 Hz), 9.53 (1H, s).

1-28		332.84	297	A	C	(300 MHz, DMSO-d6): 0.85 (3H, t, J = 6.7 Hz), 1.17 - 1.30 (4H, m), 1.88-1.94 (1H, m), 1.97 - 2.12 (1H, m), 4.29 (1H, br s), 6.93 (2H, t, J = 6.5 Hz), 7.37 (1H, t, J = 7.6 Hz), 7.60 (1H, br s), 7.92 (1H, s), 8.07 (1H, dd, J = 7.8, 14.5 Hz), 8.99 (2H, s).
1-29		458.44	345	B	C	(300 MHz, DMSO-d6): 2.08 (1H, m), 5.03 (1H, dd, J = 4.1, 6.8 Hz), 6.92 (2H, m), 7.15 - 7.39 (6H, m), 7.70 (3H, d, J = 5.6 Hz), 8.06 (1H, dd, J = 1.3, 8.3 Hz), 8.87 (1H, br), 9.25 (1H, m), 10.34 (1H, m), 13.69 (1H, s).
1-30		384.84	349	A	B	(300 MHz, DMSO-d6): 3.15 - 3.23 (1H, m), 3.47 - 3.53 (1H, m), 4.47 - 4.51 (1H, m), 6.91 - 6.98 (2H, m), 7.06 - 7.20 (4H, m), 7.35 - 7.48 (1H, m), 8.11 (1H, s), 8.13 - 8.17 (1H, m), 9.10 (2H, br s).
1-31		318.79	281	B	B	(300 MHz, DMSO-d6): 1.34 - 1.53 (1H, m), 2.30 - 2.47 (3H, m), 3.40 - 3.67 (2H, m), 5.03 - 5.14 (1H, m), 6.82 - 7.00 (2H, m), 7.28 - 7.44 (1H, m), 7.85 (1H, s), 7.97 (1H, d, J = 8.2 Hz), 8.10 (3H, br), 9.85 (1H, br s), 10.02 (1H, br s).
1-32		290.75	255	A	B	(300 MHz, DMSO-d6): 1.58 (3H, d, J = 6.9 Hz), 4.45 (1H, m), 6.91 - 6.96 (2H, m), 7.34 - 7.40 (1H, m), 7.90 (1H, s), 8.06 (1H, d, J = 8.0 Hz), 8.94 (1H, br s).

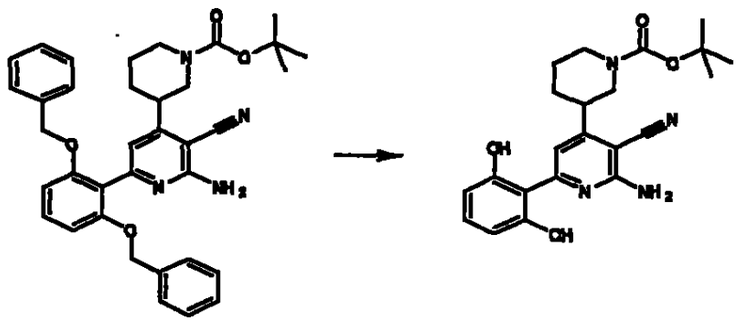
1-33		396.37	283	A	B	(300 MHz, DMSO-d6): 0.84 (3H, d, J = 6.8 Hz), 1.06 (3H, d, J = 6.9 Hz), 4.98 (1H, s), 6.90 - 6.95 (2H, m), 7.36 (1H, t, J = 8.4 Hz), 7.81 (1H, s), 7.72 (2H, br s), 8.05 (1H, d, J = 7.0 Hz), 10.21 (1H, s), 13.85 (1H, s).
1-34		368.85	331	A	B	(300 MHz, DMSO-d6): 3.18 (1H, dd, J = 8.4, 13.2 Hz), 3.21 (1H, dd, J = 5.7, 13.2 Hz), 4.54 (1H, br), 6.91 - 6.99 (2H, m), 7.10 - 7.13 (2H, m), 7.22 - 7.29 (4H, m), 7.35 - 7.55 (3H, m), 8.06 (1H, s), 8.12 (1H, d, J = 7.9 Hz), 9.02 (3H, br).
1-35		368.85	no peak	A	B	(300 MHz, DMSO-d6): 3.28 - 3.34 (1H, m), 3.48 - 3.57 (1H, m), 4.02 - 4.80 (1H, m), 6.87 - 6.93 (2H, m), 7.30 - 7.43 (1H, m), 7.53 (2H, d, J = 6.4 Hz), 7.89 (1H, d, J = 6.8 Hz), 8.79 (2H, br s).
1-36		382.35	269	A	B	(300 MHz, DMSO-d6): 1.21 (3H, d, J = 6.4 Hz), 2.88 - 3.08 (2H, m), 3.73 (1H, br s), 6.89 (1H, s), 6.92 (1H, br s), 7.35 (2H, t, J = 6.8 Hz), 7.43 (1H, br s), 7.95 (3H, br s), 13.36 (1H, s).
1-37		368.32	255	A	A	(500 MHz, DMSO-d6): 3.03 (2H, t, J = 7.5 Hz), 3.23 (2H, t, J = 7.7 Hz), 6.89 - 6.99 (2H, m), 7.35 (2H, t, J = 7.1 Hz), 7.41 (2H, br s), 7.88 - 7.98 (4H, m), 13.38 1H, s).

1-38		337.38	338	A	B	(500 MHz, DMSO-d6): 1.47 (2H, dq, J = 3.0, 12.8 Hz), 1.72 (2H, dq, J = 3.0, 12.8 Hz), 1.84 (2H, dd, J = 3.0, 12.8 Hz), 2.05 (2H, dd, J = 3.0, 12.8 Hz), 2.33 (2H, tt, J = 3.3, 12.3 Hz), 2.73 (2H, tt, J = 3.2, 12.0 Hz), 6.86 - 6.93 (2H, m), 7.23 - 7.38 (4H, m), 8.04 (1H, d, J = 7.9 Hz), 12.14 (1H, br s), 13.51 (1H, br s).
1-39		353.30		C	C	
1-40		508.05	470	B	B	(300 MHz, DMSO-d6): 1.25 (1H, br), 1.60 (5H, br m), 2.69 - 2.80 (4H, m), 3.04 (2H, d, J = 7.5 Hz), 3.12 - 3.20 (2H, m), 5.19 (1H, dd, J = 7.4, 15.4 Hz), 6.91 - 6.97 (2H, m), 7.21 - 7.45 (6H, m), 7.56 (1H, s), 7.95 - 7.99 (1H, m), 9.14 (1H, d, J = 8.1 Hz), 9.58 (1H, br), 13.33 (1H, br s).
1-41		681.61		B	B	
1-42		486.47	373	C	B	(300 MHz, DMSO-d6): 1.85 (4H, m), 3.00 (5H, m), 3.62 (3H, d, J = 11.2 Hz), 6.90 (2H, m), 7.37 (3H, m), 8.02 (1H, dd, J = 1.4, 8.4 Hz), 13.4 (1H, s).

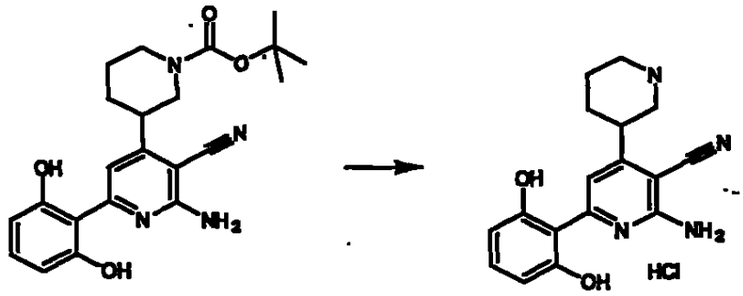
1-43		508.57	393	A	A	(500 MHz, DMSO-d6): 0.93 (6H, m), 1.68 (8H, m), 2.01 (4H, m), 3.00 (5H, m), 6.92 (2H, m), 7.35 (4H, m), 8.02 (1H, d, J = 13.2 Hz), 8.84 (1H, br), 13.4 (1H, s).
1-44		369.30	256	B	B	(300 MHz, DMSO-d6): 3.18 (2H, t, J = 6.2 Hz), 4.78 (2H, t, J = 6.2 Hz), 6.90 (2H, m), 7.23-7.82 (4H, m), 7.95 (1H, dd, J = 1.8, 8.4 Hz), 13.39(1H, s).

Example 2-1

(1) With the use of starting compound 1E instead of 1A, tert-butyl 3-{2-amino-6-[2,6-bis(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate (3.54 g, yield; 30%) was prepared in a similar manner as described in step (1) in Example 1-1.



(2) A suspension of tert-butyl 3-{2-amino-6-[2,6-bis(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate (3.46 g, 5.9 mmol) and Pd/C (10%, 600 mg) in ethyl acetate (50 mL) including acetic acid (5 mL) was stirred for 2 days at room temperature under a hydrogen atmosphere. The reaction mixture was diluted with THF (200 mL) and filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was washed with ethyl acetate and hexane, and dried under reduced pressure to give tert-butyl 3-[2-amino-3-cyano-6-(2,6-dihydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (1.82 g, yield; 76%).



(3) tert-butyl 3-[2-amino-3-cyano-6-(2,6-dihydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (200 mg, 0.49 mmol) was treated under acidic conditions in a similar manner as described in the step (3) of Example 1-1. The resulting precipitate was

collected by filtration, washed with ethyl acetate and hexane, and dried under reduced pressure to give 2-amino-6-(2,6-dihydroxyphenyl)-4-(3-piperidinyl)nicotinonitrile hydrochloride (123 mg, yield; 73%).

Molecular weight: 346.82

Mass spectrometry: 311 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

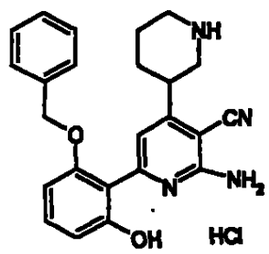
^{1}H-NMR (500 MHz, DMSO-d6): 1.66 – 1.99 (5H, m), 2.91 – 3.20 (2H, m), 3.23 – 3.42 (3H, m), 6.41 (2H, d, J = 7.9 Hz), 7.08 (1H, t, J = 7.9 Hz), 7.28 (2H, br d), 7.65 (1H, s), 8.82 (1H, br d), 9.17 (1H, br d).

Example 2-2

A suspension of tert-butyl 3-[2-amino-3-cyano-6-(2,6-dihydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (300 mg, 0.73 mmol) obtained in the step (2) of Example 2-1, benzyl bromide (0.1 mL, 0.80 mmol) and potassium carbonate (303 mg, 2.19 mmol) in a solution of acetone (15 mL) and THF (15 mL) was stirred for 2 days at room temperature. The reaction mixture was concentrated under reduced pressure, then dissolved in ethyl acetate (100 mL) and water (100 mL). The separated aqueous phase was extracted with ethyl acetate (100 mL x 2). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 4:1-2:1-1:1) to give tert-butyl 3-{2-amino-6-[2-(benzyloxy)-6-hydroxyphenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate (239 mg, yield; 65%).

To a solution of tert-butyl 3-{2-amino-6-[2-(benzyloxy)-6-hydroxyphenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate (239 mg, 0.48 mmol) in dioxane (25 mL) was added 4N HCl/dioxane (25 mL). The reaction mixture was stirred at room temperature overnight. The resulting precipitate was collected by filtration, washed

with ethyl acetate and hexane, dried under reduced pressure to give 2-amino-6-[2,-(benzyloxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinonitrile hydrochloride (184 mg, yield; 88%).



Molecular weight: 436.95

Mass spectrometry: 401 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

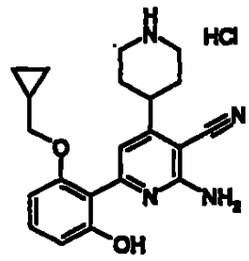
^{1}H-NMR (500 MHz, DMSO-d6): 1.07-1.14 (1H, m), 1.65-1.74 (3H, m), 2.57-2.73 (2H, m), 3.07-3.12 (1H, m), 3.17-3.23 (2H, m), 5.07 (1H, d, J = 11.3 Hz), 5.12 (1H, d, J = 11.3 Hz), 6.57 (1H, d, J = 8.3 Hz), 6.73 (1H, d, J = 8.3 Hz), 7.24 – 7.49 (8H, m), 8.72 (1H, br d), 9.01 (1H, br d), 12.54 (1H, s).

Example 2-3

With the use of the starting compound 1G instead of 1A and 4-formyl-piperidine-1-carboxylic acid tert-butyl ester prepared in a similar manner as that of the starting compound 2B, tert-butyl 4-(2-amino-3-cyano-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-4-pyridinyl)-1-piperidinecarboxylate was prepared in a similar manner as that of step (1) of Example 1-1.

To a stirred solution of tert-butyl 4-(2-amino-3-cyano-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-4-pyridinyl)-1-piperidinecarboxylate (0.63 g, 1.077 mmol) in 1,4-dioxane (25 mL) was added 4N HCl in 1,4-dioxane (25 mL). The mixture was stirred at room temperature for 12 hrs. The resulting solid was collected

with filtration and washed with diisopropyl ether to give 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinonitrile hydrochloride as a yellow solid (0.340 g, yield; 79%).



Molecular weight: 400.91

Mass spectrometry: 365 $(M+H)^+$

In vitro activity grade: A

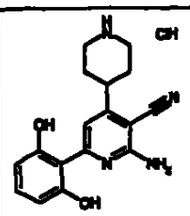
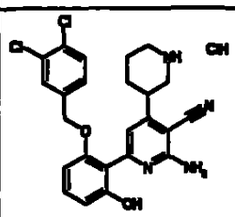
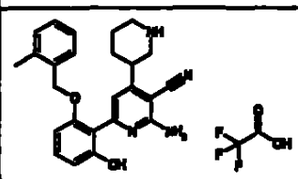
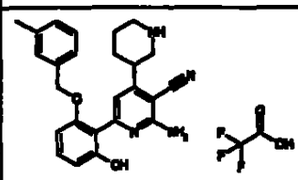
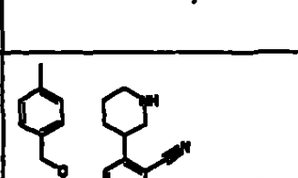
Cellular activity grade: (A549)A

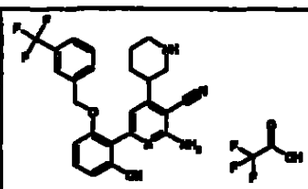
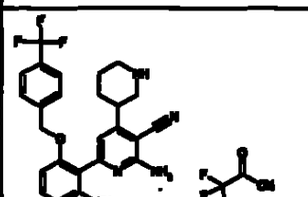
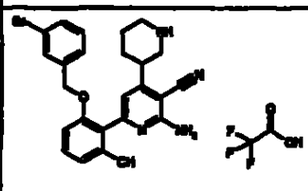
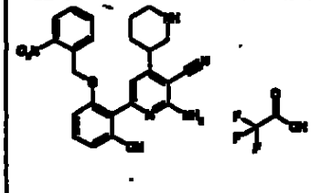
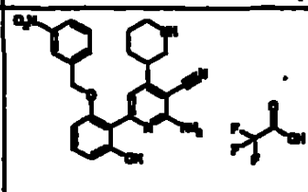
^{1}H-NMR (500 MHz, DMSO-d6): 0.31 – 0.34 (2H, m), 0.55 – 0.59 (2H, m), 1.03 – 1.04 (1H, m), 1.91 – 1.99 (4H, m), 3.06 – 3.14 (3H, m), 3.37 – 3.39 (2H, m), 3.87 (2H, d, J = 7.3 Hz), 6.55 (2H, dd, J = 9.9, 8.2 Hz), 7.23 (1H, t, J = 8.2 Hz), 9.19 – 9.11 (1H, m), 9.20 – 9.23 (1H, m).

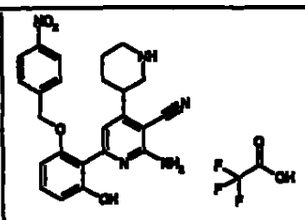
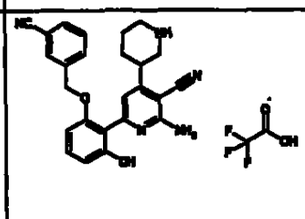
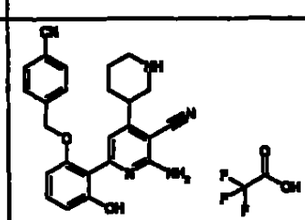
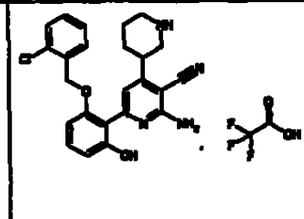
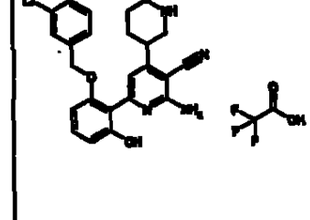
Examples 2-4 to 2-87

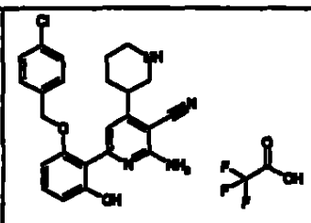
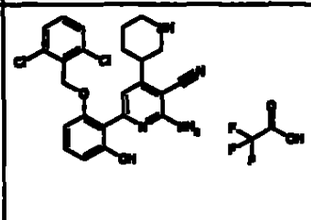
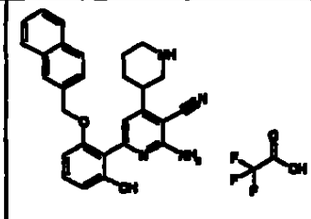
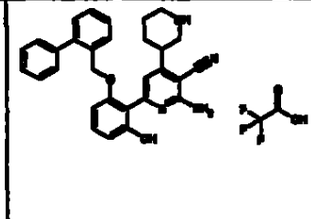
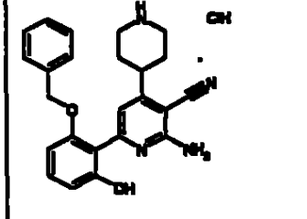
According to the similar synthetic procedure of Examples 2-1 to 2-3, compounds shown in Tables 2 were prepared.

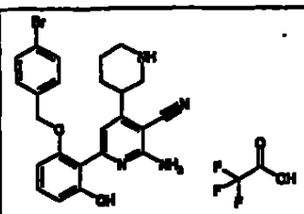
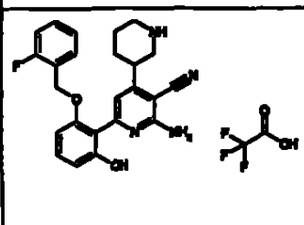
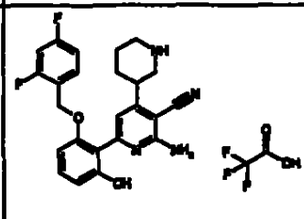
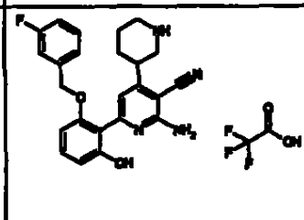
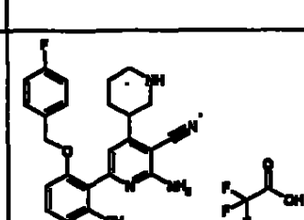
Table 2

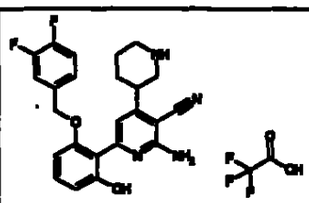
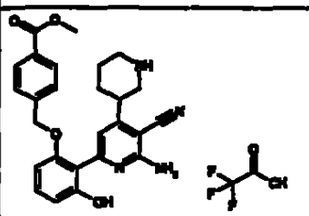
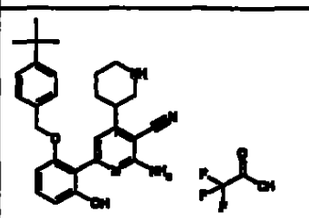
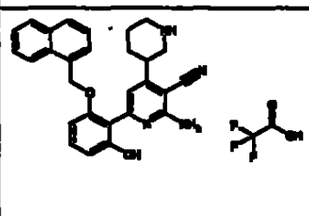
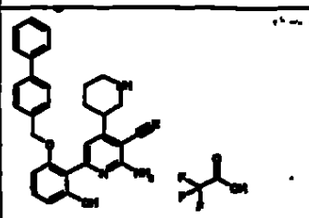
Ex. No	Structure	Mol weight	Mass	In vitro	A549	NMR
2-04		346.82	311			(500 MHz, DMSO-d6): 1.88 - 1.86 (4H, m), 3.05 - 3.10 (3H, m), 3.38 - 3.57 (2H, m), 6.43 (2H, d, J = 8.2 Hz), 7.09 (1H, t, J = 8.2 Hz), 7.56 - 7.60 (1H, brs), 7.80 (1H, s), 8.94 - 9.01 (2H, m).
2-05		505.84	470	A	B	(500 MHz, DMSO-d6): 1.26 (1H, br), 1.75 (3H, m), 2.71 (1H, br), 2.86 (1H, br), 3.18 (1H, br), 3.28 (1H, br), 5.07 (1H, d, J = 11.7 Hz), 5.12 (1H, d, J = 11.7 Hz), 6.59 (1H, m), 6.89 (1H, d, J = 8.5 Hz), 7.15 (1H, d, J = 8.2 Hz), 7.26 (2H, m), 7.45 (1H, dd, J = 1.9, 8.2 Hz), 7.89 (1H, d, J = 8.2 Hz), 8.76 (1H, br), 8.92 (1H, br), 9.09 (1H, br), 9.40 (1H, br s).
2-06		528.54	415	A	B	(500 MHz, DMSO-d6): 0.92 (1H, ddd, J = 3.5, 3.5, 12.3 Hz), 1.58 - 1.72 (3H, m), 2.27 (3H, s), 2. 30-2.70 (3H, m), 3.06 (1H, t, J = 12.0 Hz), 3.25 (1H, m), 5.08 (1H, d, J = 11.0 Hz), 5.13 (1H, d, J = 10.8 Hz), 6.56 (1H, d, J = 8.2 Hz), 6.77 (1H, d, J = 8.2 Hz), 7.23-7.31 (6H, m), 7.43 (1H, d, J = 7.8 Hz), 8.59 (1H, br), 8.74 (1H, br), 12.82 (1H, br).
2-07		528.54	415	A	B	(500 MHz, DMSO-d6): 0.92 (1H, ddd, J = 3.8, 4.1, 12.6 Hz), 1.58 - 1.72 (3H, m), 2.27 (3H, s), 2. 30-2.70 (3H, m), 3.07 (1H, m), 3.25 (1H, t, J = 9.5 Hz), 5.08 (1H, d, J = 10.7 Hz), 5.13 (1H, d, J = 10.7 Hz), 6.56 (1H, dd, J = 1.0, 8.2 Hz), 6.77 (1H, d, J = 8.2 Hz), 7.23-7.31 (6H, m), 7.43 (1H, d, J = 7.3 Hz), 8.59 (1H, br), 8.75 (1H, br), 12.83 (1H, br).
2-08		528.54	415	A	A	(500 MHz, DMSO-d6): 0.85 (1H, m), 1.62 - 1.85 (3H, m), 2.31 (3H, s), 2. 30-2.70 (3H, m), 3.08 (1H, m), 3.20-3.50 (1H, m), 5.02 (1H, d, J = 10.7 Hz), 5.07 (1H, d, J = 10.7 Hz), 6.55 (1H, dd, J = 1.0, 8.2 Hz), 6.72 (1H, d, J = 8.2 Hz), 7.22-7.27 (6H, m), 7.37 (1H, d, J = 7.9 Hz), 8.58 (1H, br), 8.76 (1H, br), 12.88 (1H, br).

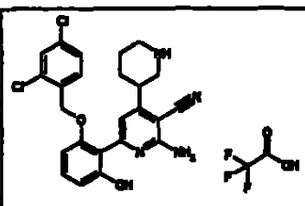
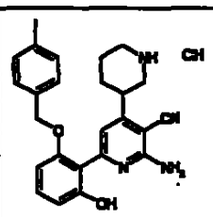
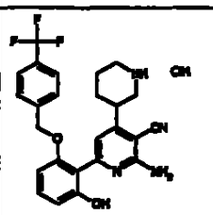
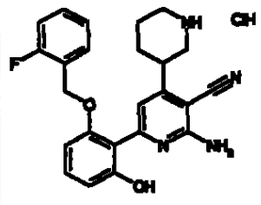
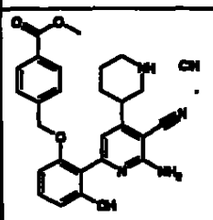
2-09		582.51	469	A	B	(500 MHz, DMSO-d6): 1.17 - 1.24 (1H, m), 1.64 - 1.72 (3H, m), 2.30 - 2.50 (2H, m), 2.63 - 2.68 (1H, m), 2.81 (1H, br t, J = 11.7 Hz), 3.12 (1H, m), 5.17 (1H, d, J = 11.7 Hz), 5.22 (1H, d, J = 11.7 Hz), 6.58 (1H, d, J = 8.2 Hz), 6.71 (1H, d, J = 8.2 Hz), 7.11 (1H, s), 7.17 (2H, br s), 7.25 (1H, t, J = 8.2 Hz), 7.84 (1H, dd, J = 7.9, 8.2 Hz), 7.71 (2H, m), 7.75 (1H, d, J = 7.9 Hz), 8.60 (1H, br), 8.80 (1H, br), 11.9 (1H, br).
2-10		582.51	469	A	B	(500 MHz, DMSO-d6): 1.24 - 1.31 (1H, m), 1.71 (3H, m), 2.60 (2H, m), 2.69 (1H, m), 2.88 (1H, br t, J = 12.3 Hz), 3.13 (1H, m), 5.19 (1H, d, J = 12.3 Hz), 5.24 (1H, d, J = 12.3 Hz), 6.57 (1H, d, J = 8.2 Hz), 6.70 (1H, d, J = 8.2 Hz), 7.17 (1H, s), 7.19 (2H, br s), 7.24 (1H, t, J = 8.2 Hz), 7.86 (2H, d, J = 7.9 Hz), 7.77 (2H, d, J = 7.9 Hz), 8.66 (2H, br), 11.95 (1H, s).
2-11		593.40	no peak	A	B	(500 MHz, DMSO-d6): 1.22 (1H, m), 1.74 (3H, m), 2.69 - 2.81 (2H, m), 3.13 (1H, t, J = 12.3 Hz), 5.07 (1H, d, J = 11.4 Hz), 5.12 (1H, d, J = 11.4 Hz), 6.57 (1H, d, J = 8.5 Hz), 6.69 (1H, d, J = 8.5 Hz), 7.16 (1H, s), 7.19 (2H, br s), 7.25 (1H, t, J = 8.5 Hz), 7.37 (1H, t, J = 7.9 Hz), 7.46 (1H, d, J = 7.9 Hz), 7.55 (1H, d, J = 7.9 Hz), 7.61 (1H, br s), 8.59 (1H, br s), 8.79 (1H, br s), 12.10 (1H, br).
2-12		559.51	448	A	B	(500 MHz, DMSO-d6): 1.24 (1H, m), 1.73 (3H, m), 2.30 - 2.70 (3H, m), 2.80 (1H, m), 3.14 (1H, m), 5.42 (1H, d, J = 13.2 Hz), 5.48 (1H, d, J = 13.2 Hz), 6.58 (1H, d, J = 8.2 Hz), 6.67 (1H, d, J = 8.2 Hz), 7.10 (1H, s), 7.19 (2H, br s), 7.24 (1H, t, J = 8.2 Hz), 7.64 (1H, dt, J = 1.3, 8.2Hz), 7.71 (1H, d, J = 7.6 Hz), 7.76 (1H, d, J = 7.6 Hz), 8.11 (2H, d, J = 8.2 Hz), 8.56 (1H, br), 8.74 (1H, br), 11.94 (1H, br).
2-13		559.51	448	A	B	(500 MHz, DMSO-d6): 1.29 (1H, m), 1.71 (3H, m), 2.30 - 2.50 (2H, m), 2.69 (1H, m), 2.84 (1H, dd, J = 11.4, 11.6 Hz), 3.14 (1H, m), 5.23 (1H, d, J = 12.3 Hz), 5.28 (1H, d, J = 12.3 Hz), 6.59 (1H, dd, J = 1.0, 8.5 Hz), 6.71 (1H, d, J = 8.5 Hz), 7.12 (1H, s), 7.16 (2H, br s), 7.25 (1H, t, J = 8.5 Hz), 7.71 (1H, t, J = 7.9 Hz), 7.89 (1H, d, J = 7.6 Hz), 8.20 (1H, dd, J = 1.3, 8.2 Hz), 8.24 (1H, s), 8.58 (1H, br), 8.82 (1H, br).

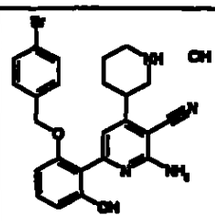
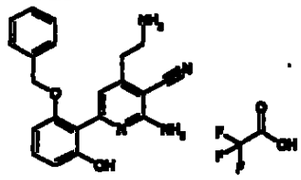
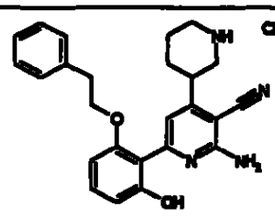
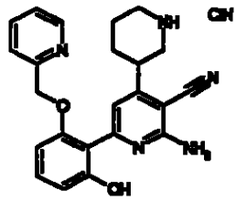
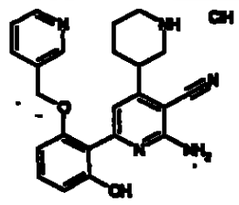
2-14		559.51	446	A	A	(500 MHz, DMSO-d6): 1.38 (1H, m), 1.75 (3H, m), 2.30 - 2.50 (1H, m), 2.73 (1H, dd, J = 10.7, 12.0 Hz), 2.88 (1H, dd, J = 10.7, 11.6 Hz), 3.14 (1H, m), 3.29 (1H, m), 5.27 (2H, dd, J = 12.9, 16.1 Hz), 6.56 (1H, dd, J = 1.0, 8.2 Hz), 6.69 (1H, d, J = 8.5 Hz), 7.13 (1H, s), 7.19 (2H, br s), 7.24 (1H, t, J = 8.2 Hz), 7.69 (1H, t, J = 8.6 Hz), 8.26 (1H, d, J = 8.6 Hz), 8.54 (1H, s), 8.79 (1H, br), 11.8 (1H, br).
2-15		539.52	426	A	A	(500 MHz, DMSO-d6): 1.24 (1H, m), 1.66 - 1.81 (3H, m), 2.30 - 2.50 (2H, m), 2.72 (1H, dd, J = 10.1, 12.3 Hz), 2.82 (1H, dd, J = 10.4, 12.0 Hz), 3.13 (1H, m), 5.12 (1H, d, J = 11.7 Hz), 5.18 (1H, d, J = 11.7 Hz), 6.58 (1H, d, J = 8.5 Hz), 6.71 (1H, d, J = 8.5 Hz), 7.13 (1H, s), 7.18 (2H, br s), 7.26 (1H, t, J = 8.5 Hz), 7.62 (1H, t, J = 7.9 Hz), 7.79 (1H, d, J = 7.9 Hz), 7.84 (1H, d, J = 7.9 Hz), 7.86 (1H, s), 8.59 (1H, br), 8.76 (1H, br), 11.95 (1H, br).
2-16		539.52	426	A	A	(500 MHz, DMSO-d6): 1.31 (1H, m), 1.66 - 1.91 (3H, m), 2.30 - 2.50 (2H, m), 2.78 (1H, m), 2.87 (1H, dd, J = 11.4, 12.3 Hz), 3.14 (1H, t, J = 12.3 Hz), 5.19 (1H, d, J = 12.6 Hz), 5.22 (1H, d, J = 12.6 Hz), 6.57 (1H, d, J = 8.2 Hz), 6.66 (1H, d, J = 8.2 Hz), 7.13 (1H, s), 7.18 (2H, br s), 7.24 (1H, t, J = 8.2 Hz), 7.62 (1H, t, J = 8.2 Hz), 7.88 (1H, d, J = 8.2 Hz), 8.58 (1H, br), 8.80 (1H, br), 11.84 (1H, br s).
2-17		548.95	435	A	B	(500 MHz, DMSO-d6): 1.06 (1H, m), 1.60 - 1.80 (3H, m), 2.50 - 2.70 (m, 4H), 3.10 (1H, m), 5.13 (1H, d, J = 11.4 Hz), 5.21 (1H, d, J = 11.4 Hz), 6.58 (1H, dd, J = 0.9, 8.2 Hz), 6.74 (1H, d, J = 8.2 Hz), 7.21 (1H, s), 7.24 (2H, br), 7.28 (1H, t, J = 8.2 Hz), 7.41 (1H, dt, J = 1.6, 7.3 Hz), 7.44 (1H, dt, J = 1.9, 7.6 Hz), 7.57 (1H, dd, J = 1.6, 7.9 Hz), 7.61 (1H, dd, J = 1.9, 7.3 Hz), 8.61 (1H, br), 8.77 (1H, br).
2-18		548.95	435	A	B	(500 MHz, DMSO-d6): 1.22 (1H, m), 1.74 (3H, m), 2.71 (2H, m), 3.13 (1H, t, J = 12.3 Hz), 5.08 (1H, d, J = 11.3 Hz), 5.13 (1H, d, J = 11.3 Hz), 6.57 (1H, d, J = 8.2 Hz), 6.70 (1H, d, J = 8.2 Hz), 7.17 (1H, s), 7.20 (2H, br), 7.25 (1H, t, J = 8.2 Hz), 7.42 (3H, m), 7.48 (1H, s), 8.62 (1H, br), 8.82 (1H, br).

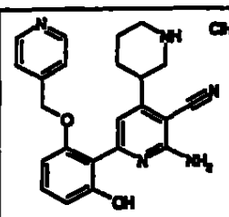
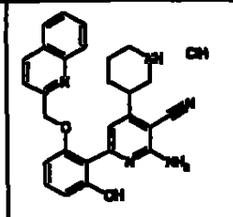
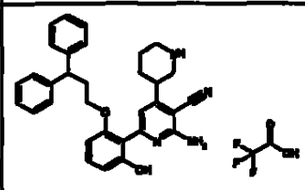
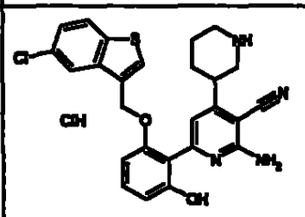
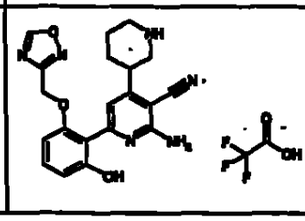
2-19		548.95	435	A	A	(500 MHz, DMSO-d6): 1.13 (1H, m), 1.73 (3H, m), 2.50 - 2.80 (3H, m), 3.11 (1H, t, J = 12.3 Hz), 5.07 (1H, d, J = 11.0 Hz), 5.12 (1H, d, J = 11.0 Hz), 6.58 (1H, d, J = 8.2 Hz), 6.70 (1H, d, J = 8.2 Hz), 7.19 (1H, s), 7.21 (2H, br), 7.25 (1H, t, J = 8.2 Hz), 7.46 (4H, dt, J = 2.5, 8.8 Hz), 8.61 (1H, br), 8.80 (1H, br), 12.33 (1H, br).
2-20		583.40	470	A	B	(500 MHz, DMSO-d6): 0.85 (1H, m), 1.53 (1H, d, J = 12.8 Hz), 1.89 (2H, m), 3.07 (1H, m), 5.24 (1H, d, J = 10.4 Hz), 5.33 (1H, d, J = 10.4 Hz), 6.60 (1H, dd, J = 0.9, 8.2 Hz), 6.84 (1H, d, J = 8.5 Hz), 7.14 (1H, s), 7.29 (2H, br), 7.32 (1H, t, J = 8.2 Hz), 7.51 (4H, dd, J = 7.8, 8.8 Hz), 7.83 (2H, d, J = 7.9 Hz), 8.64 (1H, br), 8.77 (1H, br), 12.85 (1H, br).
2-21		564.57	451	A	A	(500 MHz, DMSO-d6): 0.82 (1H, m), 1.09 (1H, m), 1.41 (2H, m), 2.08(1H, m), 2.96 (2H, m), 5.24 (1H, d, J = 10.7 Hz), 5.30 (1H, d, J = 10.7 Hz), 6.57 (1H, dd, J = 1.0, 8.2 Hz), 6.80 (1H, d, J = 8.2 Hz), 7.23 (2H, br), 7.26 (1H, s), 7.29 (1H, t, J = 8.2 Hz), 7.55 (2H, m), 7.82 (1H, dd, J = 1.8, 8.2 Hz), 7.95 (3H, m), 8.03 (1H, s), 8.55 (1H, br), 12.85 (1H, s).
2-22		590.61	477	A	B	(500 MHz, DMSO-d6): 0.94 (1H, m), 1.53 (3H, m), 3.07 (1H, t, J = 11.4 Hz), 4.90 (1H, d, J = 10.4 Hz), 4.99 (1H, d, J = 10.4 Hz), 6.51 (1H, d, J = 8.2 Hz), 6.53 (1H, d, J = 8.2 Hz), 7.19 (1H, t, J = 8.2 Hz), 7.26 (2H, br), 7.35 (6H, m), 7.48 (2H, m), 7.66 (1H, d, J = 7.3 Hz), 8.80 (1H, br), 8.76 (1H, br).
2-23		436.95	401	A	B	(500 MHz, DMSO-d6): 1.65 - 1.89 (4H, m), 2.93 - 3.10 (3H, m), 3.29 (2H, d, J = 12.3 Hz), 5.13 (2H, s), 6.62 (1H, d, J = 8.2 Hz), 6.72 (1H, d, J = 8.2 Hz), 7.13 (1H, s), 7.26 (1H, t, J = 8.2 Hz), 7.33 (1H, t, J = 7.4 Hz), 7.40 (2H, t, J = 7.4 Hz), 7.46 (2H, t, J = 7.4 Hz), 7.72 (2H, br), 9.10 (1H, br s).

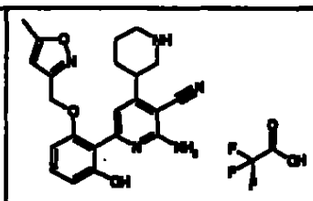
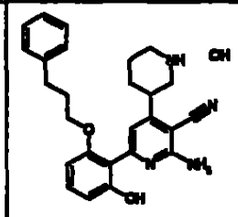
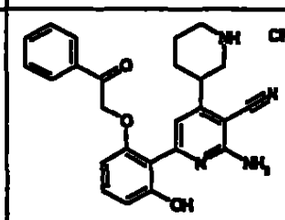
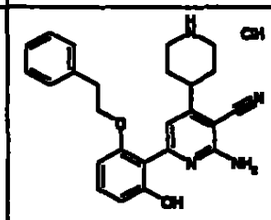
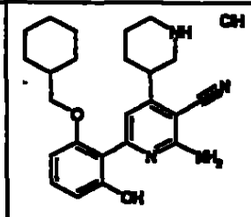
2-24		583.40	480	A	A	(500 MHz, DMSO-d6): 1.14 (1H, m), 1.74 (3H, m), 2.69 (2H, m), 3.11 (1H, t, J = 12.0 Hz), 5.05 (1H, d, J = 11.4 Hz), 5.10 (1H, d, J = 11.4 Hz), 6.56 (1H, d, J = 8.2 Hz), 6.70 (1H, d, J = 8.2 Hz), 7.19 (1H, s), 7.22 (2H, br), 7.25 (1H, t, J = 8.2 Hz), 7.44 (2H, d, J = 8.2 Hz), 7.61 (2H, d, J = 8.2 Hz), 8.60 (1H, br), 8.81 (1H, br), 12.38 (1H, br).
2-25		532.50	419	A	A	(500 MHz, DMSO-d6): 1.09 (1H, m), 1.71 (3H, m), 2.64 (2H, m), 3.10 (1H, t, J = 12.3 Hz), 3.28 (2H, t, J = 10.4 Hz), 5.13 (1H, d, J = 11.0 Hz), 5.18 (1H, d, J = 11.0 Hz), 6.58 (1H, d, J = 8.5 Hz), 6.76 (1H, d, J = 8.5 Hz), 7.20 (1H, s), 7.26 (4H, m), 7.47 (1H, m), 7.58 (1H, t, J = 7.8 Hz), 8.63 (1H, br), 8.82 (1H, br).
2-26		550.49		A	A	(500 MHz, DMSO-d6): 1.09 (1H, m), 1.71 (3H, m), 2.64 (2H, m), 3.10 (1H, t, J = 12.3 Hz), 3.28 (2H, t, J = 10.4 Hz), 5.13 (1H, d, J = 11.0 Hz), 5.18 (1H, d, J = 11.0 Hz), 6.58 (1H, d, J = 8.5 Hz), 6.76 (1H, d, J = 8.5 Hz), 7.20 (1H, s), 7.26 (4H, m), 7.47 (1H, m), 7.58 (1H, t, J = 7.8 Hz), 8.63 (1H, br), 8.82 (1H, br).
2-27		532.50	419	A	A	(500 MHz, DMSO-d6): 1.25 (1H, m), 1.73 (3H, m), 2.69 (1H, dd, J = 10.8, 11.7 Hz), 2.76 (1H, dd, J = 11.7, 11.7 Hz), 3.13 (1H, t, J = 12.3 Hz), 5.08 (1H, d, J = 11.7 Hz), 5.14 (1H, d, J = 11.7 Hz), 6.57 (1H, d, J = 8.2 Hz), 6.70 (1H, d, J = 8.2 Hz), 7.28 (6H, m), 7.45 (1H, m), 8.60 (1H, br), 8.81 (1H, br), 12.19 (1H, br).
2-28		532.50	419	A	A	(500 MHz, DMSO-d6): 1.14 (1H, m), 1.71 (3H, m), 2.69 (3H, m), 3.10 (1H, t, J = 12.3 Hz), 5.06 (1H, d, J = 11.0 Hz), 5.10 (1H, d, J = 11.0 Hz), 6.56 (1H, d, J = 8.5 Hz), 6.72 (1H, d, J = 8.5 Hz), 7.21 (1H, s), 7.25 (5H, m), 7.53 (2H, dd, J = 5.7, 8.5 Hz), 8.59 (1H, br), 8.81 (1H, br).

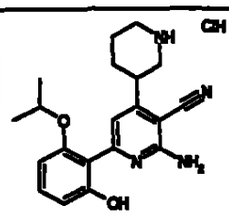
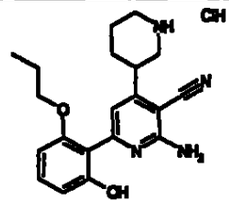
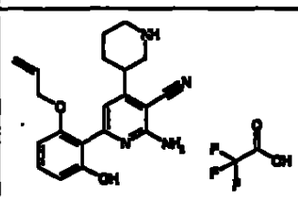
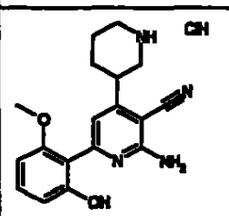
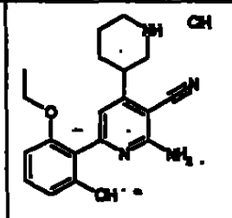
2-29		550.49	437	A	B	(500 MHz, DMSO-d6): 1.28 (1H, m), 1.73 (3H, m), 2.69 (1H, m), 2.84 (1H, dd, J = 11.4, 11.4 Hz), 3.13 (1H, t, J = 12.3 Hz), 5.05 (1H, d, J = 11.4 Hz), 5.10 (1H, d, J = 11.4 Hz), 6.57 (1H, d, J = 8.2 Hz), 6.69 (1H, d, J = 8.2 Hz), 7.17 (1H, s), 7.20 (2H, br), 7.25 (1H, t, J = 8.2 Hz), 7.33 (1H, br), 7.50 (2H, m), 8.60 (1H, br), 8.82 (1H, br) , 12.07 (1H, br).
2-30		572.55	459	A	A	(500 MHz, DMSO-d6): 1.22 (1H, m), 1.70 (3H, m), 2.65 (1H, m), 2.78 (1H, dd, J = 11.4, 11.4 Hz), 3.12 (1H, t, J = 12.3 Hz), 3.29 (2H, br), 5.17 (1H, d, J = 12.0 Hz), 5.22 (1H, d, J = 12.0 Hz), 6.57 (1H, d, J = 8.2 Hz), 6.69 (1H, d, J = 8.2 Hz), 7.17 (1H, s), 7.22 (2H, br), 7.25 (1H, t, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.99 (2H, d, J = 8.2 Hz), 8.58 (1H, br), 8.80 (1H, br).
2-31		570.62	457	A	A	(500 MHz, DMSO-d6): 1.67 - 1.78 (3H, m), 2.71 (1H, dd, J = 10.4, 11.4 Hz), 2.89 (1H, dd, J = 11.4, 11.7 Hz), 3.13 (1H, t, J = 12.3 Hz), 5.04 (1H, d, J = 11.4 Hz), 5.10 (1H, d, J = 11.4 Hz), 6.55 (1H, d, J = 8.2 Hz), 6.72 (1H, d, J = 8.2 Hz), 7.22 (2H, br s), 7.24 (1H, t, J = 8.2 Hz), 7.27 (1H, s), 7.37 (2H, d, J = 8.2 Hz), 7.41 (2H, d, J = 8.2 Hz), 8.61 (1H, br), 8.84 (1H, br), 12.20 (1H, br).
2-32		564.57	451	A	B	(500 MHz, DMSO-d6): 0.24 (1H, m), 1.13 (1H, d, J = 13.9 Hz), 1.42 - 1.52 (2H, m), 2.04 (1H, dd, J = 11.0, 12.0 Hz), 2.19 (1H, dd, J = 11.0, 12.0 Hz), 2.87 (1H, t, J = 12.0 Hz), 3.08 (1H, d, J = 11.4 Hz), 3.15 (1H, d, J = 12.0 Hz), 5.54 (1H, d, J = 11.0 Hz), 5.59 (1H, d, J = 11.0 Hz), 6.60 (1H, d, J = 8.2 Hz), 6.95 (1H, d, J = 8.2 Hz), 7.10 (1H, s), 7.23 (2H, br s), 7.34 (1H, t, J = 8.2 Hz), 7.56 (3H, m), 7.71 (1H, d, J = 6.9 Hz), 8.00 (3H, m), 8.46 (1H, br), 8.60 (1H, br).
2-33		590.61	477	A	B	(500 MHz, DMSO-d6): 1.17 (1H, m), 1.59 - 1.68 (3H, m), 2.76 (1H, dd, J = 11.4, 11.7 Hz), 3.07 - 3.17 (3H, m), 5.13 (1H, d, J = 11.4 Hz), 5.18 (1H, d, J = 11.4 Hz), 6.57 (1H, d, J = 8.2 Hz), 6.76 (1H, d, J = 8.2 Hz), 7.24- 7.94 (4H, m), 7.39 (1H, t, J = 7.6 Hz), 7.48 (1H, t, J = 7.6 Hz), 7.56 (2H, d, J = 8.2 Hz), 7.69 (2H, d, J = 7.9 Hz), 7.73 (2H, d, J = 7.9 Hz), 8.55 (1H, br d), 8.77 (1H, br d), 12.47(1H, br).

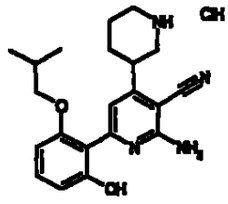
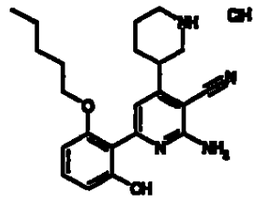
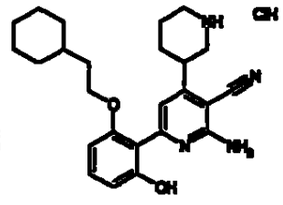
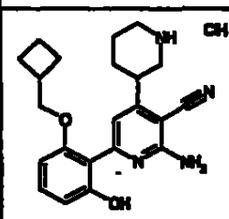
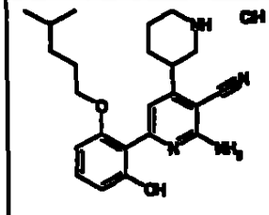
2-34		583.40	470	A	B	(500 MHz, DMSO-d6): 1.08 (1H, m), 1.64 - 1.76 (3H, m), 3.12 (1H, t, J = 12.3 Hz), 3.32 (2H, t, J = 12.9 Hz), 5.11 (1H, d, J = 11.4 Hz), 5.20 (1H, d, J = 11.4 Hz), 6.59 (1H, d, J = 8.2 Hz), 6.73 (1H, d, J = 8.2 Hz), 7.16 (1H, s), 7.25 (2H, br), 7.27 (1H, t, J = 8.2 Hz), 7.51 (1H, dd, J = 1.9, 8.2 Hz), 7.62 (1H, d, J = 8.2 Hz), 7.76 (1H, d, J = 1.9 Hz), 8.63 (1H, br), 8.81 (1H, br).
2-35		450.97	415	A	A	(500 MHz, DMSO-d6): 1.09 (1H, m), 1.68 (3H, m), 2.32 (3H, s), 3.08 - 3.31 (4H, m), 5.02 (1H, d, J = 10.6 Hz), 5.07 (1H, d, J = 10.6 Hz), 6.56 (1H, d, J = 8.3 Hz), 6.72 (1H, d, J = 8.3 Hz), 7.22 - 7.29 (5H, m), 7.36 (2H, d, J = 7.5 Hz), 8.79 (1H, br), 9.16 (1H, br).
2-36		504.94	469	A	A	(500 MHz, DMSO-d6): 1.29 (1H, m), 1.72 (3H, m), 2.92 (1H, m), 3.17 - 3.37 (3H, m), 5.18 (1H, d, J = 12.4 Hz), 5.24 (1H, d, J = 12.4 Hz), 6.59 (1H, dd, J = 2.3, 8.3 Hz), 6.70 (1H, d, J = 8.3 Hz), 7.18 (1H, d, J = 2.3 Hz), 7.25 (1H, dt, J = 7.9, 8.3 Hz), 7.66 (2H, d, J = 8.3 Hz), 7.78 (2H, d, J = 8.3 Hz), 8.78 (1H, br), 9.21 (1H, br).
2-37		454.94	419	A	A	(500 MHz, DMSO-d6): 1.15 - 1.20 (1H, m), 1.66 - 1.77 (3H, m), 2.52 - 2.73 (2H, m), 3.15 - 3.28 (3H, m), 5.14 (1H, d, J = 11.0 Hz), 5.18 (1H, d, J = 11.0 Hz), 6.62 (1H, d, J = 8.2 Hz), 6.76 (1H, d, J = 8.2 Hz), 7.20 (1H, s), 7.28 - 7.33 (3H, m), 7.48 (2H, m), 7.58 (2H, dt, J = 1.6, 7.6 Hz), 8.00 (1H, br d), 8.50 (1H, br d).
2-38		484.98	459	A	A	(500 MHz, DMSO-d6): 1.29 (1H, m), 1.73 (3H, m), 2.64 (1H, m), 2.89 (1H, dd, J = 1.4, 12.7 Hz), 3.24 (3H, m), 3.86 (3H, s), 5.17 (1H, d, J = 12.0 Hz), 5.22 (1H, d, J = 12.0 Hz), 6.62 (1H, d, J = 8.2 Hz), 6.71 (1H, d, J = 8.5 Hz), 7.20 (1H, s), 7.27 (1H, dd, J = 8.2, 8.5 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.99 (2H, d, J = 8.2 Hz), 8.95 (1H, br d), 9.41 (1H, br d).

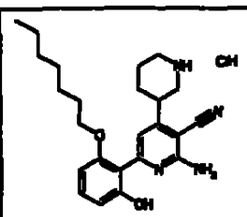
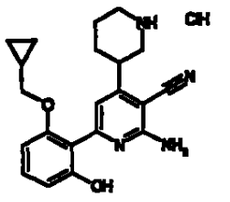
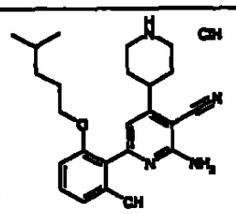
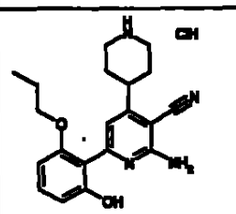
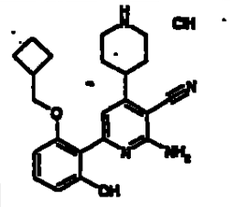
2-39		515.84	479	A	A	(500 MHz, DMSO-d6): 1.12 (1H, m), 1.73 (3H, m), 2.66 (1H, m), 2.75 (1H, t, J = 12.3 Hz), 3.13 (1H, m), 5.05 (1H, d, J = 11.0 Hz), 5.10 (1H, d, J = 11.0 Hz), 6.56 (1H, d, J = 8.2 Hz), 6.70 (1H, d, J = 8.2 Hz), 7.19 (1H, s), 7.21 (2H, br s), 7.25 (1H, t, J = 8.2 Hz), 7.44 (2H, d, J = 8.5 Hz), 7.63 (2H, d, J = 8.5 Hz), 8.03 (2H, br), 12.37 (1H, s).
2-40		474.44	361	A	A	(500 MHz, DMSO-d6): 2.92 (4H, br s), 5.15 (2H, s), 6.55 (1H, d, J = 7.2 Hz), 6.68 (1H, d, J = 8.5 Hz), 7.22 - 7.25 (3H, m), 7.30 (1H, s), 7.33 - 7.35 (1H, m), 7.40 - 7.45 (4H, m), 7.95 (1H, br s).
2-41		450.97	415	A	A	(500 MHz, DMSO-d6): 1.63 (1H, m), 1.78 - 1.90 (3H, m), 2.85 (1H, m), 3.03 (2H, dd, J = 6.6, 8.9 Hz), 3.12 (1H, m), 3.26 - 3.38 (3H, m), 4.20 (2H, dd, J = 6.6, 8.9 Hz), 6.52 (1H, d, J = 8.2 Hz), 6.63 (1H, d, J = 8.5 Hz), 7.18 - 7.24 (5H, m), 7.23 (1H, s), 7.29 (1H, dd, J = 8.2, 8.5 Hz), 7.95 (1H, br s), 9.11 (1H, br s), 9.85 (1H, br s).
2-42		437.93	402	A	B	(500 MHz, DMSO-d6): 1.42 - 1.86 (4H, m), 2.80 - 3.29 (5H, m), 5.27 - 5.36 (2H, m), 6.64 (1H, d, J = 8.2 Hz), 6.72 (1H, d, J = 8.5 Hz), 7.26 - 7.32 (2H, m), 7.51 - 7.73 (3H, m), 8.15 - 8.18 (1H, t, J = 7.5 Hz), 8.77 - 8.93 (2H, m), 9.47 (1H, br d, J = 10.4 Hz).
2-43		437.93	402	A	A	(500 MHz, DMSO-d6): 1.33 - 1.38 (2H, m), 1.73 - 1.82 (4H, m), 2.80 - 3.27 (3H, m), 5.30 (2H, s), 6.64 (1H, d, J = 8.2 Hz), 6.74 (1H, d, J = 8.5 Hz), 7.13 (1H, s), 7.29 (1H, t, J = 8.2 Hz), 7.48 (1H, br s), 7.98 (1H, m), 8.46 (1H, d, J = 7.8 Hz), 8.84 (1H, d, 5.4 Hz), 8.89 - 8.91 (1H, m), 8.95 (1H, s), 9.45 (1H, br d, J = 10.1 Hz).

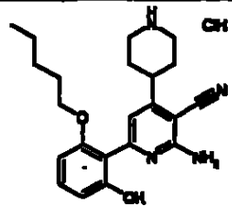
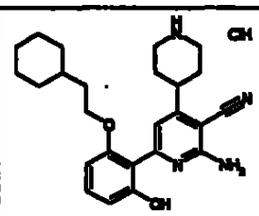
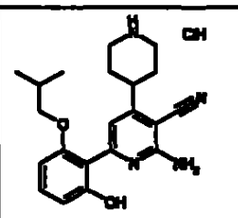
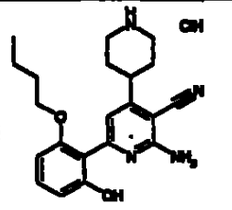
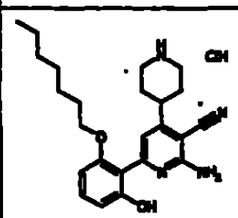
2-44		437.93	402	A	A	(500 MHz, DMSO-d6): 1.52 - 1.86 (3H, m), 2.79 - 3.33 (6H, m), 5.42 (2H, s), 6.83 (1H, d, J = 8.2 Hz), 6.85 (1H, d, J = 8.5 Hz), 7.10 (1H, s), 7.22 - 7.38 (3H, m), 7.90 (2H, d, J = 5.7 Hz), 8.82 - 8.89 (3H, m), 9.42 (1H, br d, J = 10.4 Hz).
2-45		487.99	452	A	A	(500 MHz, DMSO-d6): 1.27 - 1.29 (1H, m), 1.49 - 1.67 (3H, m), 2.90 - 3.30 (4H, m), 4.81 (2H, br s), 5.41 - 5.42 (2H, m), 6.83 (1H, d, J = 8.2 Hz), 6.75 (1H, d, J = 8.5 Hz), 7.25 - 7.29 (2H, m), 7.66 - 7.71 (2H, m), 7.85 (1H, t, J = 7.6 Hz), 8.06 (2H, t, J = 9.3 Hz), 8.57 (1H, d, J = 8.5 Hz), 8.81 - 8.83 (1H, m), 9.29 (1H, br d, J = 9.8 Hz).
2-46		618.66	505	A	B	(500 MHz, DMSO-d6): 1.53 - 1.66 (3H, m), 1.81 (1H, m), 3.02 (1H, m), 3.15 - 3.42 (4H, m), 3.73 - 3.81 (2H, m), 3.90 - 4.00 (2H, m), 4.04 (1H, m), 6.40 (1H, d, J = 8.2 Hz), 6.51 (1H, d, J = 8.5 Hz), 7.14 (1H, dd, J = 8.2, 8.5 Hz), 7.19 - 7.28 (10H, m), 7.36 (1H, s), 8.80 (1H, br s), 8.83 (1H, br s).
2-47		527.48	490	A	B	(500 MHz, DMSO-d6): 0.78 - 0.86 (1H, m), 1.36 (1H, br d, J = 12.3 Hz), 3.05 (1H, t, J = 10.4 Hz), 3.81 (2H, dd, J = 12.0, 29.6 Hz), 5.39 (2H, dd, J = 11.7, 40.0 Hz), 6.60 (1H, d, J = 8.2 Hz), 6.66 (1H, d, J = 8.5 Hz), 7.15 (1H, s), 7.29 - 7.44 (4H, m), 7.79 (1H, d, J = 1.9 Hz), 7.99 (1H, s), 8.07 (1H, d, J = 8.8Hz), 8.70 - 8.80 (1H, m), 9.07 (1H, d, J = 10.7 Hz).
2-48		508.45	393	A	A	(500 MHz, DMSO-d6): 1.62 - 1.85 (4H, m), 2.57 - 3.21 (5H, m), 5.41 (2H, s), 6.80 (1H, d, J = 8.2 Hz), 6.76 (1H, d, J = 8.5Hz), 7.28 - 7.30 (2H, m), 7.46 (1H, s), 8.81-8.83 (1H, m), 8.85 (1H, br d, J = 10.4 Hz), 9.74 (1H, s).

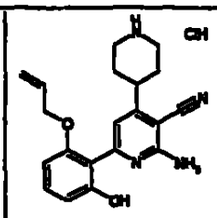
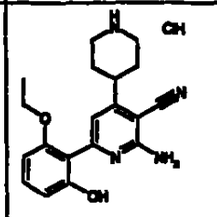
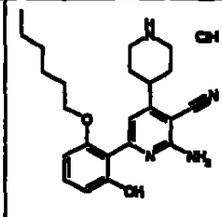
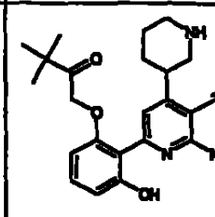
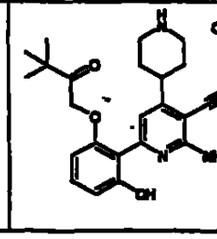
2-49		519.48	406	A	A	(500 MHz, DMSO-d6): 1.52 - 1.91 (4H, m), 2.42 (3H, s), 2.87 - 3.39 (5H, m), 5.12 - 5.28 (2H, m), 6.31 (1H, s), 6.58 (1H, d, J = 8.2 Hz), 6.71 (1H, d, J = 8.5 Hz), 7.24 - 7.28 (3H, m), 7.38 (1H, s), 8.83 - 8.85 (1H, m), 8.90 - 8.93 (1H, br d, J = 10.4 Hz).
2-50		465.00	429	A	A	(500 MHz, DMSO-d6): 1.64 - 1.76 (3H, m), 1.90 (1H, m), 2.03 - 2.08 (2H, m), 2.67 (2H, t, J = 7.6 Hz), 2.76 (1H, m), 3.06 (1H, m), 3.21 - 3.27 (2H, m), 3.35 (1H, m), 3.98 (12H, ddd, J = 4.1, 8.3, 9.5 Hz), 6.53 (1H, d, J = 8.2 Hz), 6.54 (1H, d, J = 8.2 Hz), 7.15 - 7.28 (5H, m), 7.21 (1H, t, J = 8.2 Hz), 7.31 (1H, br s), 7.33 (1H, s), 8.74 (1H, br s), 9.10 (1H, br s).
2-51		464.96	429	A	A	(500 MHz, DMSO-d6): 1.91 (3H, m), 3.03 (1H, m), 5.68 (2H, s), 6.58 (1H, d, J = 8.3 Hz), 6.76 (1H, d, J = 8.3 Hz), 7.27 (1H, t, J = 8.3 Hz), 7.37 (1H, br), 7.60 (2H, t, J = 7.2 Hz), 7.73 (1H, t, J = 7.2 Hz), 8.11 (2H, d, J = 7.2 Hz), 8.18 (1H, br), 8.92 (1H, br), 9.34 (1H, br).
2-52		450.97	415	A	A	(300 MHz, DMSO-d6): 1.91 - 1.92 (4H, m), 3.07 - 3.11 (2H, m), 3.09 (3H, t, J = 7.2 Hz), 3.36 - 3.40 (2H, m), 4.22 (2H, t, J = 7.2 Hz), 6.55 (1H, d, J = 8.3 Hz), 6.61 (1H, d, J = 7.9 Hz), 7.20 (1H, dd, J = 7.9, 8.3 Hz), 7.22 - 7.24 (5H, m), 7.25 (1H, s), 7.28 (1H, br s), 8.88 (2H, br s).
2-53		442.99	407	A	A	(300 MHz, DMSO-d6): 1.09 - 1.17 (2H, m), 1.21 - 1.25 (4H, m), 1.66 - 1.75 (5H, m), 1.81 - 1.96 (3H, m), 2.84 - 2.99 (2H, m), 3.03 - 3.16 (2H, m), 3.31 - 3.46 (2H, m), 3.67 - 3.85 (2H, m), 6.55 (1H, d, J = 7.9 Hz), 6.57 (1H, d, J = 8.3 Hz), 7.22 (1H, dd, J = 7.9, 8.3 Hz), 7.27 (1H, s), 7.45 (1H, br s), 8.98 (1H, br s), 9.44 (1H, br s).

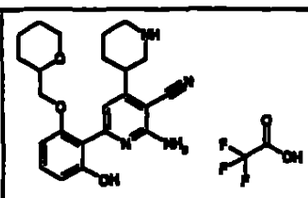
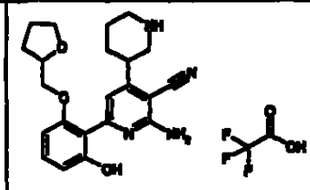
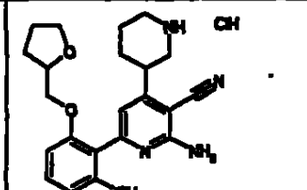
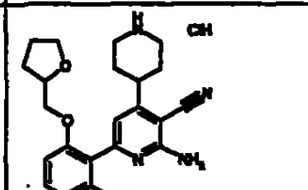
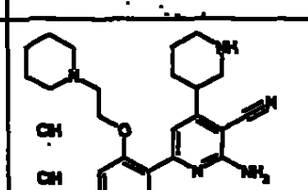
2-54		388.90	353	A	A	(300 MHz, DMSO-d6): 1.29 (6H, d, J = 6.0 Hz), 1.61 - 1.85 (4H, m), 2.88 - 3.10 (2H, m), 3.28 - 3.49 (3H, m), 4.65 (1H, sep, J = 6.0 Hz), 6.51 (1H, d, J = 7.9 Hz), 6.60 (1H, d, J = 8.7 Hz), 7.22 (1H, dd, J = 7.9, 8.7 Hz), 7.33 (1H, s), 7.42 (1H, br s), 8.87 (1H, br s), 9.24 (1H, br s).
2-55		388.90	353	A	A	(500 MHz, DMSO-d6): 0.94 (3H, t, J = 7.3 Hz), 1.67 (1H, m), 1.76 (1H, m), 1.76 - 1.85 (2H, m), 1.91 - 1.99 (2H, m), 2.88 (1H, m), 3.06 (1H, m), 3.27 (1H, m), 3.30 - 3.32 (3H, m), 3.38 (1H, m), 3.96 (2H, t, J = 6.0 Hz), 6.54 (1H, d, J = 8.2 Hz), 6.58 (1H, d, J = 8.2 Hz), 7.23 (1H, t, J = 8.2 Hz), 7.34 (1H, s), 8.88 (1H, br s) , 9.31 (1H, br s).
2-56		464.45	351	A	A	(500 MHz, DMSO-d6): 1.85 (1H, m), 1.78 (1H, m), 1.93 (2H, d, J = 11.4 Hz), 2.88 (1H, m), 3.03 (1H, m), 3.21 (1H, m), 3.35 (2H, dd, J = 10, 25 Hz), 4.57 (2H, d, J = 5.7 Hz), 5.33 (2H, m), 6.08 (1H, m), 6.56 (2H, dd, J = 8.3, 26 Hz), 7.29 (3H, M), 8.85 (1H, br), 8.97 (1H, br).
2-57		360.85	325	A	A	(500 MHz, DMSO-d6): 1.67 - 1.96 (5H, m), 2.72 - 3.42 (6H, m), 3.79 (3H, s), 6.55 (1H, d, J = 8.3 Hz), 6.58 (1H, d, J = 8.3 Hz), 7.22 (1H, s), 7.23 (1H, t, J = 8.3 Hz), 8.79 (1H, br d), 9.13 (1H, br d).
2-58		374.87	339	A	A	(500 MHz, DMSO-d6): 1.37 (3H, t, J = 6.9 Hz), 1.88 (1H, m), 1.82 (1H, m), 1.92 - 1.96 (2H, m), 2.91 (1H, m), 3.06 (1H, m), 3.23 - 3.32 (2H, m), 3.39 (1H, m), 4.06 (2H, q, J = 6.8 Hz), 6.54 (1H, d, J = 8.2 Hz), 6.58 (1H, d, J = 8.5 Hz), 7.24 (1H, dd, J = 8.2, 8.5 Hz), 7.40 (1H, s), 7.46 (1H, br s), 8.81 (1H, br s), 9.22 (1H, br s).

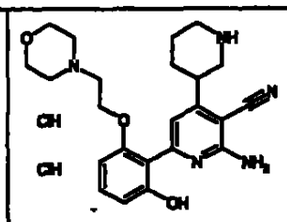
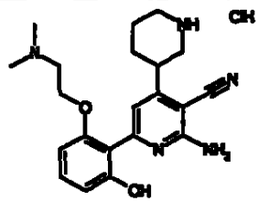
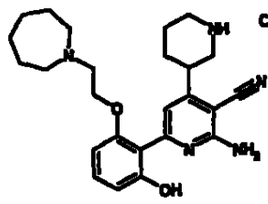
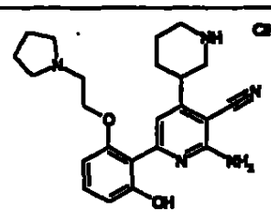
2-59		402.93	367	A	A	(500 MHz, DMSO-d6): 0.92 (6H, d, J = 6.6 Hz), 1.68 (1H, m), 1.80 (1H, m), 1.91 - 1.94 (2H, m), 2.04 (1H, sep, J = 6.6 Hz), 2.86 (1H, m), 3.07 (1H, m), 3.27 - 3.36 (3H, m), 3.76 (2H, d, J = 6.6 Hz), 6.56 (1H, d, J = 7.3 Hz), 6.57 (1H, d, J = 8.2 Hz), 7.23 (1H, dd, J = 7.3, 8.2 Hz), 7.28 (1H, s), 7.56 (1H, br s), 8.95 (1H, br s), 9.45 (1H, br s).
2-60		416.96	381	A	A	(500 MHz, DMSO-d6): 0.84 - 0.88 (2H, m), 1.29 - 1.30 (4H, m), 1.69 - 1.73 (2H, m), 1.80 - 1.95 (3H, m), 2.87 (1H, m), 3.10 (1H, m), 3.29 - 3.35 (3H, m), 3.48 (1H, m), 3.70 (1H, m), 3.97 (2H, q, J = 6.3 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.25 (1H, t, J = 8.2 Hz), 7.31 (1H, s), 7.75 (1H, br s), 9.07 (1H, br s), 9.60 (1H, br s).
2-61		457.02	421	A	A	(500 MHz, DMSO-d6): 0.85 - 0.93 (2H, m), 1.09 - 1.18 (3H, m), 1.32 (1H, m), 1.60 - 1.64 (7H, m), 1.71 (1H, m), 1.84 (1H, m), 1.90 - 1.95 (2H, m), 2.87 (1H, m), 3.09 (1H, m), 3.28 (1H, m), 3.30 - 3.34 (2H, m), 3.99 (1H, dd, J = 6.6, 9.5 Hz), 4.04 (1H, dd, J = 6.6, 9.5 Hz), 6.56 (1H, d, J = 8.2 Hz), 6.60 (1H, d, J = 8.5 Hz), 7.23 (1H, dd, J = 8.2, 8.5 Hz), 7.30 (1H, s), 7.59 (1H, br s), 8.99 (1H, br s), 9.46 (1H, br s).
2-62		414.94	379	A	A	(500 MHz, DMSO-d6): 1.63 - 1.78 (4H, m), 1.81 - 1.99 (5H, m), 2.02 - 2.09 (2H, m), 2.73 (1H, m), 2.88 (1H, m), 3.05 (1H, m), 3.22 - 3.38 (2H, m), 3.99 (2H, d, J = 6.6 Hz), 6.53 (1H, d, J = 8.5 Hz), 6.59 (1H, d, J = 8.2 Hz), 7.22 (1H, t, 8.2 Hz), 7.27 (1H, s), 7.28 (1H, br s), 8.76 (1H, br s), 9.11 (1H, br s).
2-63		430.96	395	A	A	(500 MHz, DMSO-d6): 0.84 (6H, d, J = 6.6 Hz), 1.17 - 1.25 (2H, m), 1.52 (1H, sep, J = 6.6 Hz), 1.67 - 1.75 (3H, m), 1.80 (1H, m), 1.86 - 1.96 (2H, m), 2.87 (1H, m), 3.07 (1H, m), 3.24 - 3.39 (3H, m), 3.87 - 4.13 (2H, m), 6.54 (1H, d, J = 8.2 Hz), 6.57 (1H, d, J = 8.2 Hz), 7.22 (1H, t, J = 8.2 Hz), 7.28 (1H, s), 7.43, (1H, br s), 8.87 (1H, br s), 9.27 (1H, br s).

2-64		445.01	409	A	B	(500 MHz, DMSO-d6): 0.84 (2H, d, J = 6.9 Hz), 0.85 (2H, d, J = 6.6 Hz), 1.20 - 1.33 (3H, m), 1.66 - 1.74 (3H, m), 1.75 - 1.95 (5H, m), 2.67 (1H, m), 3.10 (1H, m), 3.22 - 3.47 (4H, m), 3.90 (1H, d, J = 6.3 Hz), 3.94 - 4.02 (2H, m), 6.55 (1H, d, J = 8.2 Hz), 6.58 (1H, d, J = 8.2 Hz), 7.23 (1H, t, J = 8.2 Hz), 7.32 (1H, s), 7.48 (1H, br s), 8.98 (1H, m), 9.24 (1H, m).
2-65		400.91	365	A	A	(500 MHz, DMSO-d6): 0.33 - 0.37 (2H, m), 0.52 - 0.59 (2H, m), 1.30 (1H, m), 1.67 (1H, m), 1.82 (1H, m), 1.91 - 1.98 (2H, m), 2.07 (1H, m), 2.88 (1H, m), 3.11 (1H, m), 3.26 - 3.32 (2H, m), 3.85 (2H, d, J = 6.9 Hz), 6.53 (1H, d, J = 8.5 Hz), 6.54 (1H. d, J = 8.2 Hz), 7.23 (1H, dd, J = 8.2, 8.5 Hz), 7.37 (1H, br s), 7.54 (1H, s), 8.94 (1H, m), 9.43 (1H, m).
2-66		430.98	395	A	A	(500 MHz, DMSO-d6): 0.83 (6H, d, J = 6.6 Hz), 1.03 (2H,d, J = 6.6 Hz) 1.18 - 1.22 (2H, m), 1.51 - 1.53 (1H, m), 1.72 - 1.77 (3H, m), 1.93 - 1.95 (4H, m), 2.84 - 2.85 (1H, m), 3.06 - 3.22 (3H, m), 3.34-3.37 (2H, m), 3.99 (1H, t, J = 6.6 Hz), 6.55 - 6.59 (2H, m), 7.21 - 7.26 (2H, m), 9.03 - 9.12 (1H, br s).
2-67		388.90	353	A	A	(500 MHz, DMSO-d6): 0.92 (3H, t, J = 7.25 Hz), 1.77 (2H, m), 1.90 - 1.96 (2H, m), 3.06 - 3.13 (3H, m), 3.36 - 3.40 (2H, m), 3.97 (2H, t, J = 6.3 Hz), 6.57 (2H, dd, J = 10.0, 8.3 Hz), 7.23 - 7.27 (2H, m), 9.06 (2H, br s).
2-68		414.94	379	A	A	(500 MHz, DMSO-d6): 1.70 - 1.76 (2H, m), 1.79 - 1.92 (4H, m), 1.95 - 1.98 (2H, m), 2.00 - 2.07 (2H, m), 2.77 (1H, m), 3.07 - 3.14 (3H, m), 3.39 - 3.41 (2H, m), 4.00 (2H, d, J = 6.6 Hz), 6.56 (1H, d, J = 8.2 Hz), 6.60 (1H, d, J = 8.2 Hz), 7.19 (1H, s), 7.24 (1H, t, J = 8.2 Hz), 7.51 (1H, br s), 9.03 (2H, br s).

2-69		416.96	381	A	A	(500 MHz, DMSO-d6): 0.85 (3H, dd, J = 6.6, 7.2 Hz), 1.31 - 1.33 (4H, m), 1.74 - 1.78 (2H, m), 1.83 - 1.91 (2H, m), 1.94 - 1.99 (2H, m), 3.08 - 3.12 (3H, m), 3.37 - 3.39 (2H, m), 4.00 (2H, dd, J = 6.3, 6.6 Hz), 6.53 (1H, d, J = 8.2 Hz), 6.58 (1H, d, J = 8.5 Hz), 7.22 (1H, dd, J = 8.2, 8.5 Hz), 7.29 (1H, s), 7.30 (1H, br s), 8.75 (1H, br s), 8.83 (1H, br s).
2-70		457.02	421	A	A	(500 MHz, DMSO-d6): 0.88 - 0.93 (2H, m), 1.09 - 1.23 (3H, m), 1.34 (1H, m), 1.59 - 1.67 (7H, m), 1.88 - 1.99 (4H, m), 3.08 - 3.13 (3H, m), 3.36 - 3.38 (2H, m), 4.04 (2H, dd, J = 6.6, 6.9 Hz), 6.54 (1H, d, J = 8.2 Hz), 6.60 (1H, d, J = 8.5 Hz), 7.23 (1H, dd, J = 8.2, 8.5 Hz), 7.24 (1H, s), 7.36 (1H, br s), 8.91 (2H, br s).
2-71		402.93	367	A	A	(500 MHz, DMSO-d6): 0.92 (6H, d, J = 6.6 Hz), 1.83 - 1.92 (2H, m), 1.94 - 1.97 (2H, m), 2.08 (1H, dq, J = 6.6 Hz), 3.04 - 3.13 (3H, m), 3.38 - 3.41 (2H, m), 3.78 (2H, d, J = 6.6 Hz), 6.54 (1H, d, J = 8.2 Hz), 6.57 (1H, d, J = 8.5 Hz), 7.22 (1H, s), 7.23 (1H, dd, J = 8.2, 8.5 Hz), 7.38 (1H, br s), 8.86 (1H, br s), 8.95 (1H, br s).
2-72		402.93	367	A		(500 MHz, DMSO-d6): 0.89 (3H, dd, J = 7.3, 7.6 Hz), 1.37 (2H, dq, J = 7.3, 7.6 Hz), 1.75 (2H, dd, J = 6.6, 6.9 Hz), 1.86 - 1.97 (4H, m), 3.06 - 3.13 (3H, m), 3.37 - 3.40 (2H, m), 4.02 (2H, t, J = 6.6 Hz), 6.54 (1H, d, J = 8.2 Hz), 6.59 (1H, d, J = 8.2 Hz), 7.23 (1H, t, J = 8.2 Hz), 7.28 (1H, s), 7.47 (1H, br s), 8.86 (2H, br s).
2-73		445.01	409	A	A	(300 MHz, DMSO-d6): 0.84 (3H, t, J = 6.8 Hz), 1.22 - 1.27 (8H, m), 1.73 - 1.78 (2H, m), 1.87 - 1.94 (4H, m), 3.07 - 3.11 (3H, m), 3.35 - 3.40 (2H, m), 4.01 (2H, t, J = 6.4 Hz), 6.54 (1H, d, J = 8.3 Hz), 6.58 (1H, d, J = 7.9 Hz), 7.23 (1H, dd, J = 7.9, 8.3 Hz), 7.28 (1H, s), 7.33 (1H, br s), 8.90 (2H, br s).

2-74		388.88	351	A	A	(300 MHz, DMSO-d6): 1.76 - 1.98 (4H, m), 3.06 - 3.10 (3H, m), 3.38 - 3.42 (2H, m), 4.61 (2H, d, J = 5.3 Hz), 5.29 (1H, dd, J = 1.5, 10.6 Hz), 5.36 (1H, dd, J = 1.5, 17.3 Hz), 6.11 (1H, ddt, J = 5.3, 10.6, 17.3 Hz), 6.55 (1H, d, J = 8.3 Hz), 6.59 (1H, d, J = 7.9 Hz), 7.23 (1H, dd, J = 7.9, 8.3 Hz), 7.27 (1H, s), 7.33 (1H, br s), 8.74 (2H, br s).
2-75		374.87	339	A	A	(300 MHz, DMSO-d6): 1.40 (3H, t, J = 7.2 Hz), 1.80 - 2.01 (4H, m), 3.08 - 3.10 (3H, m), 3.39 - 3.43 (2H, m), 4.08 (2H, q, J = 6.8 Hz), 6.53 (1H, d, J = 7.9 Hz), 6.57 (1H, d, J = 8.3 Hz), 7.23 (1H, dd, J = 7.9, 8.3 Hz), 7.34 (1H, br s), 7.40 (1H, s), 8.80 (2H, br s).
2-76		430.98	395	A	A	(300 MHz, DMSO-d6): 0.36 (3H, t, J = 6.8 Hz), 1.25 - 1.34 (7H, m), 1.71 - 1.78 (2H, m), 1.82 - 1.91 (2H, m), 1.94 - 1.98 (2H, m), 3.05 - 3.37 (4H, m), 4.01 (2H, t, J = 6.4 Hz), 6.52 (1H, d, J = 8.3 Hz), 6.58 (1H, d, J = 7.9 Hz), 7.20 (1H, br s), 7.22 (1H, dd, J = 7.9, 8.3 Hz), 7.30 (1H, s), 8.61 (1H, br s), 8.75 (1H, br s).
2-77		444.97	409	A	A	(500 MHz, DMSO-d6): 1.20 (9H, s), 1.81 - 1.97 (5H, m), 2.98 (1H, m), 3.26 - 3.31 (2H, m), 3.42 (1H, m), 5.20 (2H, s), 6.55 (1H, d, J = 8.2 Hz), 6.61 (1H, d, J = 8.2 Hz), 7.25 (1H, t, J = 8.2 Hz), 7.36 (2H, br s), 8.13 (1H, s), 8.61 (1H, br s), 9.27 (1H, br s).
2-78		444.97	409	A	A	(300 MHz, DMSO-d6): 1.17 (9H, s), 1.86 - 1.95 (4H, m), 3.07 - 3.10 (3H, m), 3.35 - 3.40 (2H, m), 5.22 (2H, s), 6.44 (1H, d, J = 8.3 Hz), 6.53 (1H, d, J = 8.3 Hz), 7.18 (1H, t, J = 8.3 Hz), 7.21 (1H, br s), 7.48 (1H, br s), 8.77 (1H, br s).

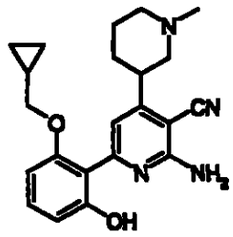
2-79		522.53	409	A	A	(500 MHz, DMSO-d6): 1.21 - 1.30 (2H, m), 1.43 - 1.51 (3H, m), 1.61 (1H, m), 1.67 - 1.82 (4H, m), 1.91 - 1.97 (2H, m), 2.89 (1H, m), 3.05 (1H, m), 3.22 (1H, m), 3.35 - 3.43 (3H, m), 3.91 (1H, m), 3.96 (1H, m), 8.52 (1H, d, J = 8.5 Hz), 8.58 (1H, d, J = 8.5 Hz), 7.22 (1H, t, J = 8.2 Hz), 7.28 (2H, br s), 7.38 (1H, s), 8.67 (1H, br s), 8.88 (1H, br s).
2-80		508.50	395	A	A	(500 MHz, DMSO-d6): 1.61 (1H, m), 1.66 - 1.81 (4H, m), 1.85 (1H, m), 1.90 - 2.04 (4H, m), 2.80 (1H, m), 3.12 (1H, m), 3.23 (1H, m), 3.40 (1H, m), 3.76 (1H, m), 3.87 (1H, m), 4.03 (1H, dd, J = 2.8, 3.1 Hz), 4.27 (1H, m), 8.52 (1H, d, J = 8.2 Hz), 8.55 (1H, d, J = 8.5 Hz), 7.24 (1H, dd, J = 8.2, 8.5 Hz), 7.29 (2H, br s), 7.81 (1H, s), 8.62 (1H, br s), 8.92 (1H, br s).
2-81		430.94	395	A	A	(500 MHz, DMSO-d6): 1.61 (1H, m), 1.71 (1H, m), 1.76 - 1.88 (3H, m), 1.87 - 2.03 (3H, m), 2.78 (1H, m), 3.13 (1H, m), 3.25 - 3.35 (3H, m), 3.75 - 3.80 (2H, m, 3.88 (1H, m), 4.03 (1H, m), 4.27 (1H, m), 7.51 (1H, d, J = 8.2 Hz), 7.56 (1H, d, J = 8.2 Hz), 7.24 (1H, t, J = 8.2 Hz), 7.53 (1H, br s), 7.56 (1H, s), 8.93 (1H, m), 9.53 (1H, m).
2-82		430.94	395	A	A	(300 MHz, DMSO-d6): 1.59 (1H, m), 1.76 - 1.97 (7H, m), 3.07 - 3.10 (3H, m), 3.37 - 3.41 (2H, m), 3.70 (2H, dd, J = 6.8, 14.7 Hz), 3.92 (1H, dd, J = 6.8, 7.2 Hz), 4.01(1H, dd, J = 6.8, 7.2 Hz), 4.22 (1H, m), 6.54 (1H, d, J = 8.3 Hz), 6.58 (1H, d, J = 8.3 Hz), 7.20 (1H, br s), 7.22 (1H, t, J = 8.3 Hz), 7.34 (1H, s), 8.74 (1H, br s), 8.92 (1H, br s).
2-83		494.47	422	B	B	(500 MHz, DMSO-d6): 1.26 - 1.38 (1H, m), 1.65 - 1.93 (10H, m), 2.84 - 3.39 (8H, m), 4.36 - 4.43 (3H, m), 6.61 (2H, d, J = 8.2 Hz), 7.05 (1H, s), 7.22 - 7.26 (3H, m), 8.76 - 8.85 (1H, m), 9.35 (1H, br d, J = 10.1 Hz), 10.56 (1H, br s).

2-84		498.44	424	A	B	(500 MHz, DMSO-d6): 1.71 - 1.93 (5H, m), 2.95 - 3.47 (12H, m), 3.75 (1H, br s), 4.36 - 4.44 (2H, br s), 6.61 (2H, d, J = 8.2 Hz), 7.01 (1H, s), 7.16 (2H, br s), 7.23 (1H, t, J = 8.4 Hz), 8.76 - 8.85 (1H, m), 9.29 (1H, br d, J = 10.4 Hz), 11.34 (1H, br s).
2-85		417.94	382	B	B	(500 MHz, DMSO-d6): 1.68 - 1.83 (2H, m), 1.92 (2H, m), 2.73 (6H, d, J = 4.4 Hz), 2.97 (1H, m), 3.17 - 3.19 (3H, m), 3.22 - 3.39 (3H, m), 4.36 (2H, br), 6.61 (1H, d, J = 8.5 Hz), 6.83 (1H, d, J = 8.2 Hz), 7.09 (1H, s), 7.21 (1H, br s), 7.25 (1H, dd, J = 8.2, 8.5 Hz), 8.80 (1H, br), 9.37 (1H, br s), 10.6 (1H, br s).
2-86		472.04	436	C	B	(500 MHz, DMSO-d6): 1.53 - 1.54 (2H, m), 1.62 - 1.64 (2H, m), 1.67 - 1.84 (6H, m), 1.91 - 1.92 (2H, m), 2.97 (1H, m), 3.05 - 3.10 (2H, m), 3.17 - 3.25 (2H, m), 3.29 - 3.45 (6H, m), 4.39 (2H, br), 6.60 (1H, d, J = 8.2 Hz), 6.81 (1H, d, J = 8.2 Hz), 7.05 (1H, s), 7.18 (1H, br s), 7.24 (1H, t, J = 8.2 Hz), 8.77 (1H, br s), 9.30 (1H, br s), 10.6 (1H, br s).
2-87		443.96	408	C	B	(500 MHz, DMSO-d6): 1.72 - 1.85 (5H, m), 1.90 - 1.93 (3H, m), 2.91 - 3.17 (3H, m), 3.21 - 3.39 (4H, m), 3.43 - 3.44 (2H, m), 3.50 - 3.51 (2H, m), 4.36 (2H, br), 6.62 (1H, d, J = 8.5 Hz), 6.85 (1H, d, J = 8.2 Hz), 7.15 (1H, s), 7.26 (1H, dd, J = 8.2, 8.5 Hz), 7.53 (1H, br s), 8.00 (1H, br s), 8.64 (1H, br s), 11.2 (1H, br s).

Example 3-1

(1) With the use of the starting compound 1G, 2B and other materials, 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinonitrile hydrochloride was prepared in a similar manner as described in Example 2-3.

(2) To a stirred solution of 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinonitrile hydrochloride (200.0 mg, 0.50 mmol) in MeOH were added formaldehyde (0.5 mL) and sodium cyanoborohydride (40.8 mg, 0.65 mmol) and stirred for 2 hrs at room temperature. The reaction was quenched by an addition of water, extracted with ethyl acetate, dried over $MgSO_4$, filtered and evaporated. The residue was triturated with hexane and dried. The crude product was purified by preparative silica gel TLC (5% MeOH in dichloromethane) to give 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(1-methyl-3-piperidinyl)nicotinonitrile as a yellow solid. (28.5 mg, yield 15%)



Molecular weight: 378.48

Mass spectrometry: 379 $(M+H)^+$

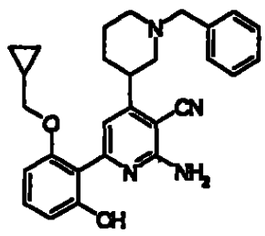
In vitro activity grade: A

Cellular activity grade: (A549)A

^{1}H-NMR (300 MHz, CDCl3): 0.37 – 0.42 (2H, m), 0.67 – 0.73 (2H, m), 0.82 – 0.88 (1H, m), 1.27 – 1.35 (1H, m), 1.76 – 2.09 (4H, m), 2.31 (3H, s), 2.91 – 3.00 (2H, m), 3.14 – 3.23 (1H, m), 3.86 (2H, pent, J = 8.8 Hz), 5.15 (2H, br s), 6.39 (1H, d, J = 8.3 Hz), 6.62 (1H, d, J = 8.3 Hz), 7.20 (1H, t, J = 8.3 Hz), 7.95 (1H, s).

Example 3-2

To a stirred solution of 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinonitrile hydrochloride (200.0 mg, 0.50 mmol),which was obtained in the step (1) of example 3-1, in MeOH was added benzaldehyde (0.25 mL, 2.49 mmol)) followed by sodium cyanoborohydride (40.8 mg, 0.65 mmol), and the stirring was continued for 2 hrs at room temperature. The reaction was quenched by an addition of water, extracted with ethyl acetate, dried over $MgSO_4$, filtered and evaporated. The residue was triturated with hexane and dried. The crude product was purified by preparative silica gel TLC (5% MeOH in dichloromethane) to give 2-amino-4-(1-benzyl-3-piperidinyl)-6-[2-(cyclopropylmethoxy)-6-hydroxy-phenyl]nicotinonitrile as a yellow solid. (35.7 mg, yield 16%)



Molecular weight: 454.58

Mass spectrometry: 455 $(M+H)^+$

In vitro activity grade: C

Cellular activity grade: (A549)C

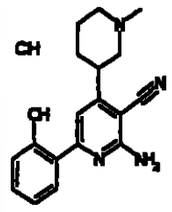
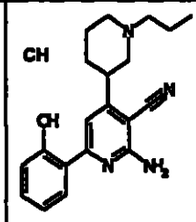
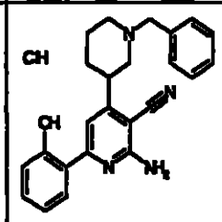
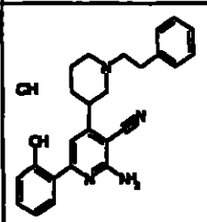
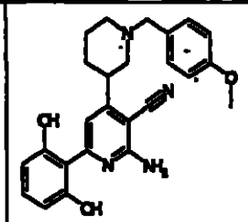
^{1}H-NMR (300 MHz, CDCl3): 0.35 – 0.37 (2H, m), 0.62 – 0.64 (2H, m), 0.83 – 1.29 (2H, m), 1.75 – 2.21 (5H, m), 2.93 – 3.24 (3H, m), 3.50 – 3.61 (2H, m), 3.78 – 3.88 (2H, m), 5.12 (2H, br s), 6.39 (1H, d, J = 8.3 Hz), 6.60 (1H, d, J = 8.3 Hz), 7.16 – 7.32 (6H, m), 7.93 (1H, s), 13.33 (1H, br s).

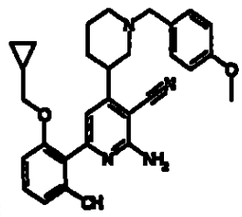
Examples 3-3 to 3-8

According to the similar synthetic procedure of Examples 3-1 to 3-2, compounds shown in Table 3 were prepared.

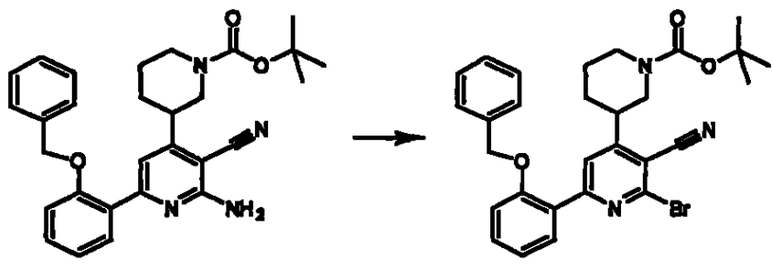
5

Table 3

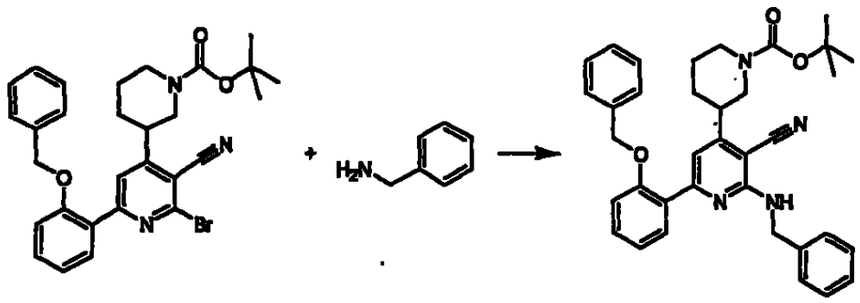
Ex. No	Structure	Mol weight	Mass	In vitro	A549	NMR
3-03		344.85	309	A	A	(300 MHz, DMSO-d6): 1.70 - 1.98 (4H, m), 2.73 (3H, d, J = 1.8 Hz), 2.93 - 2.98 (1H, m), 3.35 - 3.49 (4H, m), 6.90 - 6.95 (2H, m), 7.33 - 7.46 (3H, m), 8.02 (1H, dd, J = 8.5, 1.3 Hz), 10.62 (1H, br s).
3-04		372.90	337	A	B	(300 MHz, DMSO-d6): 0.92 (3H, t, J = 7.4 Hz), 1.71 - 1.76 (3H, m), 1.81 - 1.98 (3H, m), 2.92 - 3.04 (3H, m), 6.90 - 6.95 (2H, m), 7.34 - 7.38 (2H, m), 7.45 (1H, br s), 8.01 (1H, d, J = 7.4 Hz), 9.80 (1H, br s).
3-05		420.95	385	A	A	(300 MHz, DMSO-d6): 1.81 - 1.98 (4H, m), 2.72 - 2.73 (1H, m), 3.31 - 3.50 (4H, m), 4.26 - 4.35 (2H, m), 6.89 - 6.95 (2H, m), 7.34 - 7.51 (6H, m), 7.59 - 7.62 (2H, m), 8.00 - 8.02 (1H, m), 10.57 (1H ,br s).
3-06		434.97	399	B	B	(300 MHz, DMSO-d6): 1.78 - 2.01 (5H, m), 3.04 - 3.15 (4H, m), 3.30 - 3.67 (2H, m), 6.90 - 6.95 (2H, m), 7.24 - 7.49 (11H, m), 8.03 (1H, d, J = 7.5 Hz), 10.58 (1H, br s).
3-07		430.51	431	A	B	(500 MHz, DMSO-d6): 1.39 (1H, dd, J = 3.5, 11.7 Hz), 1.59 (1H, m), 1.73 (1H, d, J = 12.9 Hz), 1.88 (1H, d, J = 11.7 Hz), 1.95 (1H, t, J = 10.4 Hz), 2.02 (1H, t, J = 11.0 Hz), 2.84 (1H, d, J = 11.0 Hz), 2.89 (1H, d, J = 10.4 Hz), 2.97 (1H, t, J = 11.0 Hz), 3.45 (2H, m), 3.72 (3H, s), 6.36 (2H, d, J = 8.2 Hz), 6.86 (2H, d, J = 8.5 Hz), 7.06 (1H, t, J = 8.2 Hz), 7.16 (2H, br), 7.21 (1H, d, J = 8.5 Hz), 7.78 (1H, s), 11.91 (2H, s).

3-08		484.60	485	C	C	(300 MHz, CDCl3): 0.33 - 0.38 (2H, m), 0.60 - 0.66 (2H, m), 1.24 - 2.21 (6H, m), 2.94 - 3.25 (2H, m), 3.52 (2H, br s), 3.79 - 3.84 (5H, m), 5.18 (2H, br s), 6.39 (1H, d, J = 8.3 Hz), 6.60 (1H, d, J = 8.3 Hz), 6.84 (2H, d, J = 8.7 Hz), 7.16 - 7.28 (3H, m), 7.93 (1H, s).

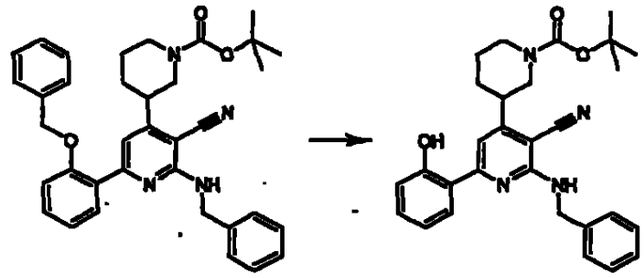
Example 4-1



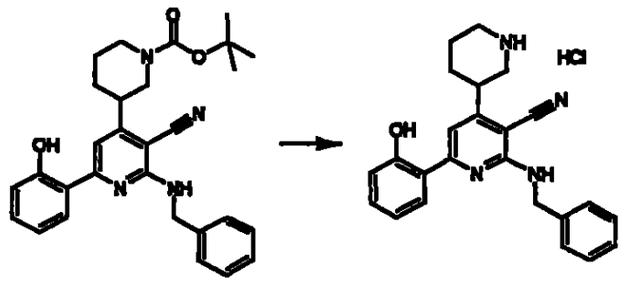
(1) A mixture of copper (II) bromide (1.106 g, 4.953 mmol) and tert-butyl nitrite (0.736 mL, 6.191 mmol) in acetonitrile (30 mL) was stirred at 65 °C for 15 min. A solution of tert-butyl 3-{2-amino-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate (2.000 g, 4.127 mmol), which was obtained in the step (1) of Example 1-1 , in acetonitrile (20 mL) was added dropwise to the mixture. The mixture was stirred at 65 °C for 2 hrs. After cooled to room temperature, the reaction mixture was diluted with ethyl acetate. The separated organic phase was washed with an aqueous 1N HCl solution and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was recrystallized from diethyl ether to give tert-butyl 3-{2-bromo-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate as a white solid (1.010 g, yield; 45%).



(2) To a stirred solution of tert-butyl 3-{6-[2-(benzyloxy)phenyl]-2-bromo-3-cyano-4-pyridinyl}-1-piperidinecarboxylate (0.300 g, 0.547 mmol) in DMSO were added triethylamine (0.229 mL, 1.341 mmol) and benzylamine (0.147 g, 1.367 mmol). The mixture was stirred at 70 °C for 12 hrs. After cooled to room temperature, the reaction mixture was quenched with water and extracted with ethyl acetate. The separated organic phase was washed with brine, dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1-2/1) to give tert-butyl 3-{6-[2-(benzyloxy)phenyl]-2-benzylamino-3-cyano-4-pyridinyl}-1-piperidinecarboxylate as a yellow amorphous. (0.290 g, yield; 92%)



(3) Then benzyl moiety was removed in a same manner as described in step (2) of Example 1-1. The residue was suspended in ethanol and filtrated to give tert-butyl 3-[2-(benzylamino)-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate as a white solid. (0.150 g, yield; 61%)



(4) tert-butyl 3-[2-(benzylamino)-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.145 g, 0.299 mmol) was treated under acidic conditions in a similar manner as described in step (3) in Example 1-1. The resulting solid was collected by filtration, and dried under reduced pressure to give 2-(benzylamino)-6-(2-hydroxyphenyl)-4-(3-piperidinyl)nicotinonitrile hydrochloride. (0.075 g, yield; 60%)

Molecular weight: 420.95

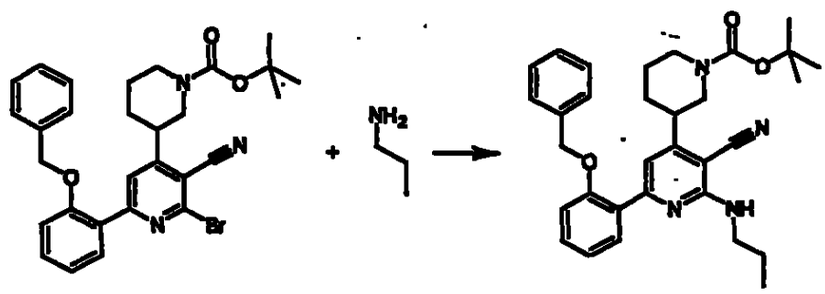
Mass spectrometry: 385 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-B/Jurkat-B

^{1}H-NMR (300 MHz, DMSO-d6): 1.80 – 1.92 (4H, m), 2.90 – 2.93 (1H, m), 3.31 – 3.40 (4H, m), 4.59 (2H, d, J = 5.6 Hz), 6.84 – 6.92 (2H, m), 7.19 – 7.31 (5H, m), 7.47 (1H, s), 8.00 (1H, d, J = 6.8 Hz), 8.11 – 8.15 (1H, m), 8.91 (1H, br s), 9.52 (1H, br s),12.59 (1H, br s), 12.90 (1H, br s).

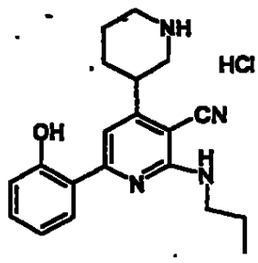
Example 4-2



To a stirred solution of tert-butyl 3-{6-[2-(benzyloxy)phenyl]-2-bromo-3-cyano-4-pyridinyl}-1-piperidinecarboxylate (0.100 g, 0.182 mmol), which was obtained in the steps (1) of Example 4-1, in DMSO (2 mL) were added propylamine (0.108 g, 1.823 mmol) and triethylamine (0.038 mL, 0.273 mmol). The mixture was stirred at 40 °C for 12 hrs. The reaction was quenched with water and the resulting reaction mixture was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The concentrates was purified by silica gel column (hexane/ethyl acetate = 4/1) to give tert-butyl 3-{6-[2-(benzyloxy)phenyl]-3-cyano-2-propylamino-4-pyridinyl}-1-piperidinecarboxylate as a colorless oil. (0.104 g, yield; quant.)

Then benzyl moiety was removed in a same manner as described in the step (2) in Example 1-1. The residue was washed with diethyl ether to give the desired product as a white solid. (0.112 g, yield; quant.)

Then tert-butyl 3-[3-cyano-6-(2-hydroxyphenyl)-2-(propylamino)-4-pyridinyl]-1-piperidinecarboxylate (0.110 g, 0.252 mmol) was treated under acidic conditions in a same manner as described in the step (3) in Example 1-1. The resulting solid was collected with filtration, and dried under reduced pressure to give 6-(2-hydroxyphenyl)-4-(3-piperidinyl)-2-(propylamino)nicotinonitrile hydrochloride. (0.062 g, yield; 66%)



Molecular weight: 372.90

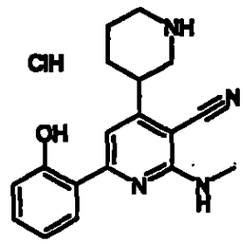
Mass spectrometry: 337 $(M+H)^+$

In vitro activity grade: C

Cellular activity grade: (A549)-C

^{1}H-NMR (300 MHz, DMSO-d6): 0.92 (3H, t, J = 7.4 Hz), 1.62 (2H, m), 1.80 – 1.95 (4H, m), 2.89 – 2.93 (1H, m), 3.33 – 3.46 (6H, m), 6.91 – 6.97 (2H, m), 7.34 – 7.40 (1H, m), 7.48 (1H, s), 7.57 (1H, br s), 8.08 – 8.17 (1H, m), 8.97 – 9.07 (1H, m), 9.67 – 9.71 (1H, m).

Example 4-3



In a similar manner as that of Example 4-2, 6-(2-hydroxyphenyl)-2-(methylamino)-4-(3-piperidinyl)nicotinonitrile hydrochloride was prepared.

Molecular weight: 344.85

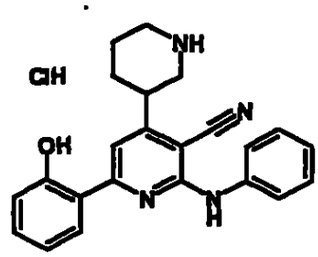
Mass spectrometry: 309 $(M + H)^+$

In vitro activity grade: C

Cellular activity grade: (A549)-C

^{1}H-NMR (300 MHz, DMSO-d6): 1.83 – 1.96 (4H, m), 3.31 (4H, s), 3.30 – 3.56 (4H, m), 6.90 – 6.96 (2H, m), 7.34 – 7.37 (1H, m), 7.39 (1H, s), 7.55 (1H, br s), 8.10 (1H, d, J = 7.9 Hz), 8.87 – 8.90 (1H, m), 9.52 – 9.54 (1H, m), 13.80 (1H, br s).

Example 4-4



In a similar manner as that of Example 4-2, 2-anilino-6-(2-hydroxyphenyl)-4-(3-piperidinyl)nicotinonitrile hydrocloride was prepared.

Molecular weight: 406.92

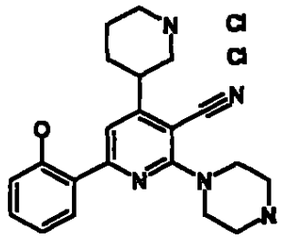
Mass spectrometry: 371 $(M+H)^+$

In vitro activity grade: D

Cellular activity grade: (A549)-B

^{1}H-NMR (300 MHz, DMSO-d6): 1.87 – 2.00 (4H, m), 2.91 – 2.95 (1H, m), 3.34 (1H m), 6.79 (1H, d, J = 8.3 Hz), 6.91 (1H, t, J = 7.2 Hz), 7.18 – 7.44 (1H, brs), 7.66 (1H, s), 8.06 (1H, d, J = 6.8 Hz), 8.84 (1H, m), 9.43 (2H, m), 12.42 (1H, br s).

Example 4-5



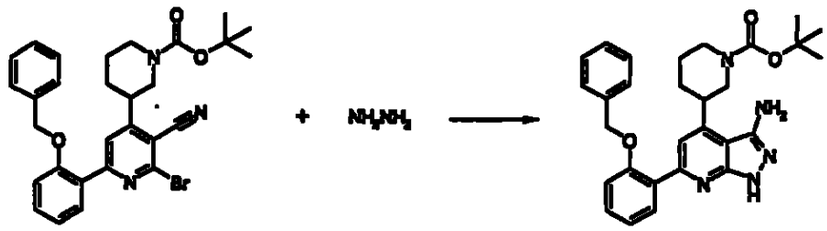
In a similar manner as that of Example 4-2, 6-(2-hydroxyphenyl)-2-(1-piperazinyl)-4-(3-piperidinyl)nicotinonitrile dihydrochloride was prepared.

Molecular weight: 436.39

Mass spectrometry: 364 $(M+H)^+$

In vitro activity grade: D ^{1}H-NMR (500 MHz, DMSO-d6): 1.81 – 1.83 (2H, m), 1.90 – 1.95 (2H, m), 2.93 – 2.95 (1H, m), 3.76 – 3.78 (4H, m), 6.98 (1H, t, J = 7.3 Hz), 7.37 – 7.40 (1H. m), 7.84 (1H, s), 8.03 – 8.05 (1H, m), 8.78 – 8.81 (1H, m), 9.14 (1H, br s), 9.24 – 9.27 (1H, m), 12.10 (1H, s).

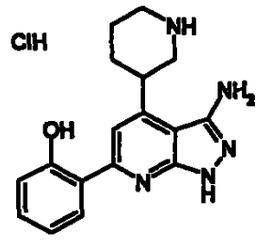
Example 5-1



(1) A mixture of tert-butyl 3-{6-[2-(benzyloxy)phenyl]-2-bromo-3-cyano-4-pyridinyl}-1-piperidinecarboxylate (0.300 g, 0.547 mmol), which was obtained in the step (1) of Example 4-1, hydrazine monohydrate (3 mL) and 1,4-dioxane (1 mL) was stirred at 100 °C for 1.5 hrs. The reaction was quenched with water and extracted with ethyl acetate. The organic phase was washed with brine and dried over Na_2SO_4, filtered, and concentrated. The residue was recrystallized from ethanol to give tert-butyl {3-[3-amino-6-(2-benzyloxy-phenyl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl]-1-piperidinecarboxylate as a yellow solid. (0.210 g, yield; 72%)

(2) Then the benzyl moiety was removed in a same manner as described in the step (2) of Example 1-1. The residue was purified by silica gel column (hexane/ethyl acetate = 2/1-1/1) to give tert-butyl 3-[3-amino-6-(2-hydroxyphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-1-piperidinecarboxylate as an orange solid. (0.080 g, yield; 49%)

To a stirred solution tert-butyl 3-[3-amino-6-(2-hydroxyphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-1-piperidinecarboxylate (0.075 g, 0.183 mmol) in 1,4-dioxane (3 mL) was added 4N HCl in 1,4-dioxane (3 mL). The mixture was stirred at room temperature for 12 hrs. The resulting solid was collected with filtration to give 2-[3-amino-4-(3-piperidinyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]phenol hydrochloride. (0.062 g, yield; 98%)



Molecular weight: 345.83

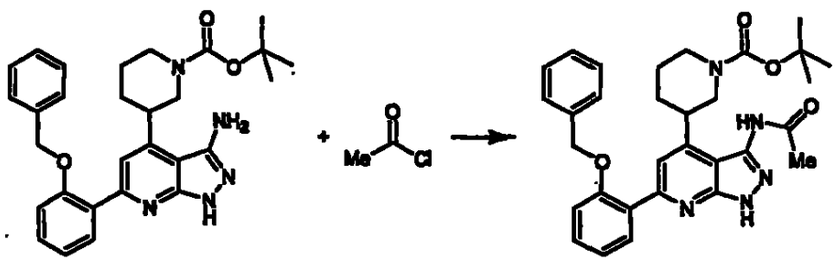
Mass spectrometry: 310 $(M+H)^+$

In vitro activity grade: C

Cellular activity grade: A549-B

^{1}H-NMR (300 MHz, DMSO-d6): 1.97 – 2.27 (4H, m), 2.95 – 3.11 (1H, m), 3.12 – 3.23 (1H, m), 3.30 – 3.39 (3H, m), 6.94 – 6.99 (2H, m), 7.32 – 7.38 (1H, m), 7.73 (1H, s), 8.12 (1H, d, J = 7.2 Hz).

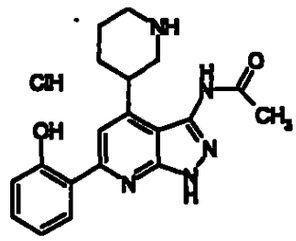
Example 5-2



To a cooled (0 °C), stirred solution of tert-butyl 3-{3-amino-6-[2-(benzyl-oxy)phenyl]-1H-pyrazolo[3,4-b]pyridin-4-yl}-1-piperidinecarboxylate (0.200 g, 0.400 mmol) obtained in the step (1) of Example 5-1 in THF (3 mL) were added pyridine (1 mL) and acetyl chloride (0.035 g, 0.440 mmol). The mixture was stirred at 0 °C for 1 hr. The reaction was quenched with water and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated. The residue was recrystallized from diisopropyl ether to give a white solid. (0.180 g, yield; 83%)

Then the benzyl moiety was removed in a same manner as described in the step (2) of Example 1-1. The residue was suspended in ethanol and filtrated to give the desired product as a white solid. (0.120 g, yield; 82%)

tert-Butyl 3-[3-(acetylamino)-6-(2-hydroxyphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-1-piperidinecarboxylate (0.115 g, 0.260 mmol) was treated under acidic conditions in a same manner as described in the step (3) of Example 1-1 to give N-[6-(2-hydroxyphenyl)-4-(3-piperidinyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]acetamide hydrochloride. (0.097 g, yield; 96%)



Molecular weight: 387.87

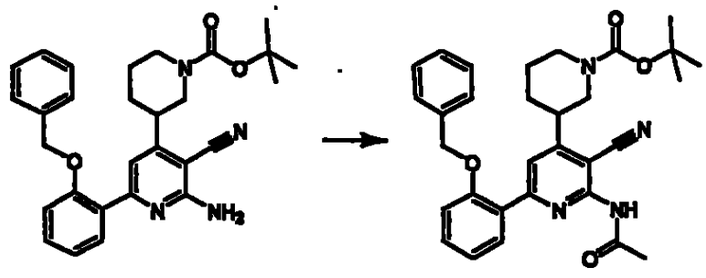
Mass spectrometry: 352 $(M+H)^+$

In vitro activity grade: D

Cellar activity grade: A549-C

^{1}H-NMR (500 MHz, DMSO-d6): 1.80 – 1.91 (4H, m), 1.95 (3H, s), 2.82 – 2.92 (1H, m), 3.34 – 3.44 (4H, m), 6.92 – 6.95 (2H, m), 7.36 – 7.39 (1H, m), 7.66 (1H, s), 8.12 (1H, d, J = 8.2 Hz), 8.83 – 8.85 (1H, m), 9.48 – 9.49 (1H, m), 9.56 (1H, s) 10.21 (1H, s), 13.59 (1H, br s).

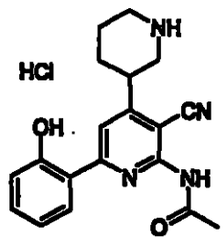
Example 6-1



To a cooled (0 °C), stirred solution of tert-butyl 3-{2-amino-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate, which was obtained in the step (1) of Example 1-1, (0.500 g, 1.032 mmol) in pyridine (10 mL) was added acetyl chloride (0.477 mL, 6.70 mmol). The mixture was stirred at 0 °C to room temperature for 3 hrs, and the stirring was continued at room temperature for 5 hrs. The reaction mixture was quenched with water, and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 9/1 - 4/1 - 2/1) to give a mixture of the desired product, tert-butyl 3-{2-(acetylamino)-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate, and the corresponding diacylated compound. The mixture obtained was dissolved in THF (5 mL), treated with an aqueous 1N NH_3 solution (1 mL), and stirred at room temperature for 1 hr. The reaction mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated to give tert-butyl 3-{2-(acetylamino)-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate as a white amorphous. (0.432 g, yield; 80%)

Then the benzyl moiety was removed in a same manner as described in the step (2) of Example 1-1. The residue was recrystallized from ethanol to give the desired product as a yellow solid. (0.110 g, yield; 31%)

tert-Butyl 3-[2-(acetylamino)-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.100 g, 0.229 mmol) was treated under acidic conditions in a similar manner as described in the step (3) of Example 1-1. The resulting precipitate was collected by filtration, washed with 1,4-dioxane, and dried under reduced pressure to give N-[3-cyano-6-(2-hydroxyphenyl)-4-(3-piperidinyl)-2-pyridinyl]acetamide hydrochloride. (0.101 g, yield; quant.)



Molecular weight: 372.86

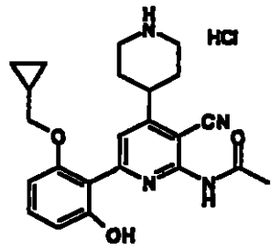
Mass spectrometry: 337 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-B

^{1}H-NMR '(500 MHz, DMSO-d6): 1.86 – 1.97 (4H, m), 2.19 (3H, s), 2.91 – 2.94 (1H, m), 3.33 – 3.47 (4H, m), 6.96 – 6.99 (2H, m), 7.38 – 7.41 (1H, m), 8.11 – 8.13 (2H, m), 8.94 – 8.96 (1H, m), 9.62 – 9.64 (1H, m), 10.97 (1H, s).

Example 6-2



With the use of the starting compound 1G and the 4-formyl piperidine-1 carboxylic acid tert-butyl ester and other materials, *N*-[3-cyano-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(4-piperidinyl)-2-pyridinyl]acetamide hydrochloride was prepared in the similar manner as that of Example 6-1.

Molecular weight: 442.95

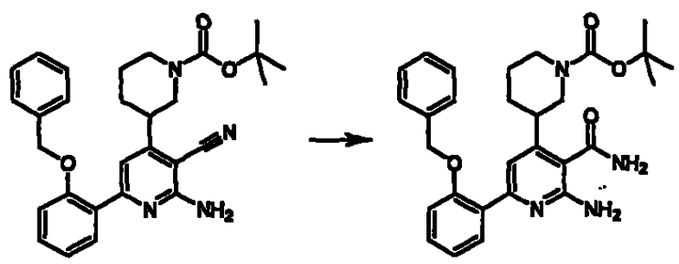
Mass spectrometry: 407 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.28 – 0.31 (2H, m), 0.55 – 0.58 (2H, m), 1.32 (1H, m), 1.98 – 2.01 (2H, m), 2.16 (3H, s), 3.09 – 3.13 (2H, m), 3.24 – 3.28 (1H, m), 3.40 – 3.42 (2H, m), 3.87 (2H, d, J = 6.9 Hz), 6.57 (2H, dd, J = 8.5, 2.8 Hz), 7.24 (1H, t, J = 8.5 Hz), 7.92 (1H, s), 9.06 – 9.15 (2H, m), 10.93 (1H, s).

Example 7-1

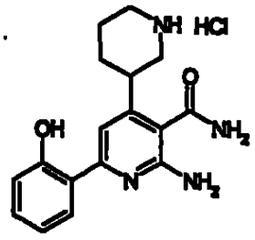


(1) To a stirred suspension of tert-butyl 3-{2-amino-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-1-piperidinecarboxylate (0.300 g, 0.619 mmol), which was obtained in the step (1) of Example 1-1, in ethanol (10 mL) was added a solution of potassium hydroxide (0.695 g, 12.381 mmol) in ethanol (20 mL). The reaction mixture was stirred at 70 °C for 60 hrs. After cooled to room temperature, the reaction mixture was poured into water and the resulting solid was filtrated and dried under reduced pressure to give tert-butyl 3-{2-amino-6-[2-(benzyloxy)phenyl]-3-carbamoyl-4-pyridinyl}-1-piperidinecarboxylat as a white amorphous. (0.226 g, yield; 73%)

(2) Then benzyl moiety was removed in a same manner as described in the step (2) of Example 1-1. The residue was suspended in ethanol and filtrated to give tert-butyl 3-[2-amino-3-(carbamoyl)-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate as a white solid. (0.045 g, yield; 46%)

(3) tert-butyl 3-[2-amino-3-(carbamoyl)-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.040 g, 0.097 mmol) was treated under acidic conditions in a similar manner as described in the step (3) of Example 1-1 to give 2-amino-6-(2-

hydroxyphenyl)-4-(3-piperidinyl)nicotinamide hydrochloride as a yellow solid. (0.008 g, yield; 24%)



Molecular weight: 348.84

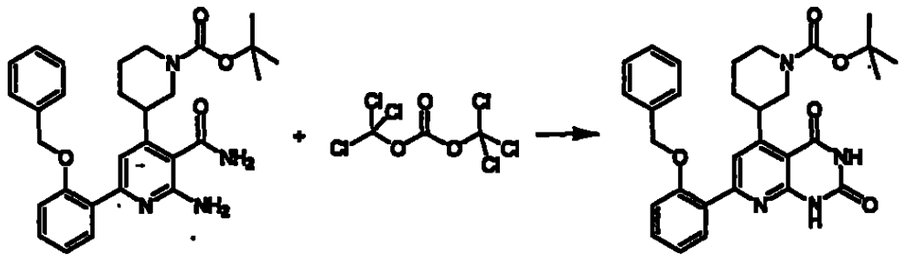
Mass spectrometry: 313 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-B

^{1}H-NMR (300 MHz, DMSO-d6): 1.68 – 1.92 (4H, m), 2.90 – 2.93 (1H, m), 3.17 – 3.34 (4H, m), 6.89 – 6.97 (2H, m), 7.29 – 7.34 (2H, m), 7.80 – 7.86 (2H, m), 8.09 (1H, brs), 8.80 – 8.82 (1H, m), 9.34 – 9.37 (1H, m).

Example 7-2

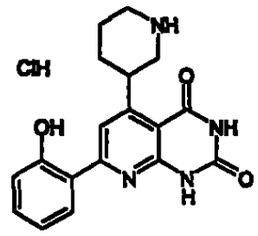


To a cooled (0 °C), stirred solution of tert-butyl 3-{2-amino-6-[2-(benzyl-oxy)phenyl]-3-carbamoyl-4-pyridinyl}-1-piperidinecarboxylate (0.400 g, 0.800 mmol), which was obtained in the step (1) of Example 7-1, in THF (10 mL) were added triethylamine (0.50 mL, 3.58 mmol) followed by triphosgene (0.354 g, 1.19 mmol). The reaction mixture was stirred at room temperature for 12 hrs. The reaction was quenched with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The

residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1-1/1) and recrystallized from ethanol to give tert-butyl 3-{7-[2-(benzyloxy)phenyl]-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-5-yl}-1-piperidinecarboxylate as a white solid. (0.406 g, yield; 97%)

Then the benzyl moiety was removed in a same manner as described in the step (2) of Example 1-1. The residue was washed with ethanol to give tert-butyl 3-[7-(2-hydroxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-5-yl]-1-piperidinecarboxylate as a white solid. (0.036 g, yield; 29%)

tert-butyl 3-[7-(2-hydroxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-5-yl]-1-piperidinecarboxylate (0.036 g, 0.80 mmol) in dioxane (3 mL) was treated under acidic conditions in a similar manner as described in the step (3) of Example 1-1 to give 7-(2-hydroxyphenyl)-5-(3-piperidinyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride as a yellow solid. (0.016 g, yield; 52%)



Molecular weight: 374.83

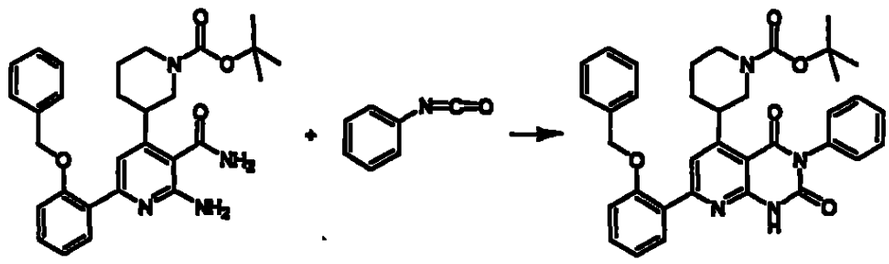
Mass spectrometry: 339 $(M+H)^+$

In activity grade: A

Cellular activity grade: (A549)-C

^{1}H-NMR (500 MHz, DMSO-d6): 1.78 – 1.83 (2H, m), 1.94 – 1.95 (2H, m), 2.90 – 2.92 (1H, m), 4.68 – 4.69 (1H, m), 6.97 – 6.99 (2H, m), 7.39 – 7.42 (1H, m), 7.85 (1H, s), 8.16 (1H, dd, J = 8.4, 1.4 Hz), 8.75 (1H, br s), 9.43 (1H, m), 11.45 (1H, d, J = 1.4 Hz), 12.05 (1H, d, J = 1.4 Hz), 12.44 (1H, br s).

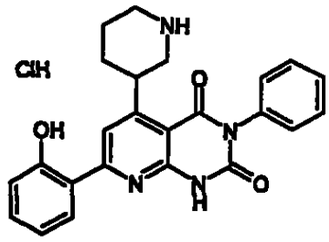
Example 7-3



To a stirred solution of tert-butyl 3-{2-amino-6-[2-(benzyloxy)phenyl]-3-carbamoyl-4-pyridinyl}-1-piperidinecarboxylate (0.100 g, 0.199 mmol), which was obtained in the step (1) of Example 7-1, in phenyl ether (1 mL) was added phenyl isocyanate (0.047 g, 0.398 mmol). The mixture was stirred at 140 °C for 12 hrs. After cooled to room temperature, the resulting solid (urea) was removed by filtration. The filtrate was concentrated under reduced preasure. The residue was purified by silica gel column chromatography to give tert-butyl 3-[7-(2-benzyloxy phenyl) –2,4-dioxo-3-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-5-yl]-1-piperidinecarboxylate as a white amorphous. (0.090 g, yield; 78%)

Then benzyl moiety was removed in a same manner as described in the step (2) of Example 1-1. The residue was washed with ethanol to give the desired product as a white solid. (0.060 g, yield; 83%)

tert-butyl 3-[7-(2-hydroxyphenyl)-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-5-yl]-1-piperidinecarboxylate (0.050 g, 0.100 mmol) was treated under acidic conditions in a similar manner as described in the step (3) of Example 1-1 to give 7-(2-hydroxyphenyl)-3-phenyl-5-(3-piperidinyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride as a yellow solid. (0.016 mg, yield; 37%)



Molecular weight: 450.93

Mass spectrometry: 415 $(M+H)^+$

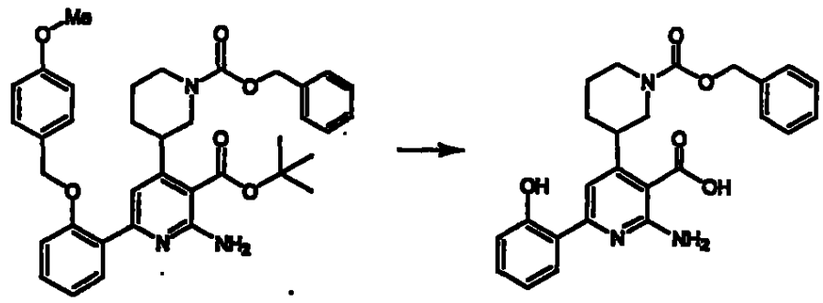
In vitro activity grade: B

Cellular activity grade: (A549)-C

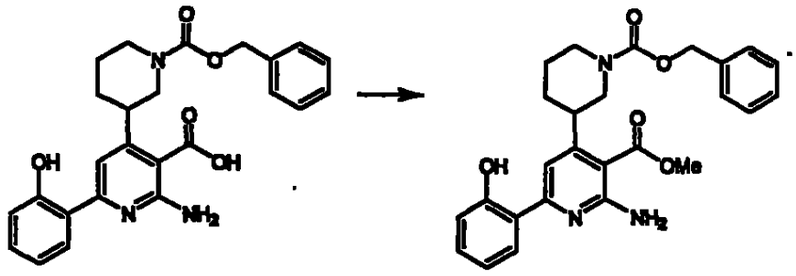
^{1}H-NMR (300 MHz, DMSO-d6): 1.71 – 1.96 (4H, m), 2.71 – 2.91 (1H, m), 3.27 – 3.53 (3H, m), 4.56 (1H, m), 6.98 – 7.03 (2H, m), 7.34 – 7.53 (6H, m), 7.89 (1H, s), 8.18 – 8.21 (1H, m), 8.69 – 8.70 (1H, m), 9.24 – 9.25 (1H, m), 12.47 (1H, s).

Example 8-1

(1) A solution of 1-{2-[(4-methoxybenzyl)oxy]phenyl}ethanone (14.2 g, 55.4 mmol)(starting compound 1D), benzyl 3-formyl-1-piperidinecarboxylate (13.7 g, 55.4 mmol)(starting compound 2C), tert-butyl cyanoacetate (7.8 g, 55.4 mmol), and ammonium acetate (9.8 g, 166.1 mmol) in 1,2-dimethoxyethane (60 mL) was stirred under reflux for 3.5 hrs. After cooled to room temperature, the mixture was partitioned between ethyl acetate and water. The separated organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate:hexane, 1:2) to give tert-butyl 2-amino-4-{1-[(benzyloxy)carbonyl]-3-piperidinyl}-6-{2-[(4-methoxybenzyl)oxy]phenyl}nicotinate as a pale yellow oil (4.89 g, yield; 14%).

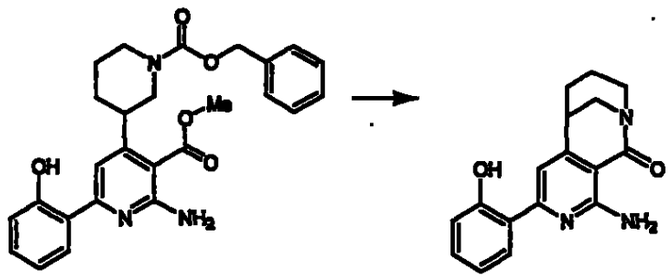


(2) To a solution of tert-butyl 2-amino-4-{1-[(benzyloxy)carbonyl]-3-piperidinyl}-6-{2-[(4-methoxybenzyl)oxy]phenyl}nicotinate (0.95 g, 1.67 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (10 mL), and the stirring was continued at room temperature overnight. The mixture was concentrated under reduced pressure. The residue was diluted with toluene, then concentrated under reduced pressure to remove excess of trifluoroacetic acid by azeotropic distillation to give 2-amino-4-{1-[(benzyloxy)carbonyl]-3-piperidinyl}-6-(2-hydroxyphenyl)nicotinic acid (1.1 g, yield; quant.).



(3) To a solution of 2-amino-4-{1-[(benzyloxy)carbonyl]-3-piperidinyl}-6-(2-hydroxyphenyl)nicotinic acid (1.1 g, 2.5 mmol) in THF (10 mL) and MeOH (5 mL) was added dropwise trimethylsilyldiazomatane (4.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 1.5 hrs, and the reaction was quenched by acetic acid. The mixture was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 3:1) followed by recrystallization from a mixture of CH_2Cl_2 and hexane to give methyl 2-amino-4-{1-

[(benzyloxy)carbonyl]-3-piperidinyl}-6-(2-hydroxyphenyl)nicotinate as a yellow solid (0.39 g, yield; 34%).



(4) To a solution of methyl 2-amino-4-{1-[(benzyloxy)carbonyl]-3-piperidinyl}-6-(2-hydroxyphenyl)nicotinate (60 mg, 0.130 mmol) in methanol (2.0 mL) and THF (1.0 mL) was added 10% Pd-C (200 mg). The mixture was stirred at room temperature under a hydrogen atmosphere (1 atm) for 6.5 hrs. The mixture was filtrated on Celite®, and washed with MeOH and THF successively. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (hexane:ethyl acetate, 2:1) to give 6-amino-4-(2-hydroxy-phenyl)-5,9-diaza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-8-one as a yellow solid (16 mg, yield; 40%).

Molecular weight: 295.34

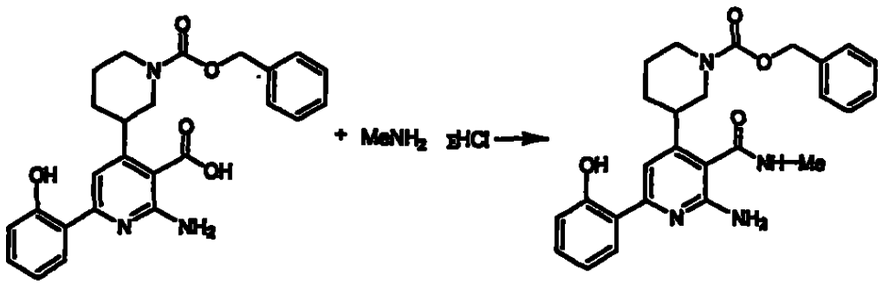
Mass spectrometry: 296 $(M+H)^+$

In vitro activity grade: B

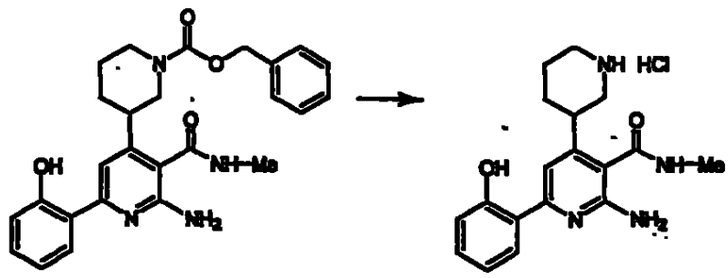
Cellular activity grade: (A549)-B

^{1}H-NMR (300 MHz, CDCl3-d): 1.42 (1H, d, J = 14.3 Hz), 1.84 (1H, m), 1.92 (1H, d, J = 13.6 Hz), 2.17 (1H, m), 2.85 (1H, s), 3.16 (1H, td, J = 3.0, 12.7 Hz), 3.35 (1H, dd, J = 1.9, 12.2 Hz), 3.63 (1H, d, J = 13.2Hz), 3.92 (1H, dd, J = 4.5, 12.8 Hz), 6.88 (1H, td, J = 1.1, 8.3 Hz), 6.99 (1H, dd, J = 1.1, 8.3 Hz), 7.04 (1H, s), 7.32 (1H, td, J = 1.1, 8.3 Hz), 7.75 (1H, dd, J = 1.5, 8.0 Hz).

Example 8-2



To a solution of 2-amino-4-{1-[(benzyloxy)carbonyl]-3-piperidinyl}-6-(2-hydroxyphenyl)nicotinic acid (750 mg, 1.676 mmol),which was obtained in the step (2) of Example 8-1, methylamine hydrochloride (230 mg, 3.352 mmol), triethylamine (340 mg, 3.35 mmol), and 1-hydroxybenzotriazole (360 mg, 2.68 mmol), was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (390 mg, 2.0 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at room temperature overnight. The reaction mixture was extracted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Hexane:ethyl acetate, 2:1) to give benzyl 3-{2-amino-6-(2-hydroxyphenyl)-3-(N-methylcarbamoyl)-4-pyridinyl}-1-piperidinecarboxylate as a pale yellow solid (337 mg, yield; 44%).



To a solution of benzyl 3-{2-amino-6-(2-hydroxyphenyl)-3-(N-methylcarbamoyl)-4-pyridinyl}-1-piperidinecarboxylate (130 mg, 0.274 mmol) in MeOH (2 mL) and THF (2 mL) was added Pd-C (180 mg). The mixture was stirred at room temperature under a hydrogen atmosphere overnight. The reaction mixture was filtered on

Celite®, washed with THF, and then concentrated under reduced pressure. The residue was diluted with ethyl acetate, and added 4N HCl in 1,4-dioxane. The resulting yellow precipitates were washed with acetonitrile. The collected solid was dried under reduced pressure to give 2-amino-6-(2-hydroxyphenyl)-N-methyl-4-(3-piperidinyl)nicotinamide hydrochloride(10 mg, yield; 81%).

Molecular weight: 362.86

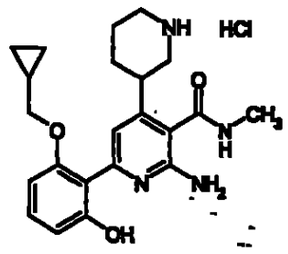
Mass spectrometry: 327 $(M + H)^+$

In vitro activity grade: B

Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 1.69 – 1.77 (2H, m), 1.82 – 1.86 (2H, m), 2.80 (3H, d, J = 4.4 Hz), 2.88 (1H, m), 3.03 (1H, m), 3.19-3.29 (3H, m), 6.89 – 6.93 (3H, m), 7.29-7.32 (2H, m), 7.85 (1H, br), 8.50 (1H, br), 8.85 (1H, br), 9.16 (1H, br).

Example 8-3



With the use of the starting compound 1G (instead of 1D), 2C and other materials, 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-N-methyl-4-(3-piperidinyl)-nicotinamide hydrochloride was prepared in the similar manner as that of Example 8-1 and 8-2.

Molecular weight: 432.95

Mass spectrometry: 397 $(M + H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

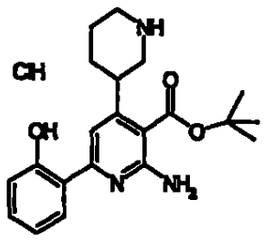
^{1}H-NMR (300 MHz, DMSO-d6): 0.29 – 0.34 (2H, m), 0.49 – 0.55 (2H, m), 1.21 (1H, m), 1.74 – 1.89 (5H, m), 2.84 (3H, d, J = 4.5 Hz), 3.10 – 3.11 (2H, m), 3.25 – 3.28 (2H, m), 3.78 – 3.90 (2H, m), 6.59 (1H, d, J = 8.3 Hz), 6.65 (1H, d, J = 8.3 Hz), 7.20 (1H, s), 7.26 (1H, t, J = 8.3 Hz), 7.56 (1H, br s), 8.76 (1H, br s), 9.08 (1H, br s), 13.8 (1H, br s).

Example 9-1

(1) A mixture of the starting compound 1A (3.500 g, 15.47 mmol), starting compound 2B (3.299 g, 15.47 mmol), tert-butyl cyanoacetate (2.184 g, 15.47 mmol), ammonium acetate (3.577 g, 46.40 mmol) and 1,2-dimethoxyethane (17 mL) was heated at reflux for 3.5 hrs. After cooled to room temperature, the mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane: ethyl acetate, 4:1) to give tert-butyl 2-amino-6-[2-(benzyloxy)phenyl]-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]nicotinate. (1.892 g, yield; 22%)

(2) Then benzyl moiety was removed in a similar manner as described in the step (2) of Example 1-1. The resulting solid was suspended in ethanol, collected by filtration, washed with ethanol, and dried under reduced pressure to give tert-butyl 2-amino-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]-6-(2-hydroxyphenyl)nicotinate (0.322 g, yield; 38%)

(3) tert-Butyl 2-amino-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]-6-(2-hydroxyphenyl)nicotinate (0.050 g, 0.106 mmol)) was treated under acidic conditions in a similar manner as described in the step (3) of Example 1-1. to give tert-butyl 2-amino-6-(2-hydroxyphenyl)-4-(3-piperidinyl)nicotinate hydrochloride (0.034 g, yield; 79%).



Molecular weight: 405.92

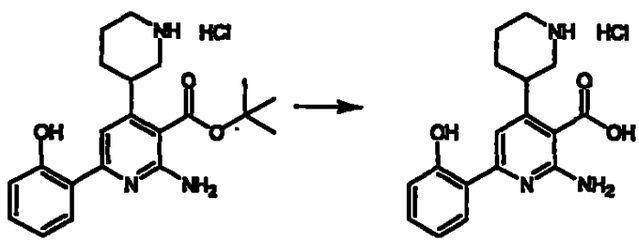
Mass spectrometry: 370 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 1.60 (9H, s), 1.76 – 1.95 (4H, m), 2.90 – 2.97 (1H, m), 3.20 – 3.46 (4H, m), 6.89 – 6.94 (2H, m), 7.31 – 7.36 (1H, m), 7.38 (1H, s), 8.02 (1H, dd, J = 1.3, 8.2 Hz), 9.09 (1H, br), 9.29 (1H, br), 13.78 (1H, br).

Example 9-2



To a solution of tert-butyl 2-amino-6-(2-hydroxyphenyl)-4-(3-piperidinyl)nicotinate hydrochloride (0.023 g, 0.057 mmol), which was obtained in Example 9-1, in methylene chloride (1.0 mL) was added trifluoroacetic acid (TFA) (1.0 mL). After being stirred for 6 hrs, the mixture was concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane (3.0 mL), and then treated with a HCl solution of 1,4-dioxane (4N, 0.2 mL). The resulting precipitates were collected by filtration under an argon atmosphere, washed with 1,4-dioxane and acetonitrile, and dried under reduced pressure to give 2-amino-6-(2-hydroxyphenyl)-4-(3-piperidinyl)-nicotinic acid hydrochloride (0.020 g, yield; quant.).

Molecular weight: 349.82

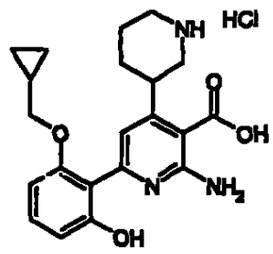
Mass spectrometry: 314 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 1.75 – 1.93 (4H, m), 2.92 (1H, br m), 2.92 – 3.39 (3H, m), 3.63 – 3.67 (1H, br m), 6.91 – 6.96 (2H, m), 7.32 – 7.36 (1H, m), 7.37 (1H, s), 7.95 (1H, d, J = 7.9 Hz), 8.84 (1H, br), 9.41 (1H, br), 13.80 (1H, br).

Example 9-3



With the use of 1-(2-benzyloxy-6-cyclopropylmethoxy-phenyl)-ethanone prepared in the similar manner as that of the starting compound 1G, the starting compound 2B and other materials, 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinic acid hydrochloride was prepared in a similar manner as described in Example 9-2.

Molecular weight: 419.91

Mass spectrometry: 384 $(M+H)^+$

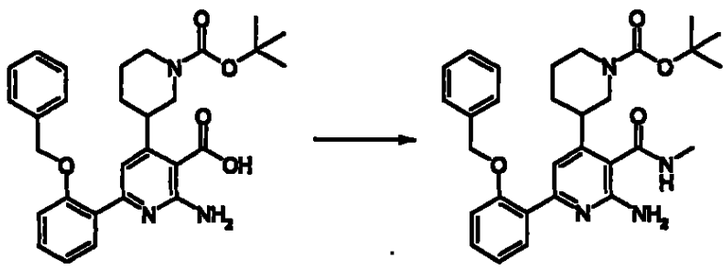
In vitro activity grade: A

Cellular activity grade: (A549)-C

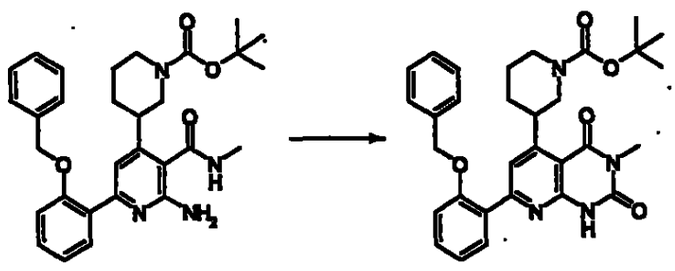
^{1}H-NMR (500 MHz, DMSO-d6): 0.31 – 0.32 (2H, m), 0.51 – 0.53 (2H, m), 1.20 (1H, m), 1.70 – 1.74 (2H, m), 1.89 – 1.91 (2H, m), 2.89 (1H, m), 3.18 (1H, m), 3.26 – 3.28 (3H, m), 3.83 (2H, dd, J = 6.9, 7.3 Hz), 6.58 (1H, d, J = 8.2 Hz), 6.65 (1H, d, J = 8.5

Hz), 7.28 (1H, dd, J = 8.2, 8.5 Hz), 7.30 (1H, s), 7.81 (1H, br s), 8.92 (1H, br s), 9.37 (1H, br s).

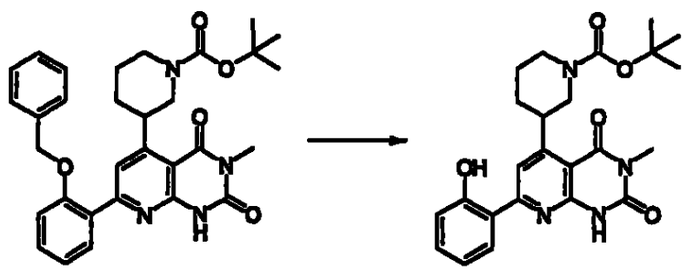
Example 10-1



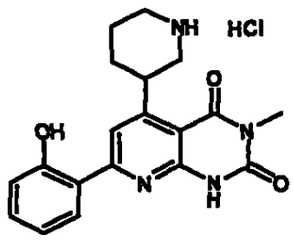
(1) To a solution of 2-amino-6-[2-(benzyloxy)phenyl]-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]nicotinic acid (0.500 g, 0.993 mmol) which was derived from the product in the step (1) of Example 9-1, methylamine hydrochloride (0.134 g, 1.896 mmol), triethylamine (0.277 mL, 1.986 mmol), and 1-hydroxybenzotriazole (0.215 g, 1.589 mmol) in dichloromathane (10.0 mL), at 0 °C under an argon atmosphere was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.228 g, 1.191 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, then extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered, then concentrated under reduced pressure. The resulting residue was purified by column chromatography on Silica-gel (dichloromathane / methanol = 19/1) to give tert-butyl 3-{2-amino-6-[2-(benzyloxy)phenyl]-3-[(methylamino)carbonyl]-4-pyridinyl}-1-piperidinecarboxylate as a yellow oil (0.11 g, 21%).



(2) To a cooled (-20 °C) solution of tert-butyl 3-{2-amino-6-[2-(benzyloxy)phenyl]-3-[(methylamino)carbonyl]-4-pyridinyl}-1-piperidinecarboxylate (0.120 g, 0.232 mmol) and triethylamine (0.213 g, 2.090 mmol) in tetrahydrofuran (10 mL) was added triphosgene (0.069 g, 0.232 mmol) under an argon atmosphere. The stirring was continued at 0 °C to room temperature overnight. The reaction mixture was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (hexane / ethyl acetate = 2/1) to give tert-butyl 3-{7-[2-(benzyloxy)phenyl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidin-5-yl}-1-piperidinecarboxylate as a pale yellow solid (0.0655 g, 52%).



(3) tert-butyl 3-{7-[2-(benzyloxy)phenyl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidin-5-yl}-1-piperidinecarboxylate (0.065 g, 0.120 mmol) was treated in a similar manner as that of the step (2) of Example 1-1. The residue was purified by preparative TLC (hexane / ethyl acetate = 1/1) to give tert-butyl 3-[7-(2-hydroxyphenyl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-5-yl]-1-piperidinecarboxylate (0.010 g, 18%), which is then treated as described in the step (3) of Example 1-1 to obtain 7-(2-hydroxy-phenyl)-3-methyl-5-piperidin-3-yl-1H-pyrido[2,3-d]pyrimidine-2,4-dione hydrochloride.



Molecular weight: 388.86

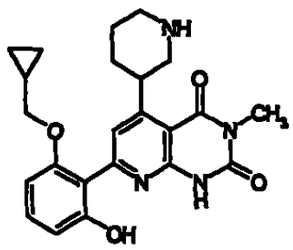
Mass spectrometry: 353 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: A549-B

^{1}H-NMR (500 MHz, DMSO-d6): 1.81 – 1.85 (2H, m), 1.96 – 1.98 (2H, m), 2.91 (1H, m), 3.26 (3H, s), 3.31 – 3.40 (3H, m), 4.70 (1H, m), 6.97 – 7.00 (2H, m), 7.39 (1H, m), 7.86 (1H, s), 8.16 (1H, m), 8.73 (1H, br), 9.17 (1H, br), 12.37 (1H, s).

Example 10-2



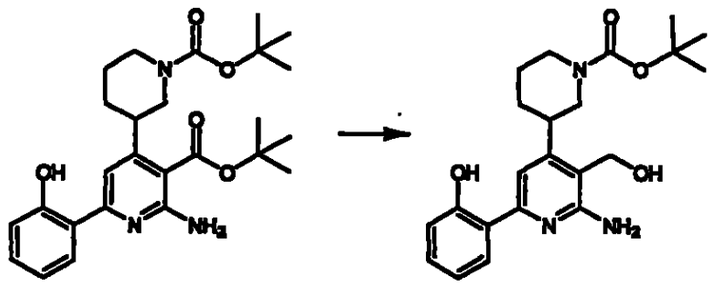
With the use of 1-(2-benzyloxy-6-cyclopropylmethoxy-phenyl)-ethanone prepared in the similar manner as that of the starting compound 1G, the starting compound 2B and other materials, 7-(2-Cyclopropylmethoxy-6-hydroxy-phenyl)-3-methyl-5-piperidin-3-yl-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione was prepared in a similar manner as that of Example 10-1.

Molecular weight: 458.95

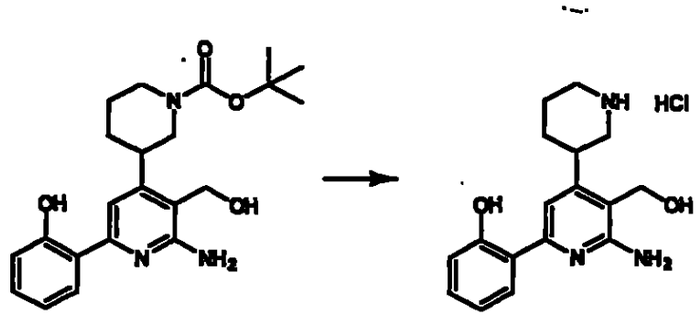
In vitro activity grade: A

^{1}H-NMR (500 MHz, DMSO-d6): 0.31 – 0.34 (2H, m), 0.56 – 0.60 (2H, m), 1.27 (1H, m), 1.67 (1H, m), 1.79 (1H, m), 1.91 – 2.01 (2H, m), 2.87 (1H, m), 3.06 (1H, m), 3.27 (3H, s), 3.30 (1H, m), 3.39 (1H, m), 3.83 (1H, dd, J = 7.3, 9.8 Hz), 3.91 (2H, dd, J = 6.9, 9.8 Hz), 4.65 (1H, m), 6.58 (2H, d, J = 8.5 Hz), 7.25 (1H, dd, J = 8.2, 8.5 Hz), 7.91 (1H, s), 8.83 (1H, br s), 9.32 (1H, br s), 12.2 (1H, br s).

Example 11-1



(1) To a cold (0 °C) solution of tert-butyl 2-amino-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]-6-(2-hydroxyphenyl)nicotinate, obtained in the step (2) of Example 9-1, (0.200 g, 0.426 mmol) in THF (3.0 mL) under an argon atmosphere was added $LiBH_4$ (0.019 g, 0.85 mmol). After stirred at room temperature overnight, the mixture was quenched with water, and then extracted with ethyl acetate and 0.5N HCl. The separated organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 1:1) to give tert-butyl 3-[2-amino-3-(hydroxymethyl)-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidine-carboxylate. (0.161 g, yield; 95%)



tert-Butyl 3-[2-amino-3-(hydroxymethyl)-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.160 g, 0.401 mmol) in 1,4-dioxane (3.0 mL) was treated under acidic conditions in a similar manner as described in the step (3) of Example 1-1 to give 2-[6-amino-5-(hydroxymethyl)-4-(3-piperidinyl)-2-pyridinyl]phenol hydrochloride. (0.132 g, yield; 98%)

Molecular weight: 335.84

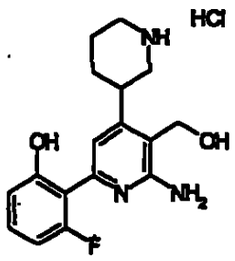
Mass spectrometry: 300 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 1.75 – 1.98 (4H, m), 2.90 (1H, br), 3.14 – 3.33 (3H, m), 3.56 – 3.60 (1H, br), 4.58 (2H, dd, J = 13.0, 20.2 Hz), 6.96 (1H, t, J = 7.6 Hz), 7.06 (1H, d, J = 7.9 Hz), 7.19 (1H, s), 7.37 (1H, br t, J = 7.3 Hz), 7.65 (1H, br d, J = 7.6 Hz), 9.03 (1H, br), 9.32 (1H, br), 13.59 (1H, br).

Example 11-2



With the use of starting compound 1I and 2B, and other materials, 2-[6-amino-5-(hydroxymethyl)-4-(3-piperidinyl)-2-pyridinyl]-3-fluorophenol hydrochloridewas prepared in a similar manner as that of Example 11-1.

Molecular weight: 353.83

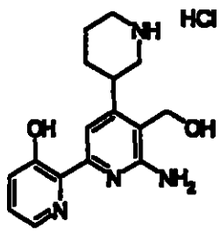
Mass spectrometry: 318 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 1.03 (3H, t, J = 7.6 Hz), 1.83 (4H, m), 3.00 (2H, m), 3.31 (2H, m), 3.71 (1H, m), 4.56 (2H, dd, J = 13.1, 19.4), 5.16 (1H, br), 6.79 (2H, m), 7.12 (1H, s), 7.32 (1H, m), 8.52 (1H, d, J = 9.8 Hz), 8.86 (1H, d, J = 9.8 Hz), 14.0 (1H, br).

Example 11-3



With the use of the starting compound 1F, the starting compound 2B, and other materials, 6'-amino-5'-(hydroxymethyl)-4'-(3-piperidinyl)-2,2'-bipyridin-3-ol hydrochloride was prepared in a similar manner as that of Example 11-1.

Molecular weight: 336.82

Mass spectrometry: 301 $(M+H)^+$

In vitro activity grade: A

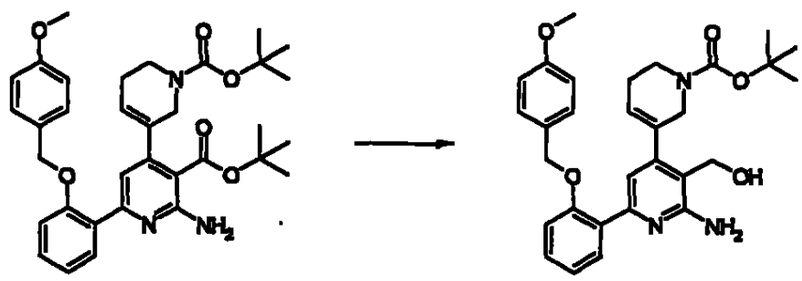
Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 1.81 – 1.95 (3H, m), 2.46 – 2.64 (1H, m), 3.00 – 3.06 (2H, m), 3.28 – 3.39 (2H, m), 3.54 – 3.60 (1H, m), 4.56 (1H, d, J = 13.0 Hz), 4.59 (1H, d, J = 13.0 Hz), 7.41 – 7.50 (2H, m), 7.81 (1H, s), 8.24 (1H, d, J = 3.8 Hz), 8.92 (1H, br), 9.07 (1H, br).

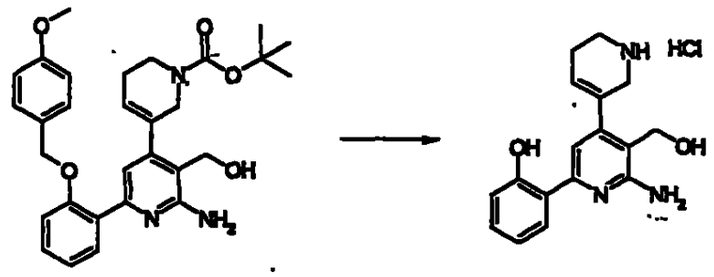
Example 11-4

(1) With the use of the starting compound 1D instead of 1A and 2H instead of 2B, di(tert-butyl) 2'-amino-6'-{2-[(4-methoxybenzyl)oxy]phenyl}-5,6-dihydro-3,4'-

bipyridine-1,3'(2H)-dicarboxylate was prepared in a similar method as that of step (1) of Example 9-1.



(2) To a cooled (0 °C) solution of di(tert-butyl) 2'-amino-6'-{2-[(4-methoxybenzyl)oxy]phenyl}-5,6-dihydro-3,4'-bipyridine-1,3'(2H)-dicarboxylate (50.0 mg, 0.09 mmol) in THF (4.5 mL) was added sodium bis(2-methoxyethoxy)aluminum hydride (0.10 mL) dropwise, then stirred for 1 hr at 0 °C. The reaction was quenched by an addition of saturated NH_4Cl solution, filtered, and washed with ethyl acetate. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by preparative silica gel TLC (15% acetone in chloroform) to give tert-butyl 2'-amino-3'-(hydroxymethyl)-6'-{2-[(4-methoxybenzyl)oxy]phenyl}-5,6-dihydro-3,4'-bipyridine-1(2H)-carboxylate as a white foam (25 mg, yield 57%).



(3) tert-butyl 2'-amino-3'-(hydroxymethyl)-6'-{2-[(4-methoxybenzyl)oxy]phenyl}-5,6-dihydro-3,4'-bipyridine-1(2H)-carboxylate (25.0 mg, 0.05 mmol) was treated with 2N HCl in dioxane (4.0 mL) overnight at room temperature. The resulting solid was collected by filtration, washed with ether and dried under reduced pressure to

give 2-[6'-amino-5'-(hydroxymethyl)-1,2,5,6-tetrahydro-3,4'-bipyridin-2'-yl]phenol hydrochloride. (14 mg, yield 87%)

Molecular weight: 333.82

Mass spectrometry: 298 $(M+H)^+$

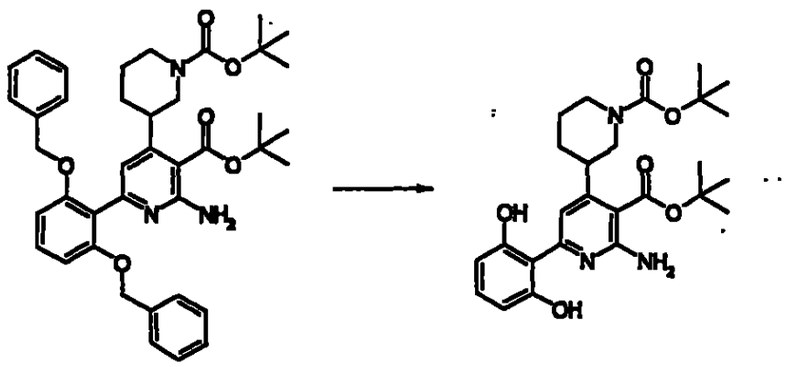
In vitro activity grade: A

Cellular activity grade: (A549)-A

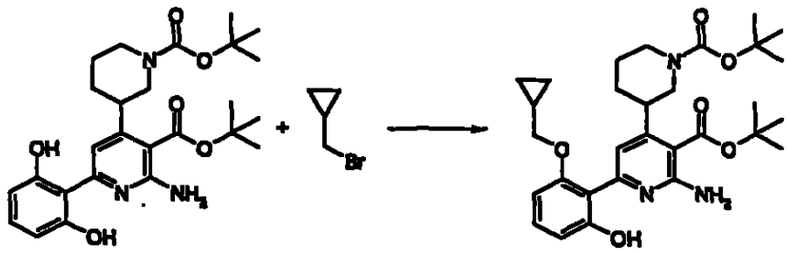
^{1}H-NMR (300 MHz, D2O): 2.51 (2H, br s), 3.35 (2H, br s), 3.83 (2H, s), 4.58 (2H, s), 6.04 (1H, br s), 6.93 – 7.01 (3H, m), 7.34 – 7.47 (2H, m).

Example 12-1

(1) A mixture of 1-[2,6-bis(benzyloxy)phenyl]ethanone (8.00 g, 24.067 mmol) (starting compound 1E), tert-butyl 3-formyl-1-piperidinecarboxylate (5.133 g, 24.067 mmol) (starting compound 2B), tert-butylcyanoacetate (3.398 g, 24.067 mmol), and ammonium acetate (5.432 g, 72.202 mmol) in 1,2-dimethoxyethane (24 mL) was stirred at 100 °C in a sealed tube overnight. After cooled to room temperature, the reaction mixture was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was diluted with 30 mL of dichloromethane, and MnO_2 was added to the mixture, and then the mixture was stirred at room temperature for 5 hrs. The mixture was filtered on Celite®, and concentrated under reduced pressure. The resulting residue (liquid) was purified by column chromatography on silica gel (hexane / ethyl acetate =2/1) to give tert-butyl 2-amino-6-[2,6-bis(benzyloxy)phenyl]-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]nicotinate as a pale yellow oil. (2.5 g, yield; 16 %)

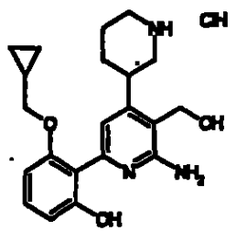


(2) A suspension of tert-butyl 2-amino-6-[2,6-bis(benzyloxy)phenyl]-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]nicotinate (1.00 g, 1.052 mmol) and 10% Paradium-carbon (0.500 g) in 20 mL of ethyl acetate was stirred at room temperature under a hydrogen atmosphere (1 atm) overnight. After paradium carbon was removed by filtration on Celite®, the filtrate was concentrated under reduced pressure to give tert-butyl 2-amino-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]-6-(2,6-dihydroxyphenyl)-nicotinate as a brown oil. (0.710 g, yield; 97%)



(3) To a solution of tert-butyl 2-amino-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]-6-(2,6-dihydroxyphenyl)nicotinate (1.280 g, 2.636 mmol) and K_2CO_3 (3.643 g, 26.36 mmol) in DMF (100 mL) was added (bromomethyl)cycropropane (0.268 mL, 2.768 mmol). The stirring was continued at 50 °C for 20 hrs. After the solvent was removed by evaporation, the residue was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered, then concentrated under reduced pressure. The resulting residue was purified by column chromatography on Silica-gel(hexane / ethyl acetate = 3/1) to give tert-butyl 2-amino-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]nicotinate as a brown solid (0.820 g, yield; 58%).

tert-butyl 2-amino-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]-6-[2-(cyclopropyl-methoxy)-6-hydroxyphenyl]nicotinate was treated in a similar manner as that of the step (1) of Example 11-1 and then in a similar manner as that of the step (3) of Example 1-1 to obtain 2-[6-amino-5-(hydroxymethyl)-4-(3-piperidinyl)-2-pyridinyl]-3-(cyclopropylmethoxy)phenol hydrochloride.



Molecular weight: 405.93

Mass spectrometry: 370 $(M + H)^+$

In vitro activity grade: A

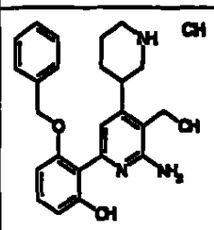
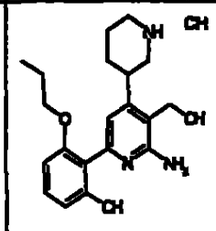
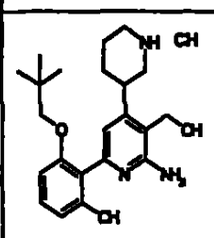
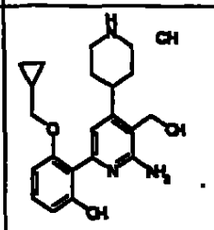
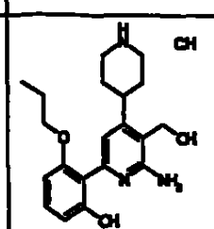
Cellular activity grade: (A549)-A

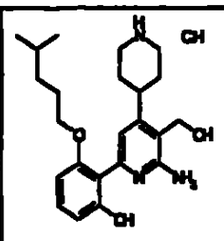
^{1}H-NMR (300 MHz, DMSO-d6): 0.26 – 0.29 (2H, m), 0.47 – 0.52 (2H, m), 1.13 (1H, m), 1.75 – 1.83 (5H, m), 2.90 – 2.93 (2H, m), 3.04 – 3.17 (2H, m), 3.81 – 3.86 (2H, m), 4.60 (2H, s), 6.55 (1H, d, J = 8.3 Hz), 6.60 (1H, d, J = 8.3 Hz), 7.06 (1H, s), 7.27 (1H, t, J = 8.3 Hz), 7.59 (1H, br), 8.96 (1H, br), 9.25 (1H, br), 13.58 (1H, br).

Examples 12-2 to 12-7

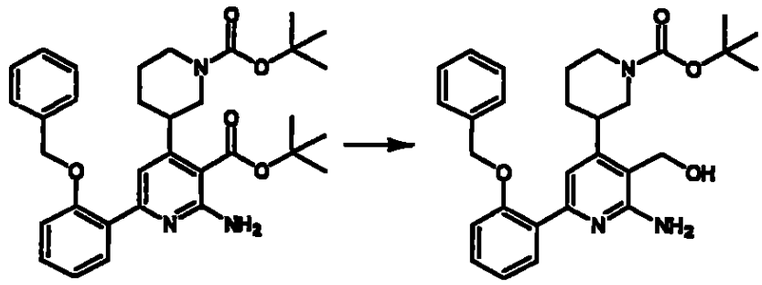
According to the similar synthetic procedure of Example 12-1, compounds shown in Table 4 were prepared.

Table 4

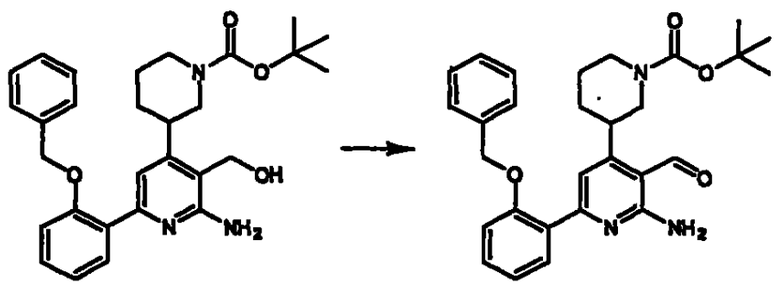
Ex. No	Structure	Mol weight	Mass	In vitro	A549	NMR
12-02		441.96	406	A	B	(500 MHz, DMSO-d6): 1.53 - 1.88 (4H, m), 2.84 - 3.20 (3H, m), 4.54 (1H, d, J = 13.2 Hz), 4.57 (1H, d, J = 13.2 Hz), 5.08 (2H, s), 6.70 (1H, d, J = 8.2 Hz), 6.76 (1H, d, J = 8.5 Hz), 7.05 (1H, s), 7.29 - 7.41 (6H, m), 7.80 (1H, br), 8.95 (1H, br), 9.25 (1H, br), 10.42 (1H, br), 13.57 (1H, br).
12-03		393.92	358	A	A	(500 MHz, DMSO-d6): 0.87 (3H, t, J = 7.2 Hz), 1.84 (2H, q, J = 6.9 Hz), 1.88 - 1.90 (3H, m), 2.07 (1H, m), 2.88 (1H, m), 3.05 (1H, m), 3.22 - 3.24 (2H, m), 3.58 (1H, m), 3.92 (2H, t, J = 6.6 Hz), 4.59 (2H, d, J = 3.1 Hz), 4.96 (1H, br), 6.62 (1H, d, J = 8.2 Hz), 6.88 (1H, d, J = 8.2 Hz), 7.00 (1H, s), 7.29 (1H, t, J = 8.2 Hz), 7.58 (1H, br), 8.92 (1H, br), 9.21 (1H, br), 13.57 (1H, br).
12-04		421.97	386	A	A	(500 MHz, DMSO-d6): 0.83 (9H, s), 0.82 - 1.05 (4H, m), 1.75 - 1.93 (4H, m), 2.87 (1H, br), 3.02 - 3.07 (4H, m), 4.61 (2H, dd, J = 13.2, 18.6 Hz), 4.99 (1H, br), 6.60 (1H, d, J = 8.5 Hz), 6.67 (1H, d, J = 8.2 Hz), 6.79 - 6.89 (1H, m), 6.98 (1H, s), 7.07 (1H, br), 7.27 - 7.29 (1H, br), 7.62 (1H, br), 13.72 (1H, br).
12-05		405.93	370	A	A	(500 MHz, DMSO-d6): 0.29 - 0.32 (2H, m), 0.46 - 0.50 (2H, m), 1.19 (1H, m), 1.89 - 2.05 (2H, m), 3.01 - 3.07 (2H, m), 3.34 - 3.48 (3H, m), 3.84 (2H, d, J = 6.9 Hz), 4.61 (2H, s), 6.59 (1H, d, J = 8.5 Hz), 6.89 (1H, d, J = 8.2 Hz), 6.80 (1H, s), 7.27 (1H, dd, J = 8.2, 8.5 Hz), 7.75 (1H, br s), 9.14 - 9.25 (2H, m), 13.6 (1H, br).
12-06		393.92	358	A	A	(500 MHz, DMSO-d6): 0.85 (3H, t, J = 7.3 Hz), 1.63 - 1.67 (2H, m), 1.82 - 1.85 (2H, m), 1.90 - 1.95 (2H, m), 3.03 - 3.08 (2H, m), 3.34 - 3.45 (4H, m), 3.92 (2H, t, J = 6.6 Hz), 4.60 (2H, s), 6.62 (1H, d, J = 8.2 Hz), 6.68 (1H, d, J = 8.2 Hz), 6.75 (1H, s), 7.28 (1H, t, J = 8.2 Hz), 7.63 (1H, br), 8.98 (2H, br).

12-07		436.00	400	A	A	(500 MHz, DMSO-d6): 0.79 - 0.82 (7H, m), 1.12 - 1.16 (2H, m), 1.42 - 1.49 (1H, m), 1.60 - 1.68 (2H, m), 1.82 - 1.84 (2H, m), 1.93 - 1.96 (2H, m), 3.93 - 3.95 (2H, m), 4.60 (2H, s), 6.61 (1H, d, J = 8.2 Hz), 6.68 (1H, d, J = 8.2 Hz), 6.74 (1H, s), 7.28 (1H, t, J = 8.2 Hz), 7.68 (2H, s), 9.07 (2H, s), 10.38 (1H, bra).

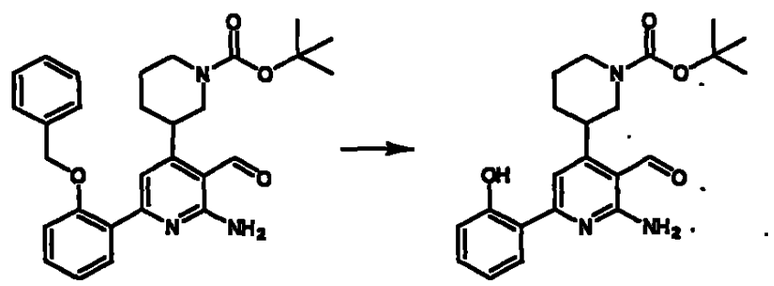
Example 13-1



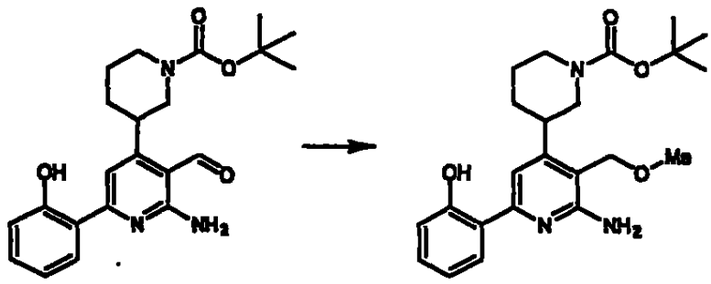
(1) To a cold (0 °C) solution of tert-butyl 2-amino-6-[2-(benzyloxy)phenyl]-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]nicotinate, which was obtained in the step (1) of Example 9-1, (2.590 g, 4.627 mmol) in THF (25 mL) was added $LiBH_4$ (0.202 g, 9.255 mmol). The mixture was stirred at room temperature for 5 hrs, and then quenched with water. The mixture was extracted with ethyl acetate and water. The separated organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 2:3) to give tert-butyl 3-[2-amino-6-[2-(benzyloxy)phenyl]-3-(hydroxymethyl)-4-pyridinyl]-1-piperidine-carboxylate. (0.904 g, yield; 40%)



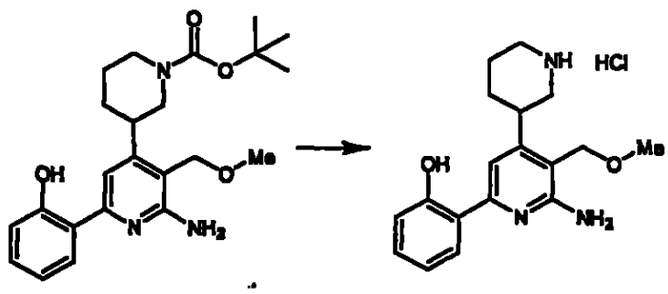
(2) To a solution of tert-butyl 3-[2-amino-6-[2-(benzyloxy)phenyl]-3-(hydroxymethyl)-4-pyridinyl]-1-piperidinecarboxylate (0.900 g, 1.838 mmol) in methylene chloride (20 mL) was added manganese (IV) oxide (3.20 g, 36.8 mmol). After stirred at room temperature for 40 min, the mixture was filtered to remove the manganese salt. The filtrate was concentrated under reduced pressure. The resulting solid was purified by recrystallization from a mixture of ethyl acetate and hexane to give tert-butyl 3-[2-amino-6-[2-(benzyloxy)phenyl]-3-formyl-4-pyridinyl]-1-piperidinecarboxylate. (0.651 g, yield; 73%)



(3) Then the benzyl moiety was removed in a similar manner as described in the step (2) of Example 1-1. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 2:1) to give tert-butyl 3-[2-amino-3-formyl-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate. (0.536 g, yield; quant.)



(4) To a solution of tert-butyl 3-[2-amino-3-formyl-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.100 g, 0.252 mmol) in 1,4-dioxane (2.0 mL) under an argon atmosphere was added a HCl solution of 1,4-dioxane (4N, 2.0 mL), and the stirring was continued at room temperature for 1 hr. The mixture was diluted with Et_2O, and the supernatant was decanted. The precipitates were washed twice with Et_2O, and dried under reduced pressure to give a pale yellow solid, which was then dissolved in methanol (2.0 mL). The mixture was allowed to cool with ice-water bath. Then sodium cyanoborohydride (0.047 g, 0.76 mmol) was added to the mixture under an argon atmosphere. The mixture was allowed to warm to room temperature, and the stirring was continued overnight. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of methylene chloride (2.0 mL) and THF (2.0 mL). To the mixture was added triethylamine (0.140 mL, 1.006 mmol) followed by di-tert-butyl dicarbonate (0.110 g, 0.503 mmol), and the stirring was continued for 2 hrs. The resulting mixture was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 2:1) to give tert-Butyl 3-[2-amino-6-(2-hydroxyphenyl)-3-(methoxymethyl)-4-pyridinyl]-1-piperidinecarboxylate. (0.033 g, yield; 47%)



(4) tert-Butyl 3-[2-amino-6-(2-hydroxyphenyl)-3-(methoxymethyl)-4-pyridinyl]-1-piperidinecarboxylate (0.025 g, 0.060 mmol) was treated under acidic conditions in a similar manner as described in the step (3) of Example 1-1 to give 2-[6-amino-5-(methoxymethyl)-4-(3-piperidinyl)-2-pyridinyl]phenol hydrochloride.

Molecular weight: 349.86

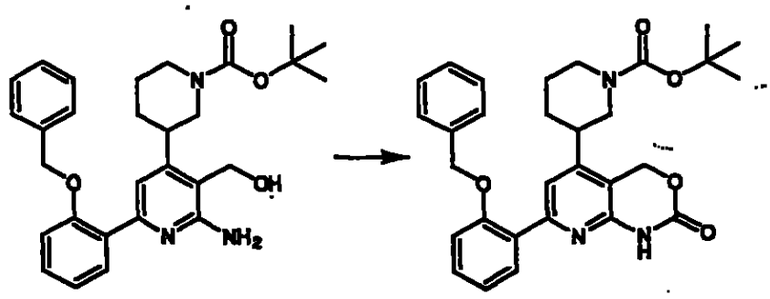
Mass spectrometry: 314 $(M + H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

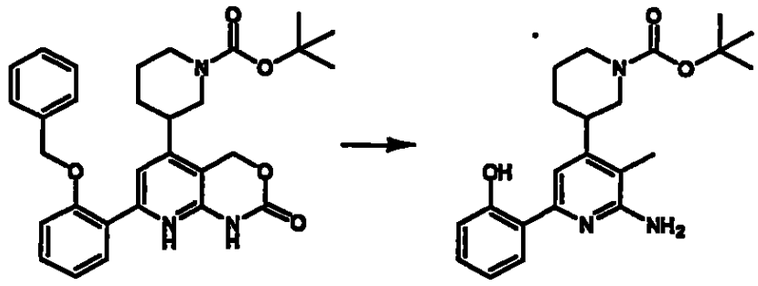
^{1}H-NMR (500 MHz, DMSO-d6): 1.40 – 1.74 (4H, m), 2.80 – 2.92 (2H, m), 4.03 – 4.13 (2H, m), 4.42 (1H, d, J = 11.5 Hz), 4.50 (1H, d, J = 11.5 Hz), 6.22 – 6.32 (2H, m), 6.81 – 6.85 (2H, m), 7.17 (1H, s), 7.21 (1H, br t, J = 7.3 Hz), 7.93 (1H, br d, J = 7.6 Hz), 14.30 (1H, br).

Example 14-1

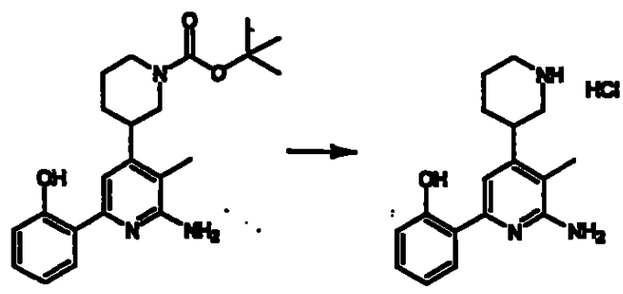


To a cold (0 °C) solution of tert-butyl 3-[2-amino-6-[2-(benzyloxy)phenyl]-3-(hydroxymethyl)-4-pyridinyl]-1-piperidinecarboxylate (0.104 g, 0.212 mmol)

obtained in the step (1) of Example 13-1 in THF (2.0 mL) including triethylamine (0.089 mL, 0.64 mmol) was added triphosgene (0.044 g, 0.15 mmol). After stirred for 30 min, the mixture was allowed to warm to room temperature, and the stirring was continued for further 1 hr. The resulting mixture was quenched with water and extracted with ethyl acetate. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 5:3) to give tert-butyl 3-{7-[2-benzyloxy]phenyl]-2-oxo-1,4-dihydro-2H-pyrido[2,3-d][1,3]-oxazin-5-yl}-1-piperazinecarboxylate. (0.058 g, yield; 53%)



A solution of tert-butyl 3-{7-[2-benzyloxy]phenyl]-2-oxo-1,4-dihydro-2H-pyrido-[2,3-d][1,3]oxazin-5-yl}-1-piperazinecarboxylate (0.050 g, 0.097 mmol) in ethyl acetate (3.0 mL) was hydrogenated at 1 atm in the presence of palladium on charcoal (10%, 0.10 g) overnight. The resulting mixture was filtered on Celite® and washed with ethyl acetate and THF. The combined filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 2:1) to give tert-Butyl 3-[2-amino-6-(2-hydroxyphenyl)-3-methyl-4-pyridinyl]-1-piperidinecarboxylate. (0.027 g, yield; 73%)



tert-Butyl 3-[2-amino-6-(2-hydroxyphenyl)-3-methyl-4-pyridinyl]-1-piperidinecarboxylate (0.025 g, 0.065 mmol) was treated under acidic conditions in a similar manner as described in the step (3) of Example 1-1 to give 2-[6-amino-5-methyl-4-(3-piperidinyl)-2-pyridinyl]phenol hydrochloride. (0.017 g, yield; 82%)

Molecular weight: 319.84

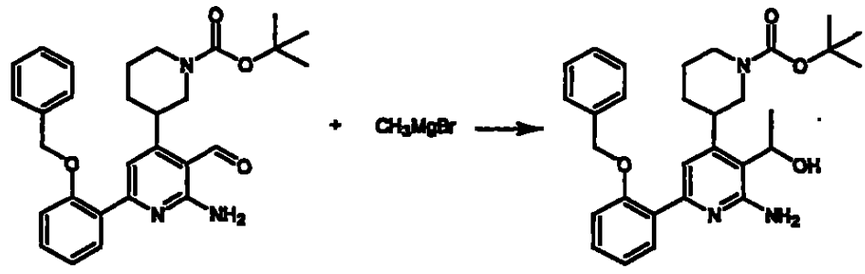
Mass spectrometry: 284 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A/Jurkat-B

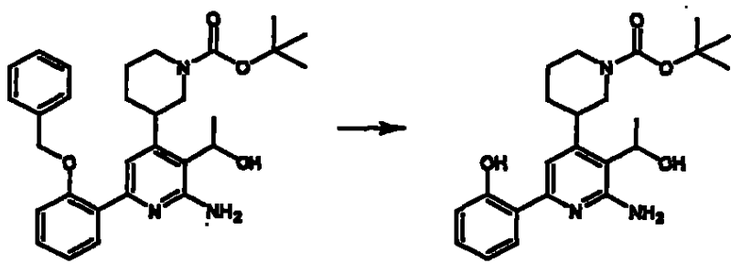
^{1}H-NMR '(500 MHz, DMSO-d6): 1.08 – 1.75 (4H, m), 2.10 (3H, s), 2.55 – 2.98 (3H, m), 4.12 (1H, br), 6.19 (2H, br d, J = 15.1 Hz), 6.79 – 6.83 (2H, m), 7.12 (1H, s), 7.18 (1H, br t, J = 7.9 Hz), 7.88 (1H, br).

Example 15-1

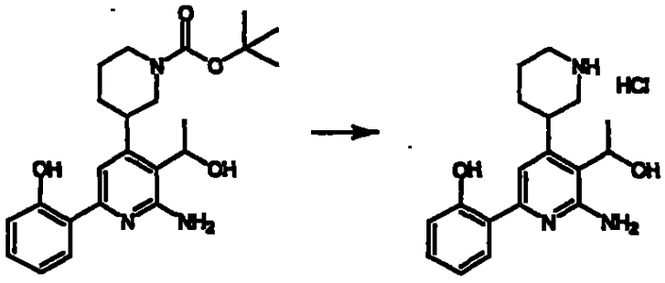


(1) To a cold (-20 °C) solution of tert-butyl 3-{2-amino-6-[2-(benzyloxy)phenyl]-3-formyl-4-pyridinyl}-1-piperidinecarboxylate (400 mg, 0.82 mmol), which was obtained in the step (2) of Example 13-1, in THF (2.0 mL) was added dropwise a solution methyl magnesium bromide in THF (7.38 mL, 7.38 mol). The mixture was stirred at –20 °C for 2 hrs , quenched with saturated aqueous NH_4Cl solution, and extracted with ethyl acetate. The separated organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 3:2)

to give tert-butyl 3-[2-amino-6-[2-(benzyloxy)phenyl]-3-(1-hydroxyethyl)-4-pyridinyl]-1-piperidinecarboxylate as a yellow oil. (356 mg, yield; 86%)



(2) Then benzyl moiety was removed in a similar manner as described in the step (2) of Example 1-1 to give tert-Butyl 3-[2-amino-3-(1-hydroxyethyl)-6-(2-hydroxy-phenyl)-4-pyridinyl]-1-piperidinecarboxylate as a pale yellow oil. (147 mg, yield; 96%)



(3) tert-Butyl 3-[2-amino-3-(1-hydroxyethyl)-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (30 mg, 0.07 mmol) was treated under acidic conditions in a similar manner as described in the step (3) of Example 1-1 to give 2-[6-amino-5-(1-hydroxyethyl)-4-(3-piperidinyl)-2-pyridinyl]phenol hydrochloride as a yellow solid. (20 mg, yield; 78%)

Molecular weight: 349.86

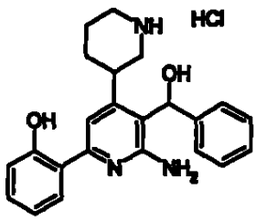
Mass spectrometry: 296 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 1.83 – 1.92 (7H, m), 2.90 – 2.91 (1H, m), 3.13 – 3.15 (1H, m), 3.57 (3H, s), 5.29 – 5.39 (1H, m), 6.89 – 6.99 (1H, m), 7.05 – 7.10 (1H, m), 7.17 (1H, d, J = 3.16 Hz), 7.27 – 7.40 (2H, m), 7.62 (1H, d, J = 5.0 Hz), 7.68 – 7.87 (2H, m), 13.50 (1H, br s).

Example 15-2



In a similar manner as that of Example 15-1, 2-[6-amino-5-[hydroxy(phenyl)methyl]-4-(3-piperidinyl)-2-pyridinyl]phenol hydrochloride was prepared.

Molecular weight: 411.94

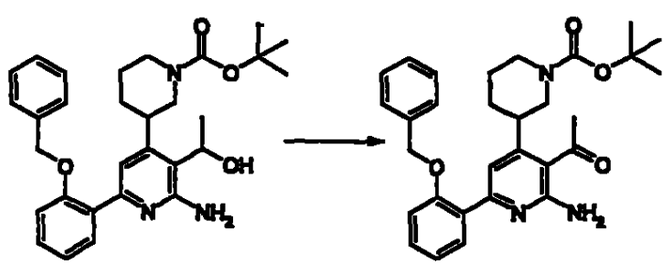
Mass spectrometry: 376 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-B

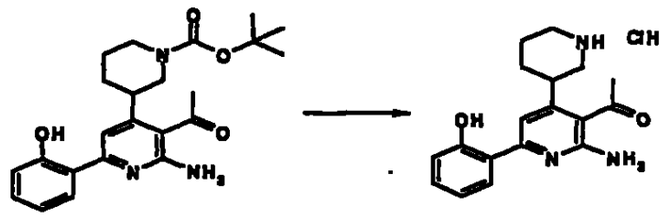
^{1}H-NMR (500 MHz, DMSO-d6): 1.67 – 1.74 (2H, m), 1.89 – 1.99 (2H, m), 2.88 – 2.93 (1H, m), 3.14 – 3.24 (4H, m), 6.32 (1H, s), 6.91 (1H, d, J = 2.2 Hz), 6.92 – 7.01 (2H, m), 7.24 – 7.32 (3H, m), 7.34 – 7.40 (6H, m), 7.42 – 7.44 (1H, m), 7.75 (1H, d, J = 7.9 Hz).

Example 15-3



To a stirred solution of tert-butyl 3-[2-amino-6-[2-(benzyloxy)phenyl]-3-(1-hydroxyethyl)-4-pyridinyl]-1-piperidinecarboxylate (0.100 g, 0.199 mmol) obtained in the step (1) of Example 15-1 in dichrolomethane (1 mL) was added MnO_2 (0.350 g, 3.971 mmol). The mixture was stirred at room temperature for 2 hrs. The mixture was filtered on Celite® and concentrated under reduced pressure to give tert-butyl 3-{3-acetyl-2-amino-6-[2-(benzyloxy)phenyl]-4-pyridinyl}-1-piperidine carboxylate.

tert-butyl 3-{3-acetyl-2-amino-6-[2-(benzyloxy)phenyl]-4-pyridinyl}-1-piperidine carboxylate (0.090 g, 0.169 mmol) was then treated in a similar manner as that of the step (2) of Example 1-1. The residue was recrystallized from ethyl alcohol to give tert-butyl 3-[3-acetyl-2-amino-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidine-carboxylate as a pale yellow solid. (0.019 g, yield 27 %)



Then tert-butyl 3-[3-acetyl-2-amino-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidine-carboxylate (0.020 g, 0.044 mmol) was treated in a similar manner as that of the step (3) of Example 1-1. The resulting precipitate was collected by filtration, washed with acetonitril, and dried under reduced pressure to give 1-[2-amino-6-(2-hydroxy-phenyl)-4-(3-piperidinyl)-3-pyridinyl]ethanone hydrochloride. (0.014 g, yield 89%)

Molecular weight: 347.85

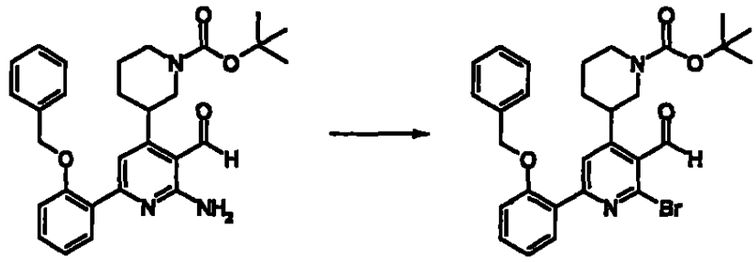
Mass spectrometry: 312 $(M+H)^+$

In vitro activity grade: A

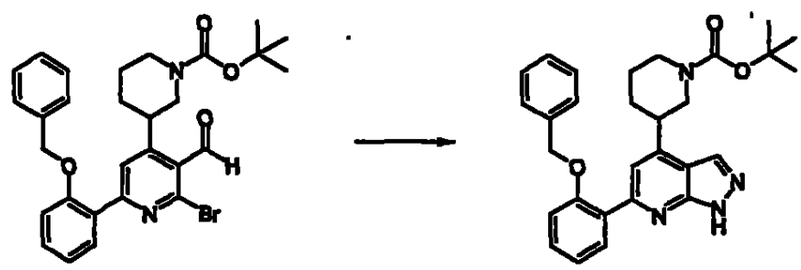
Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO): 1.17 – 1.87 (4H, m), 2.92 – 2.98 (1H, m), 2.56 (3H, s), 3.00 – 3.29 (4H, m), 6.98 – 6.91 (4H, m), 7.30 (1H, dd, J = 7.3, 7.9 Hz), 7.37 (1H, s), 8.73 (1H, d, J = 7.6 Hz), 13.73 (1H, br s).

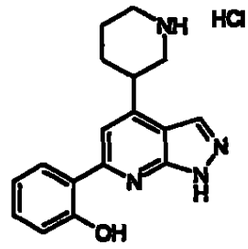
Example 16-1



To a solution of copper (II) bromide (0.82 g, 3.692 mmol) in acetonitrile (10 mL) was added tert-butyl nitrate (0.550 mL, 4.614 mmol). The mixture was stirred at 65 °C for 15 min. A solution of tert-butyl 3-{2-amino-6-[2-(benzyloxy)phenyl]-3-formyl-4-pyridinyl}-1-piperidinecarboxylate (1.50 g, 3.076 mmol), which was obtained in the step (2) of Example 13-1, in acetonitrile (10 mL) was added to the mixture, and stirred at 65 °C for 3 hrs. After cooled to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane / ethyl acetate = 4/1 – 2/1 – 1/1) to give tert-butyl 3-{6-[2-(benzyl-oxy)phenyl]-2-bromo-3-formyl-4-pyridinyl}-1-piperidinecarboxylate as a white solid (0.260 g, yield; 15%).



To a stirred solution of tert-butyl 3-{6-[2-(benzyloxy)phenyl]-2-bromo-3-formyl-4-pyridinyl}-1-piperidinecarboxylate (0.150 g, 0.272 mmol) in 1,4-dioxane (1 mL) was added hydrazine monohydrate (0.5 mL). The reaction mixture was stirred at 90 °C for 15 hrs. After cooled to room temperature, the reaction was quenched with water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from diethyl ether to give tert-butyl 3-{6-[2-(benzyloxy)phenyl]-1H-pyrazolo[3,4-b]pyridin-4-yl}-1-piperidinecarboxylate as a white solid (0.030 g, 23%). Then tert-butyl 3-{6-[2-(benzyloxy)phenyl]-1H-pyrazolo[3,4-b]pyridin-4-yl}-1-piperidinecarboxylate was treated in a similar manner as that of the step (2) of Example 1-1 and then the step (3) of Example 1-1 to obtain 2-(4-Piperidin-3-yl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)-phenol hydrochloride.



Molecular weight: 330.82

Mass spectrometry: 295 $(M+H)^+$

In vitro activity grade: B

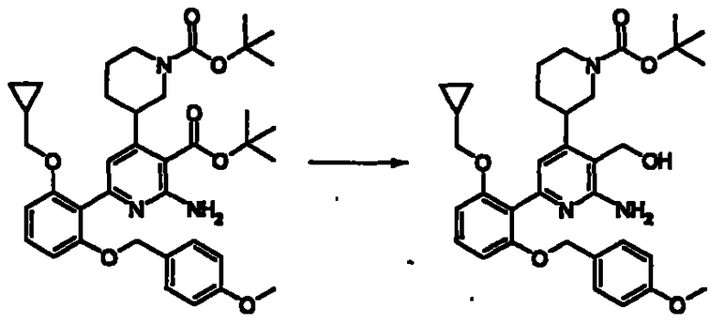
Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 1.91 – 2.05 (4H, m), 6.97 – 7.00 (2H, m), 7.35 – 7.87 (1H, m), 7.87 (1H, s), 8.16 (1H, d, J = 7.3 Hz), 8.42 (1H, s), 8.96 (1H, br s), 9.26 (1H, br s).

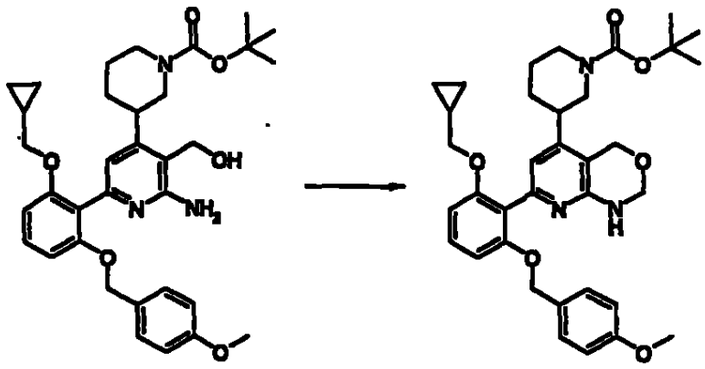
Example 17-1

(1) A mixture of the starting compound 1G (10.00 g, 30.638 mmol), 2B (13.069 g,

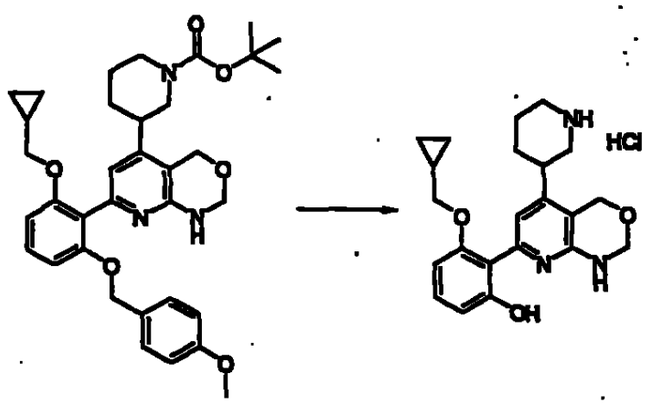
61.275 mmol), tert-butylcyanoacetate (8.650 g, 61.275 mmol), and ammonium acetate (6.902 g, 91.913 mmol) in dioxane (10 mL) was stirred at 90 °C overnight. After cooled to room temperature, the reaction mixture was diluted with ethyl acetate (100 mL). To the mixture was added chloranil (1.507 g, 6.128 mmol), and stirred at room temperature. After 1.5 hrs, ascorbic acid (1.079 g, 6.128 mmol) was added to the mixture. After stirred for 1.5 hrs, the mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. The resulting residue was purified by column chromatography on Silica-gel (hexane / ethyl acetate = 2/1) to give tert-butyl 2-amino-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]-6-{2-(cyclopropyl-methoxy)-6-[(4-methoxybenzyl)oxy]phenyl}nicotinate as a pale brown form (4.9 g, 24 %)



(2) To a cooled solution of tert-butyl 2-amino-4-[1-(tert-butoxycarbonyl)-3-piperidinyl]-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}nicotinate (4.9 g, 7.426 mmol) in tetrahydrofuran (60 mL) was added dropwise Vitride® (10 mL) under an argon atmosphere. The stirring was continued at 0 °C for 1 hr. After quenched by saturated aqueous NH_4Cl solution, saturated aqueous potassium sodium tartrate was added to the mixture, then the mixture was stirred vigorously. The mixture was extracted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give tert-butyl 3-[2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-(hydroxymethyl)-4-pyridinyl]-1-piperidinecarboxylate, which was used for the next step without further purification (4.38 g, yield; quant.).



(3) To a stirred solution of tert-butyl 3-[2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-(hydroxymethyl)-4-pyridinyl]-1-piperidine-carboxylate (0.501 g, 0.850 mmol) in 1,4-dioxane was added 37 % formaldehyde solution (5.000 mL) and 1N HCl (5.000 mL). The mixture was stirred at room temperature for 2 hrs. The reaction mixture was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (ethyl acetate/hexane =3/2) to give 1,1-dimethylethyl (tert-butyl) –3-{7-[2-[(cyclopropylmethyl)oxy]-6-({[4-(methyloxy)-phenyl]methyl}oxy)phenyl]-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-5-yl}-1-piperidinecarboxylate as a colorless foam (0.319 g, yield; 62%).



(4) To a stirred solution of 1,1-dimethylethyl(tert-butyl)-3-{7-[2-[(cyclopropylmethyl)oxy]-6-({[4-(methyloxy)phenyl]methyl}oxy)phenyl]-1,4-dihydro-2*H*-pyrido[2,3-*d*][1,3]oxazin-5-yl}-1-piperidinecarboxylate (0.050 g, 0.083 mmol) in 1,4-Dioxane was added 4N HCl in 1,4-dioxane (2.000 mL). The mixture was stirred at room temperature for 6 hrs. The reaction mixture was concentrated under reduced pressure. The resulting residue was washed with acetonitrile to give 3-(cyclopropylmethoxy)-2-[5-(3-piperidinyl)-1,4-dihydro-2*H*-pyrido[2,3-*d*][1,3]oxazin-7-yl]-phenol hydrochloride as a colorless solid (0.033 g, yield; 95%).

Molecular weight: 417.94

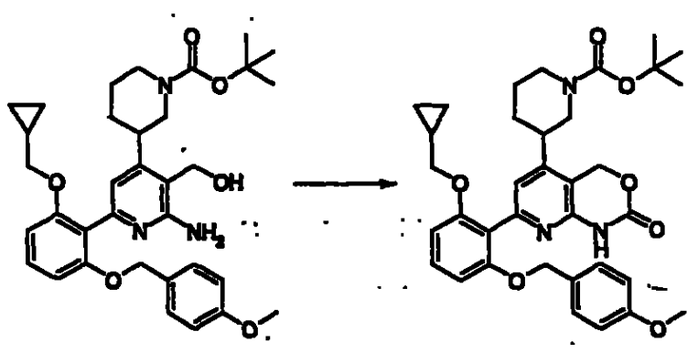
Mass spectrometry: 382 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

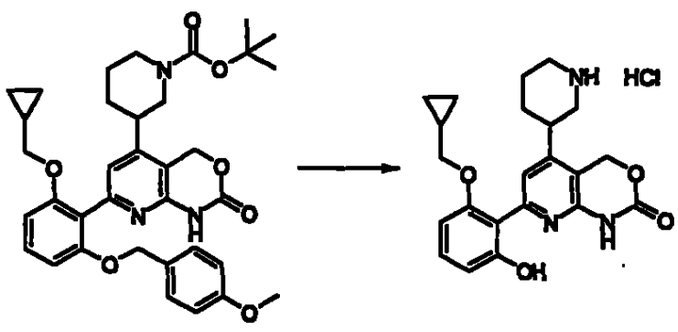
^{1}H-NMR (500 MHz, DMSO-d6): 0.30 (2H, br s), 0.51 (2H, br s), 1.17 (1H, m), 1.84 (4H, m), 2.86 (1H, m), 4.91 (2H, br), 5.01 (2H, br), 6.58 (1H, d, J = 7.9 Hz), 6.64 (1H, br), 7.16 (1H, br), 7.26 (1H, t, J = 7.9 Hz), 8.30 (1H, br), 9.14 (1H, br), 9.29 (1H, br), 13.95 (1H, br).

Example 18-1



To a cooled (0 °C) solution of tert-butyl 3-[2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-(hydroxymethyl)-4-pyridinyl]-1-piperidinecarboxylate (5.0 g, 8.478 mmol), which was obtained in the step (2) of Example 17-1, and diisopropylethyl amine (4.12 mL, 25.435 mmol) in tetrahydrofuran (200 mL)

under argon atmosphere was added dropwise to a solution of triphosgene (1.258 g, 4.239 mmol) in tetrahydrofuran (100 mL) . The mixture was allowed to warm to room temperature, and the stirring was continued for 3 hrs. After quenched by water, the mixture was extracted with ethyl acetate. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on Silica-gel (hexane / ethyl acetate = 1/1) to give tert-butyl 3-(7-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-2-oxo-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-5-yl)-1-piperidinecarboxylate as a white form (3.2 g, yield; 61%).



To a solution of tert-butyl 3-(7-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)-oxy]phenyl}-2-oxo-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-5-yl)-1-piperidine-carboxylate (2.0 g, 3.248 mmol) in dioxane (15 mL) was added 4N HCl in dioxane (30 mL) at room temperature. The stirring was continued for 3 hrs. After the solvent was removed by evaporation, the resulting solid was triturated with acetonitril, collected by filtration, and washed with acetonitrile. The solid was dried under reduced pressure to give 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one hydrochloride as a white solid (0.865 g, yield; 62%).

Molecular weight: 431.92

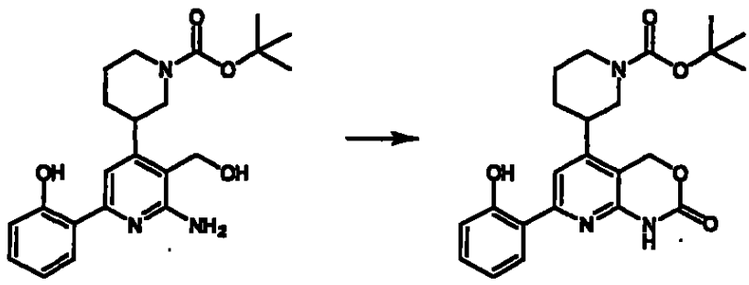
Mass spectrometry: 396 $(M+H)^+$

In vitro activity grade: A

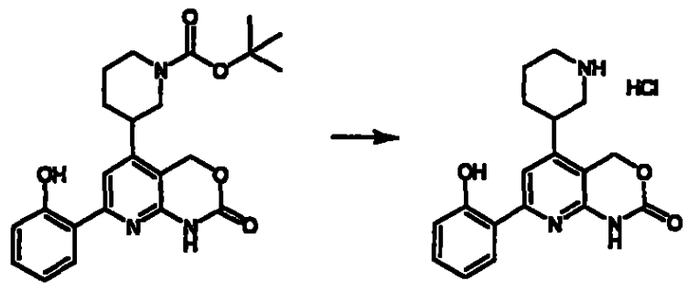
Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.26 – 0.37 (2H, m), 0.51 – 0.63 (2H, m), 1.20 – 1.31 (1H, m), 1.72 – 1.95 (4H, m), 2.80 – 2.96 (2H, m), 3.17 – 3.37 (3H, m), 3.79 – 3.88 (2H, m), 5.48 (1H, d, J = 14.2 Hz), 5.53 (1H, d, J = 14.2 Hz), 6.54 (2H, d, J = 8.2 Hz), 7.17 (1H, t, J = 8.2 Hz), 7.77 (1H, s), 9.05 (1H, br), 9.27 (1H, br), 10.96 (1H, s).

Example 18-2



To a cold (0 °C) solution of tert-butyl 3-[2-amino-3-(hydroxymethyl)-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.297 g, 0.74 mmol), which was obtained in the step (1) of Example 11-1 in THF (3.00 mL) including triethylamine (0.226 g, 2.23 mmol) was added triphosgene (0.221 g, 0.74 mmol). After 30 min, the mixture was allowed to warm to room temperature and the stirring was continued for 1 hr. The reaction was quenched with an aqueous $NaHCO_3$ solution, and extracted with ethyl acetate. The organic phase was washed with aqueous NH_4Cl solution, water, and brine successively. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate, 3:2) to give tert-butyl 3-[7-(2-hydroxyphenyl)-2-oxo-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-5-yl]-1-piperidinecarboxylate as a pale yellow solid. (46.2 mg, yield; 14.6%)



To a solution of tert-butyl 3-[7-(2-hydroxyphenyl)-2-oxo-1,4-dihydro-2H-pyrido-[2,3-d][1,3]oxazin-5-yl]-1-piperidinecarboxylate (45 mg, 0.11 mmol) in 1,4-dioxane (1.0 mL) was added 4N HCl in 1,4-dioxane (2.0 mL). The mixture was stirred for 1 hr at room temperature. The resulting solid was collected by filtration, washed with 1,4-dioxane, and dried under reduced pressure to give 7-(2-hydroxyphenyl)-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one hydrochloride as a white solid. (22.8 mg, yield; 60%)

Molecular weight: 361.83

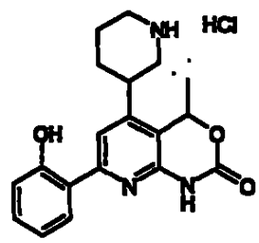
Mass spectrometry: 326 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A /Jurkat-B

^{1}H-NMR (500 MHz, DNSO-d6): 1.80 – 1.96 (5H, m), 2.86 – 2.93 (1H, m), 3.13 – 3.26 (3H, m), 5.46 – 5.55 (2H, m), 6.91 – 6.94 (2H, m), 7.30 – 7.33 (1H, m), 7.77 (1H, s), 8.03 – 8.04 (1H, m), 11.15 (1H, s), 12.46 (1H, br s).

Example 18-3



With the use of tert-butyl 3-[2-amino-3-(1-hydroxyethyl)-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate, which was obtained in the step (2) of Example 15-1, 7-(2-Hydroxy-phenyl)-4-methyl-5-piperidin-3-yl-1,4-dihydro-benzo[*d*][1,3]-oxazin-2-one hydrochloride was prepared in a similar manner as that of Example 18-2.

Molecular weight: 375.86

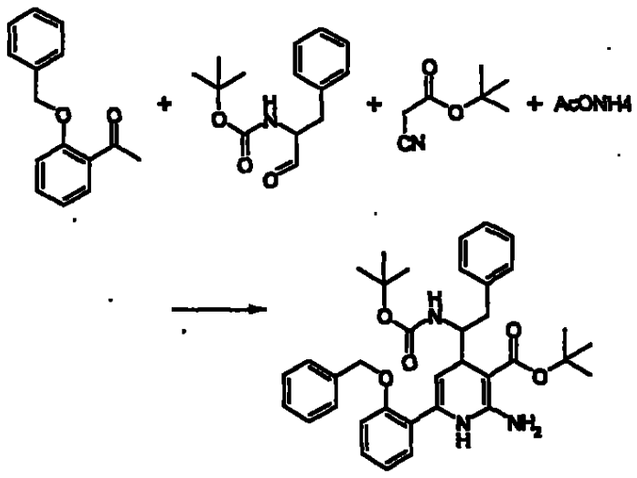
Mass spectrometry: 340 $(M+H)^+$

In vitro activity grade: B

Cellular activity grade: (A549)-B

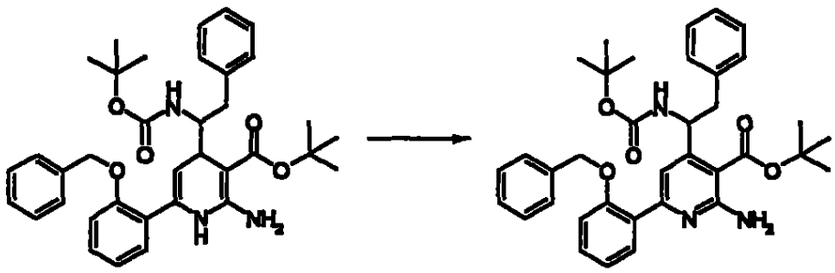
^{1}H-NMR (500 MHz, DMSO-d6): 1.52 – 1.53 (3H, m), 1.80 – 2.04 (5H, m), 2.91 – 2.95 (1H, m), 3.13 – 3.21 (3H, m), 5.83 – 5.85 (1H, m), 6.92 – 6.95 (3H, m), 7.32 (1H, dd, J = 7.9, 7.3 Hz), 8.04 (1H, d, J = 7.6 Hz), 11.2 (1H, s), 12.44 (1H, br s).

Example 18-4/18-5

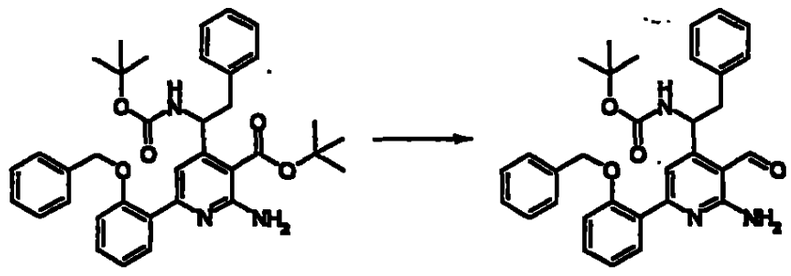


A mixture of the starting compound 1A (3.000 g, 13.258 mmol), N-tert-butoxy-carbonyl-phenylalaninal (3.305 g, 13.258 mmol), tert-butyl cyanoacetate (1.872 g, 13.258 mmol), ammonium acetate (3.066 g, 39.774 mmol) and 1,2-dimethoxyethane (5.0 mL) was heated at reflux for 6 hrs. After cooled to room temperature, the mixture was extracted with ethyl acetate and saturated $NaHCO_3$ solution. The

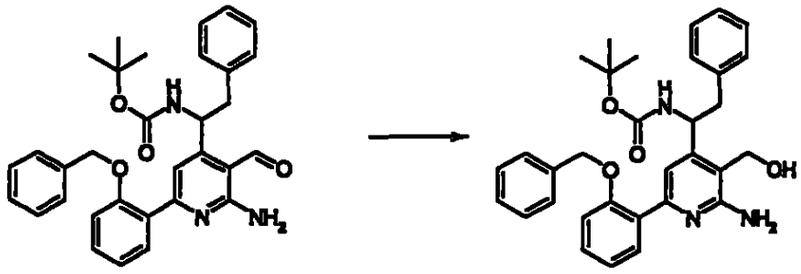
separated organic phase was washed with water and brine successively, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with diisopropyl ether to give tert-butyl 2-amino-6-[2-(benzyloxy)phenyl]-4-{1-[(tert-butoxycarbonyl)amino]-2-phenylethyl}-1,4-dihydro-3-pyridinecarboxylate as a yellow solid (1.281 g, yield; 16%).



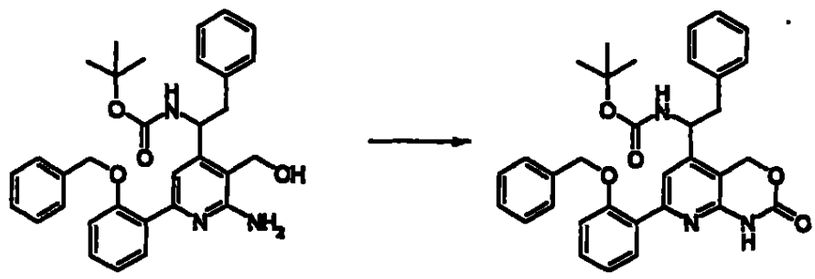
To a solution of tert-butyl 2-amino-6-[2-(benzyloxy)phenyl]-4-{1-[(tert-butoxycarbonyl)amino]-2-phenylethyl}-1,4-dihydro-3-pyridinecarboxylate (1.200 g, 2.007 mmol) in methylene chloride (20.0 mL) at room temperature was added chloranil (0.543 g, 2.208 mmol), and the stirring was continued for 1 hr. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate and 10% aqueous $NaHCO_3$ solution. The separated organic phase was washed with water and brine successively, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was crystallized from ethanol to give tert-butyl 2-amino-6-[2-(benzyloxy)phenyl]-4-{1-[(tert-butoxycarbonyl)amino]-2-phenylethyl}nicotinate as a pale yellow solid (0.972 g, yield; 84%).



To a cold (0 °C) solution of tert-butyl 2-amino-6-[2-(benzyloxy)phenyl]-4-{1-[(tert-butoxycarbonyl)amino]-2-phenylethyl}nicotinate (0.100 g, 0.198 mmol) in THF (1.50 mL) was added dropwise Vitride® (0.500 mL), and the stirring was continued for 2 hrs. The mixture was quenched at 0 °C with saturated aqueous NH_4Cl solution, and extracted with ethyl acetate. The separated organic phase was washed with water and brine successively, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane: ethyl acetate, 1: 1) to give tert-butyl -1-{2-amino-6-[2-(benzyloxy)phenyl]-3-formyl-4-pyridinyl}-2-phenylethylcarbamate as a colorless oil (0.044 g, yield; 51%).



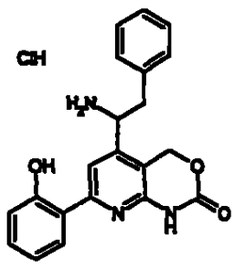
To a solution of tert-butyl 1-{2-amino-6-[2-(benzyloxy)phenyl]-3-formyl-4-pyridinyl}-2-phenylethylcarbamate (0.040 g, 0.092 mmol) in ethanol (1.0 mL) was added $NaBH_4$ (0.010 g, 0.26 mmol), and the stirring was continued for 3 hrs. The mixture was extracted with ethyl acetate and saturated aqueous ammonium chloride solution. The separated organic phase was washed with water and brine successively, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was crystallized from ethanol to give tert-butyl 1-[2-amino-6-[2-(benzyloxy)phenyl]-3-(hydroxymethyl)-4-pyridinyl]-2-phenylethylcarbamate as a pale yellow solid (0.023 g, yield; 57%).



To a cold (0 °C) solution of tert-butyl 1-[2-amino-6-[2-(benzyloxy)phenyl]-3-(hydroxymethyl)-4-pyridinyl]-2-phenylethylcarbamate (0.210 g, 0.400 mmol) in THF (3.0 mL) including triethylamine (0.167 mL, 1.199 mmol) was added dropwise a solution of triphosgene (0.059 g, 0.200 mmol) in THF (1.0 mL). After stirred at 0 °C for 45 min, the mixture was allowed to warm to room temperature, and the stirring was continued for 30 min. The reaction mixture was cooled at 0 °C, and then quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane: ethyl acetate, 2: 1) to give tert-butyl 1-{7-[2-(benzyloxy)phenyl]-2-oxo-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-5-yl}-2-phenylethylcarbamate as a colorless oil (0.170 g, yield; 77%).

Then in a similar manner as that of the step (2) of Example 1-1 and the step (3) of Example 1-1, tert-butyl 1-{7-[2-(benzyloxy)phenyl]-2-oxo-1,4-dihydro-2H-pyrido-[2,3-d][1,3]oxazin-5-yl}-2-phenylethylcarbamate was treated to give 5-(1-Amino-2-phenyl-ethyl)-7-(2-hydroxy-phenyl)-1,4-dihydro-pyrido[2,3-*d*][1,3]oxazin-2-one hydrochloride.

Example 18-4/18-5



Molecular weight: 397.86

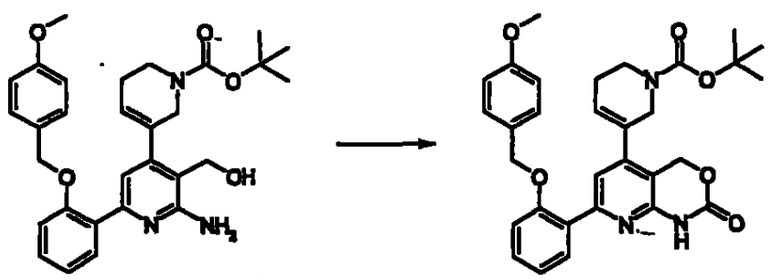
Mass spectrometry: 362 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 3.11 (1H, dd, J = 10.1, 12.9 Hz), 3.44 (1H, dd, J = 5.0, 12.9 Hz), 4.25 (1H, d, J = 14.5 Hz), 4.71 – 4.74 (1H, m), 5.35 (1H, d, J = 14.5 Hz), 6.93 – 6.99 (2H, m), 7.08 (2H, dd, J = 1.9, 7.3 Hz), 7.23 – 7.28 (3H, m), 7.33 – 7.36 (1H, m), 8.13 (1H, dd, J = 1.3, 7.9 Hz), 8.37 (1H, s), 8.98 (3H, br), 11.18 (1H, s), 12.32 (1H, br).

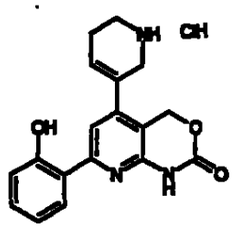
Example 18-6



To a cooled (0 °C) solution of tert-butyl 2'-amino-3'-(hydroxymethyl)-6'-{2-[(4-methoxybenzyl)oxy]phenyl}-5,6-dihydro-3,4'-bipyridine-1(2H)-carboxylate (25.0 mg, 0.05 mmol), which was obtained in the step (2) of Example 11-4, and triethylamine (0.02 mL, 0.14 mmol) in THF (3.0 mL) was added a solution of

triphosgene (5.7 mg, 0.02 mmol) in THF (3.0 mL), and the stirring was continued for 30 min. The reaction mixture was allowed to warm to room temperature. The reaction was cooled to 0 °C and then quenched by an addition of saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by preparative silica gel TLC (10% acetone in chloroform) to give tert-butyl 5-(7-{2-[(4-methoxybenzyl)oxy]phenyl}-2-oxo-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-5-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate as a white solid. (21.7 mg, yield 83%)

Then the tert-butyl and methoxy benzyl were removed in a similar manner as that of the steo(2) of Example 1-1.



Molecular weight: 359.82

Mass spectrometry: 324 $(M+H)^+$

In vitro activity grade: A

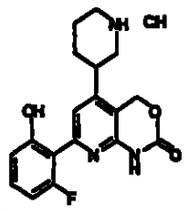
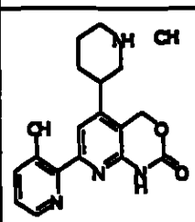
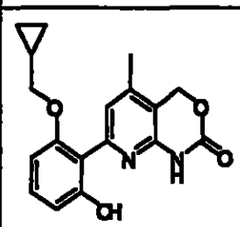
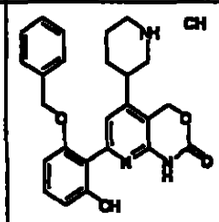
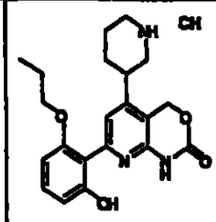
Cellular activity grade: (A549)-A

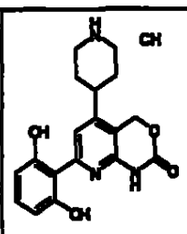
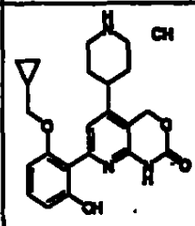
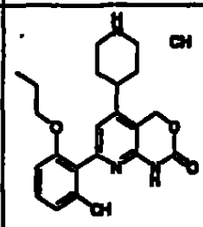
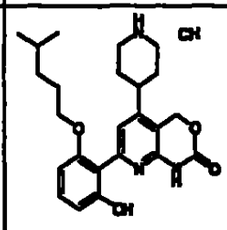
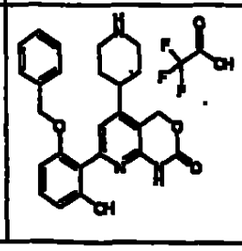
^{1}H-NMR (500 MHz, MeOH-d4): 2.63 – 2.65 (2H, m), 3.44 – 3.49 (2H, m), 4.02 (2H, br d, J = 1.9 Hz), 5.45 (2H, s), 6.04 (1H, s), 6.88 – 6.95 (2H, m), 7.29 – 7.32 (1H, m), 7.63 (1H, s), 7.90 (1H, dd, J = 1.3, 7.9 Hz).

Examples 18-7 to 18-16

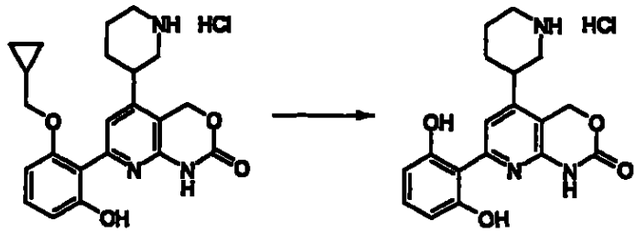
According to the similar synthetic procedure of Examples 18-1 to 18-6, compounds shown in Table 5 were prepared.

Table 5

Ex. No	Structure	Mol weight	Mass	In vitro	A549	NMR
18-07		379.82	no peak	A	A	(500 MHz, DMSO-d6): 1.82 (4H, m), 3.02 (3H, m), 3.29 (2H, d, J = 21.5 Hz), 5.50 (2H, dd, J = 23.9, 39.8 Hz), 6.73 (1H, d, J = 23.9 Hz), 6.78 (1H, m), 7.28 (1H, dd, J = 13.6, 24.8 Hz), 7.34 (1H, s), 8.58 (1H, m), 8.97 (1H, m), 10.95 (1H, s).
18-08		362.82	327	A	A	(500 MHz, DMSO-d6): 1.88 - 1.94 (4H, m), 3.26 - 3.33 (2H, m), 3.57 - 3.59 (1H, m), 3.63 - 3.74 (2H, m), 5.51 (1H, d, J = 14.2 Hz), 5.58 (1H, d, J = 14.2 Hz), 7.38 - 7.40 (2H, m) , 8.14 (1H, s), 8.22 (1H, t, J = 2.8 Hz), 11.25 (1H,s).
18-09		326.36	327	C	A	(500 MHz, CDCl3): 0.34 - 0.44 (2H, m), 0.61 - 0.72 (2H, m), 1.24 - 1.35 (1H, m), 2.33 (3H, s), 3.89 (2H, d, J = 6.9 Hz), 5.39 (2H, s), 6.45 (1H, dd, J = 1.0, 8.5 Hz), 6.65 (1H, dd, J = 1.0, 8.5 Hz), 7.18 (1H, t, J = 8.5 Hz), 7.54 (1H, br s), 8.10 (1H, s), 12.48 (1H, br s).
18-10		467.96	432	A	A	(500 MHz, DMSO-d6): 1.25 - 1.32 (1H, m), 1.53 - 1.83 (3H, m), 2.58 - 2.80 (2H, m), 3.01 - 3.07 (1H, m), 3.13 - 3.18 (1H, m), 3.27 - 3.30 (1H, m), 5.07 (2H, dd, J = 11.0, 18.2 Hz), 5.44 (2H, dd, J = 14.2, 24.0 Hz), 6.58 (1H, d, J = 8.2 Hz), 6.72 (1H, d, J = 8.2 Hz), 7.22 (1H, t, J = 8.2 Hz), 7.34 - 7.46 (6H, m), 8.77 (1H, br), 9.04 (1H, br), 10.92 (1H, s).
18-11		419.91	384	A	A	(300 MHz, DMSO-d6): 0.90 (3H, t, J = 7.2 Hz), 1.72 (2H, m), 1.84 - 1.88 (2H, m), 2.85 - 2.92 (2H, m), 3.18 - 3.34 (4H, m), 3.90 - 3.95 (2H, m), 5.48 (2H, d, J = 5.6 Hz), 6.55 (2H, dd, J = 8.3, 8.5 Hz), 7.17 (1H, t, J = 8.3 Hz), 7.54 (1H, s), 8.86 (1H, br), 9.13 (1H, br), 10.89 (1H, s).

18-12		377.83	342	B	C	(500 MHz, DMSO-d6): 1.70 - 1.73 (2H, m), 1.78 - 1.89 (2H, m), 2.87 - 2.90 (2H, m), 3.00 - 3.05 (2H, m), 4.05 (1H, m), 5.49 (2H, s), 6.39 (1H, d, J = 8.2 Hz), 6.42 (1H, d, J = 8.2 Hz), 7.04 (1H, m), 7.92 (1H, m), 8.55 (1H, br), 8.77 (1H, br), 10.95 (1H, s), 10.99 (1H, s).
18-13		431.92	396	A	A	(500 MHz, DMSO-d6): 0.28 - 0.30 (2H, m), 0.55 - 0.58 (2H, m), 1.31 (1H, m), 1.86 (4H, m), 3.01 - 3.04 (3H, m), 3.35 - 3.38 (2H, m), 3.84 (2H, d, J = 6.9 Hz), 5.50 (2H, s), 6.83 (2H, d, J = 8.2 Hz), 7.17 (1H, t, J = 8.2 Hz), 7.74 (1H, s), 8.82 (1H, br), 9.00 (1H, br), 10.95 (1H, s).
18-14		419.91	384	A	A	(500 MHz, DMSO-d6): 0.90 (3H, t, J = 7.5 Hz), 1.75 (2H, m), 1.85 (4H, m), 3.02 (3H, m), 3.36 (2H, m) 3.95 (2H, t, J = 7.6 Hz), 5.49 (2H, s), 6.53 (1H, d, J = 7.9 Hz), 6.57 (1H, d, J = 8.2 Hz), 7.18 (1H, t, J = 8.2 Hz), 7.50 (1H, s), 8.88 (1H, br), 8.99 (1H, br), 10.90 (1H, s).
18-15		461.99	426	A	A	(500 MHz, DMSO-d6): 0.81 (6H, d, J = 6.6 Hz), 1.14 - 1.19 (2H, m), 1.47 - 1.51 (1H, m), 1.67 - 1.71 (2H, m), 1.83 - 1.90 (4H, m), 2.96 - 3.06 (3H, m), 3.31 - 3.33 (2H, m), 3.95 - 3.97 (2H, m), 5.49 (2H, s), 6.53 - 6.58 (2H, m), 7.17 (1H, t, J = 8.3 Hz), 7.42 (1H, s), 9.05 - 9.11 (1H, m), 10.88 (1H, s).
18-16		545.52		A	B	(500 MHz, DMSO-d6): 1.58 - 1.64 (4H, m), 2.95 (4H, br s), 5.09 (2H, s), 5.45 (2H, s), 6.55 - 6.59 (1H, m), 6.70 (1H, d, J = 8.3 Hz), 7.20 (1H, t, J = 8.1 Hz), 7.33 - 7.38 (6H, m), 8.26 (1H, br s), 8.57 (1H, br s), 10.85 (1H, br s), 11.11 (1H, br s).

Example 19-1



A mixture of 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one hydrochloride (0.070 g, 0.160 mmol), which was obtained in Example 18-1, and 2.5N HCl in 1,4-dioxane (4 mL) was stirred at 80 °C overnight. After cooled to room temperature, the mixture was concentrated under reduced pressure. The resulting residue was diluted with dichloromethane (3 mL), and triethylamine (0.064 g, 0.497 mmol) was added. To the cooled (0 °C) mixture was added di-tert-butyl dicarbonate (0.047 g, 0.218 mmol) under an argon atmosphere. The stirring was continued at room temperature overnight. After quenched by water, the mixture was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane / ethyl acetate = 1/1) to give tert-butyl 3-[7-(2,6-dihydroxyphenyl)-2-oxo-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-5-yl]-1-piperidinecarboxylate (0.019 g, 19 %). To a solution of tert-butyl 3-[7-(2,6-dihydroxyphenyl)-2-oxo-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-5-yl]-1-piperidinecarboxylate in dioxane (1 mL) was added 4N HCl in dioxane (1 mL) at room temperature. The stirring was continued for 3 hrs. After the solvent was removed by evaporation, the resulting residue was washed with acetonitril, and dried under reduced pressure to give 7-(2,6-dihydroxyphenyl)-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]-oxazin-2-one hydrochloride as a brown solid (0.007 g, 46 %).

Molecular weight: 377.83

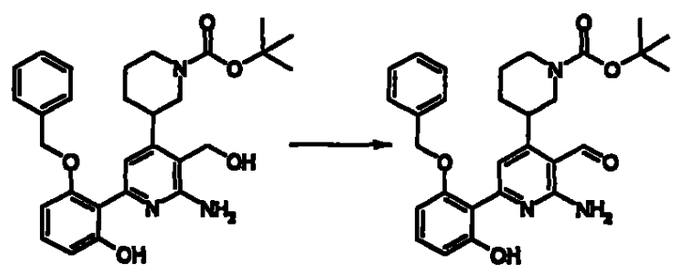
Mass spectrometry: 342 $(M+H)^+$

In vitro activity grade:

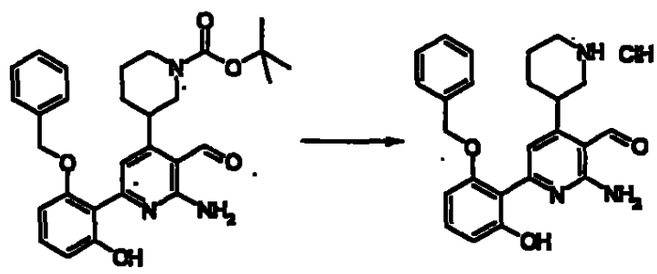
Cellular activity grade: (A549)-

^{1}H-NMR (500 MHz, DMSO-d6): 1.73 – 1.89 (4H, m), 2.89 – 2.94 (2H, m), 3.19 (1H, m), 3.25 – 3.32 (2H, m), 5.46 (1H, d, J = 14.2 Hz), 5.51 (1H, d, J = 14.2 Hz), 6.41 (2H, d, J = 8.2 Hz), 7.03 (1H, t, J = 8.2 Hz), 7.88 (1H, s), 8.90 (1H, br), 9.14 (1H, br), 11.01 (1H, s).

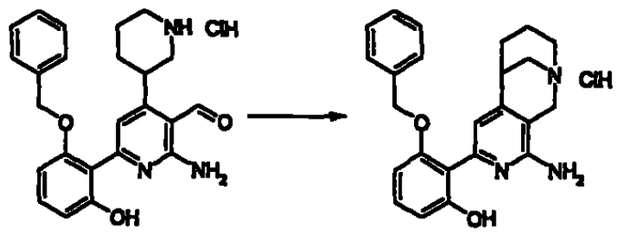
Example 20-1



To a stirred solution of tert-butyl 3-[2-amino-6-[2-(benzyloxy)-6-hydroxyphenyl]-3-(hydroxymethyl)-4-pyridinyl]-1-piperidinecarboxylate (0.100 g, 0.198 mmol), which was obtained in the similar procedure as that of Example 13-1, in dichrolomethane (3 mL) was added MnO_2 (0.340 g, 3.956 mmol). The mixture was stirred at room temperature for 2 hrs. The mixture was filtered on Celite® and concentrated under reduced pressure. The residue was recrystallized from ethyl alcohol to give tert-butyl 3-{2-amino-6-[2-(benzyloxy)-6-hydroxyphenyl]-3-formyl-4-pyridinyl}-1-piperidine-carboxylate as a yellow solid. (0.092 g, yield 93%)



To a stirred solution of tert-butyl 3-{2-amino-6-[2-(benzyloxy)-6-hydroxyphenyl]-3-formyl-4-pyridinyl}-1-piperidinecarboxylate (0.090 g, 0.183 mmol) in 1,4-dioxane (2 mL) was added 4N HCl in dioxane (2 mL). The mixture was stirred at room temperature for 2 hrs. The resulting precipitate was collected by filtration, washed with acetonitril, and dried under reduced pressure to give 2-amino-6-[2-(benzyloxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinaldehyde hydrochloride. (0.103 g, yield quant.)



To a cold (0 °C) solution of 2-amino-6-[2-(benzyloxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinaldehyde hydrochloride (0.100 g, 0.227 mmol) in methanol was added $NaBH_3CN$ (0.040 mL, 0.682 mmol) under an argon atmosphere. The mixture was stirred at room temperature for 12 hrs and concentrated under reduced pressure. The residue was extracted with ethyl acetate and water. The separated organic phase was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 2/1) to give 2-(6-amino-5,9-diazatricycle[7.3.1.02,7]trideca-2,4,6-trien-4-yl)-3-(benzyloxy)phenol as a white solid.

To a stirred solution of 2-(6-amino-5,9-diazatricyclo[7.3.1.02,7]trideca-2,4,6-trien-4-yl)-3-(benzyloxy)phenol in 1,4-dioxane (2 mL) was added 4N HCl in dioxane (2 mL). The mixture was stirred at room temperature for 2 hrs. The resulted precipitate was collected by filtration, washed with acetonitril, and dried under reduced pressure to give 2-(6-amino-5,9-diazatricyclo[7.3.1.02,7]trideca-2,4,6-trien-4-yl)-3-(benzyloxy)phenol hydrochloride.(0.018 g, yield 19%)

Molecular weight: 423.95

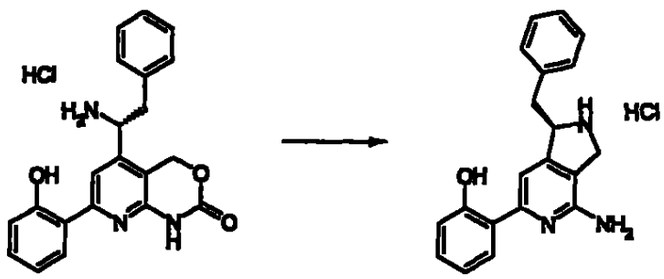
Mass spectrometry: 388 $(M+H)^+$

In vitro activity grade: B

Cellular activity grade: (A549)-C

^{1}H-NMR (500 MHz, DMSO-d6): 1.10 – 1.23 (2H, m), 1.41 (1H, d, J = 12.3 Hz), 1.71 – 1.80 (1H, m), 2.79 (1H, d, J = 12.9 Hz), 2.89 – 2.91 (2H, m), 2.97 (1H, d, J = 12.9 Hz), 3.44 (2H, d, J = 18.3 Hz), 3.81 (1H, d, J = 18.0 Hz), 5.09 – 5.17 (2H, m), 6.01 (1H, s), 6.64 (1H, d, J = 8.5 Hz), 7.13 (1H, t, J = 8.2 Hz), 7.33 – 7.41 (4H, m), 7.49 (2H, d, J = 1.6 Hz).

Example 20-2



A mixture of 5-[(1R)-1-amino-2-phenylethyl]-7-(2-hydroxyphenyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one hydrochloride (0.014 g, 0.035 mmol), which was obtained in Example 18-4, in acetonitrile (3.0 mL) was heated at reflux for 2 hrs. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane (1.0 mL), treated with 4N HCl solution in 1,4-dioxane (0.5 mL), and concentrated under reduced pressure. The residue was triturated with acetonitrile, and dried under reduced pressure to give 2-[(1R)-4-amino-1-benzyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]phenol hydrochloride as a white solid (0.010 g, yield; 80%).

Molecular weight: 353.85

Mass spectrometry: 318 $(M+H)^+$

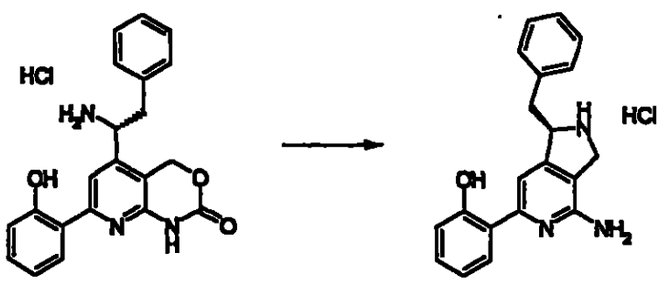
In vitro activity grade: A

Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 3.30 (1H, dd, J = 9.1, 14.1 Hz), 3.54 (1H, dd, J = 5.0, 14.1 Hz), 4.26 – 4.42 (2H, br m), 5.20 (1H, br), 6.91 (1H, t, J = 7.9 Hz), 6.97 (1H, d, J = 8.2 Hz), 7.29 – 7.39 (2H, m), 7.41 (1H, t, J = 7.9 Hz), 7.62 (1H, d, J = 7.3 Hz), 10.14 (1H, br), 10.31 (1H, br), 13.90 (1H, br).

Example 20-3

In a similar manner as described in Examples 20-1 and 20-2, 2-[(1S)-4-amino-1-benzyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]phenol hydrochloride was prepared.



Molecular weight: 353.85

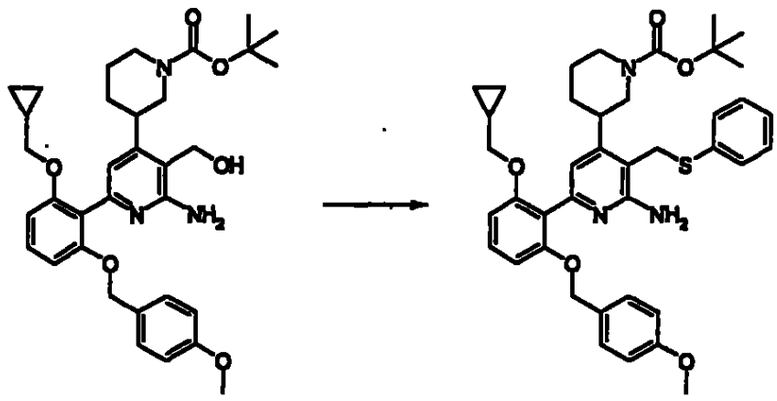
Mass spectrometry: 318 $(M+H)^+$

In vitro activity grade: A

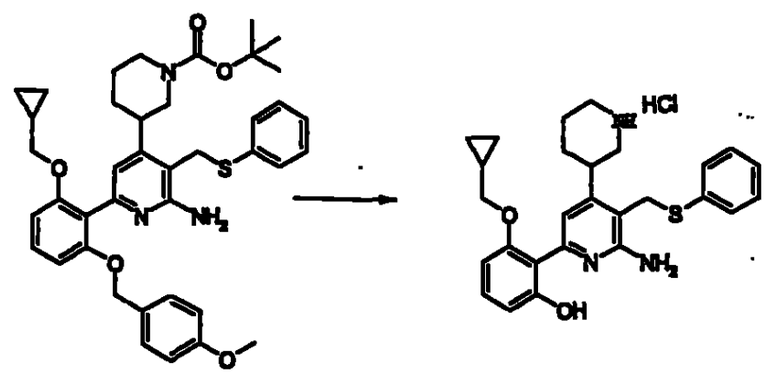
Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 3.30 (1H, dd, J = 9.1, 14.1 Hz), 3.54 (1H, dd, J = 5.0, 14.1 Hz), 4.26 – 4.42 (2H, br m), 5.20 (1H, br), 6.91 (1H, t, J = 7.9 Hz), 6.97 (1H, d, J = 8.2 Hz), 7.29 – 7.39 (2H, m), 7.41 (1H, t, J = 7.9 Hz), 7.62 (1H, d, J = 7.3 Hz), 10.14 (1H, br), 10.31 (1H, br), 13.90 (1H, br).

Example 21-1



(1) To a stirred solution of tert-butyl 3-[2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-(hydroxymethyl)-4-pyridinyl]-1-piperidinecarboxylate (0.050 g, 0.085 mmol), which was obtained in the step (2) of Example 17-1, and phenyl disulfide (0.055 g, 0.254 mmol) in tetrahydrofuran (3 mL) was added tributyl phosphine (0.060 mL, 0.254 mmol). The mixture was stirred at room temperature for 24 hrs. The mixture was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue (liquid) was purified by column chromatography on silica gel (hexane / ethyl acetate = 3/1 - 1/1) to give tert-butyl 3-{2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-[(phenylsulfanyl)methyl]-4-pyridinyl}-1-piperidinecarboxylate (0.021 g, yield; 37%) as a form.



(2) To a stirred solution of tert-butyl 3-{2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-[(phenylsulfanyl)methyl]-4-pyridinyl}-1-piperidine-carboxylate in 1,4-dioxane (2 mL) was added 4 N HCl in dioxane (2 mL). The mixture was stirred at room temperature overnight, and diluted with ethyl acetate. The resulting precipitate was collected by filtration, washed with ethanol, and dried under reduced pressure to give 2-[6-amino-5-[(phenylsulfanyl)methyl]-4-(3-piperidinyl)-2-pyridinyl]-3-(cyclopropylmethoxy)phenol hydrochloride.

Molecular weight: 498.09

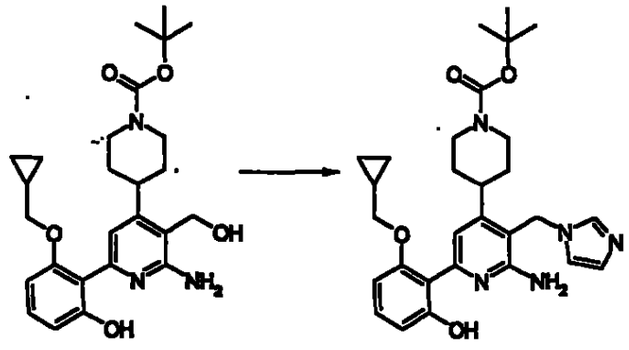
Mass spectrometry: 462 $(M + H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 0.30 (2H, br s), 0.51 (2H, br s), 1.67 (2H, m), 1.80 (1H, br), 4.26 (1H, d, J = 12.6 Hz), 4.37 (1H, br), 6.59 (2H, br), 7.36 (2H, t, J = 7.6 Hz), 7.46 (2H, d, J = 7.6 Hz), 7.72 (1H, br), 8.61 – 8.98 (2H, br), 10.36 (1H, br), 13.58 (1H, br).

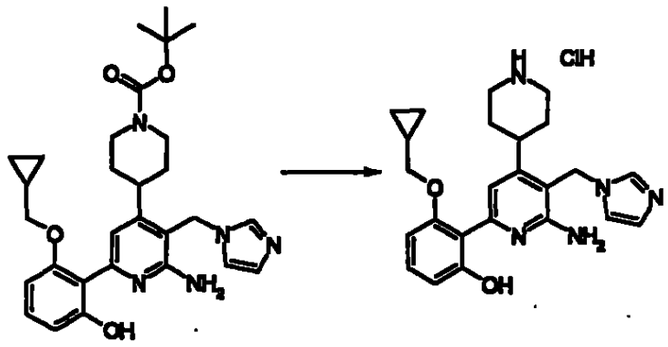
Example 21-2



(1) With the use of the starting compound 1G, tert-butyl 4-formyl-piperidine-1-carboxylic acid prepared in a similar manner as that of the starting compound 2B, and other materials, tert-butyl 4-[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxy-

phenyl]-3-(hydroxymethyl)-4-pyridinyl]-1-piperidinecarboxylate was prepared in a similar manner as that of the step (1) of Example 11-1.

(2) To a stirred solution of tert-butyl 4-[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-(hydroxymethyl)-4-pyridinyl]-1-piperidinecarboxylate (0.250 g, 0.528 mmol) in acetonitrile(10 mL) was added 1,1'-carbonyldiimidazole (0.170 g, 1.056 mmol) at room temperature. After stirred for 2 hrs, the reaction mixture was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting solid was collected by filtration, washed with hexane, and dried under reduced pressure to give tert-butyl 4-[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-(1H-imidazol-1-ylmethyl)-4-pyridinyl]-1-piperidinecarboxylate. (0.242 g, yield 88%)



(3) To a stirred solution of tert-butyl 4-[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-(1H-imidazol-1-ylmethyl)-4-pyridinyl]-1-piperidinecarboxylate (0.260 g, 0.500 mmol) in 1,4-dioxane (10 mL) was added 4N HCl in dioxane (10 mL). The mixture was stirred at room temperature for 2 hrs. The resulting precipitate was collected by filtration, washed with acetonitrile, and dried under reduced pressure to give 2-[6-amino-5-(1H-imidazol-1-ylmethyl)-4-(4-piperidinyl)-2-pyridinyl]-3-(cyclopropylmethoxy)phenol hydrochloride. (0.248 g, yield; quant.)

Molecular weight: 455.99

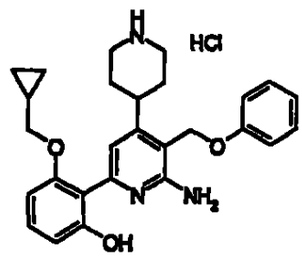
Mass spectrometry: 420 $(M + H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.32 (2H, d, J = 4.7 Hz), 0.52 (2H, d, J = 4.7 Hz), 1.27 (1H, br s), 1.71 (2H, d, J = 13.6 Hz), 1.91 – 1.98 (2H, m), 3.00 – 3.31 (2H, m), 3.32 – 3.35 (3H, m), 3.86 (2H, d, J = 6.9 Hz), 5.62(2H, s), 6.58 (1H, d, J = 8.5 Hz), 6.64 (1H, d, J = 6.9 Hz), 7.26 (1H, dd, J = 8.5, 7.9 Hz), 7.66 (1H, s), 7.71 (1H, s), 9.31 (1H, s).

Example 21-3



With the use of diphenyl carbonate instead of 1,1'-carbonyldiimidazole, 2-[6-amino-5-(phenoxymethyl)-4-(4-piperidinyl)-2-pyridinyl]-3-(cyclopropylmethoxy)phenol hydrochloride was prepared in a similar manner as that of Example 21-2.

Molecular weight: 482.03

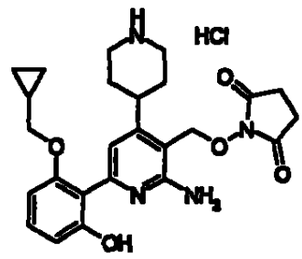
Mass spectrometry: 446 $(M + H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.31 (2H, d, J = 4.7 Hz), 0.50 (2H, d, J = 6.9 Hz), 1.16 – 1.19 (1H, m), 1.84 (2H, d, J = 13.2 Hz), 1.91 –1.99 (2H, m), 2.96 (2H, m), 3.57 (1H, s), 3.76 (2H, d, J = 6.6 Hz), 5.20 (2H, s), 6.61 (1H, d, J = 8.2 Hz), 6.66 (1H, d, J = 6.0 Hz), 6.75 (1, d, J = 8.5 Hz), 7.20 (1H, t, J = 7.3 Hz), 7.08 (2H, d, J = 7.9 Hz), 7.15 (1H, t, J = 7.9 Hz), 7.36 (2H, t, J = 7.9 Hz).

Example 21-4



With the use of N,N'-disuccinimidyl carbonate instead of 1,1'-carbonyldiimidazole, 1-{[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(4-piperidinyl)-3-pyridinyl]methoxy}-2,5-pyrrolidinedione hydrochloride was prepared in a similar manner as that of Example 21-2.

Molecular weight: 503.00

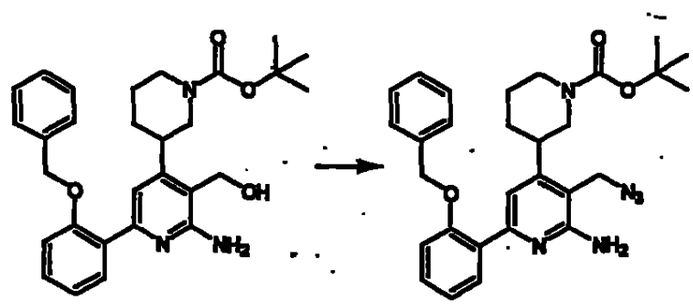
Mass spectrometry: 467 $(M+H)^+$

In vitro activity grade: A

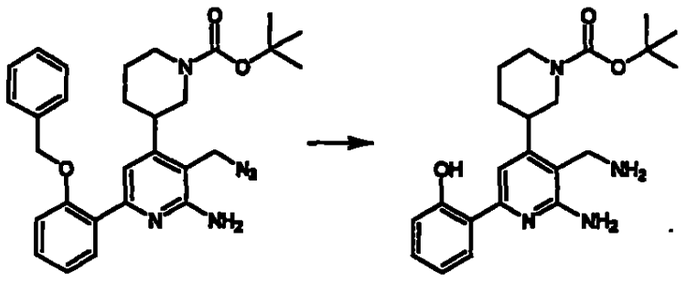
Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.19 (2H, d, J = 5.0 Hz), 0.52 (2H, d, J = 7.3 Hz), 1.21 (1H, br s) , 1.91 – 1.96 (4H, m), 2.71 (4H, s), 3.03 (2H, d, J = 8.2 Hz), 3.85 (2H, d, J = 6.9 Hz), 5.18 (2H, s), 6.59 (1H, d, J = 8.5 Hz), 6.64 (1H, d, J = 7.6 Hz), 7.05 (1H, br s), 7.27 (1H, t, J = 7.9 Hz), 7.60 (1H, br s), 8.82 (1H, br s), 8.92 (1H, d, J = 9.1 Hz).

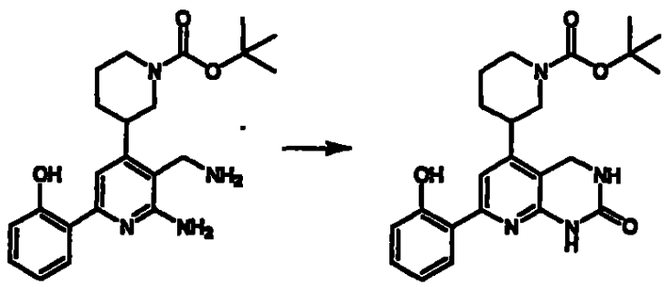
Example 22-1



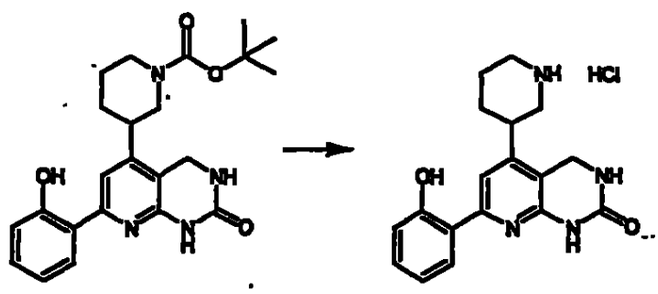
(1) To a cold (0 °C) solution of tert-butyl 3-[2-amino-6-[2-(benzyloxy)phenyl]-3-(hydroxymethyl)-4-pyridinyl]-1-piperidinecarboxylate (0.050 g, 0.102 mmol), obtained in the step (1) of Example 13-1, in toluene (1.0 mL) was added diphenylphosphoryl azide (0.024 mL, 0.112 mmol) followed by 1,8-diazabicyclo-[5.4.0.]undec-7-ene (0.017 mL, 0.112 mmol). After 30 min, the mixture was allowed to warm to room temperature, and the stirring was continued for 2 hrs. The mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 2:1) to give tert-butyl 3-{2-amino-3-(azidomethyl)-6-[2-(benzyloxy)phenyl]-4-pyridinyl}-1-piperidinecarboxylate. (0.038 g, yield; 72%)



(2) A solution of tert-butyl 3-{2-amino-3-(azidomethyl)-6-[2-(benzyloxy)phenyl]-4-pyridinyl}-1-piperidinecarboxylate (0.030 g, 0.058 mmol) in ethyl acetate (1.0 mL) was hydrogenated at 1 atm in the presence of palladium on charcoal (10%, 0.015 g) overnight. The resulting mixture was filtered and washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure to give tert-butyl 3-[2-amino-3-(aminomethyl)-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate, which was used for the next step without further purification.



(3) To a cold (0 °C) solution of tert-butyl 3-[2-amino-3-(aminomethyl)-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.020 g, 0.050 mmol) in THF (2.0 mL) under an argon atmosphere was added 1,1'-carbonyldiimidazole (0.009 g, 0.055 mmol). After stirred for 15 min, the mixture was quenched with saturated sodium bicarbonate solution. The resulting mixture was partitioned between ethyl acetate and saturated ammonium chloride solution. The separated organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (2.0 mL). The mixture was heated at 60 °C for 1 hr and allowed to cool to room temperature. The resulting precipitates were collected by filtration, washed with ethyl acetate and dried under reduced preasure to give tert-Butyl 3-[7-(2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-5-yl]-1-piperidinecarboxylate. (0.007 g, yield; 33%)



(4) tert-Butyl 3-[7-(2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrido[2,3-d]-pyrimidin-5-yl]-1-piperidinecarboxylate (0.006 g, 0.014 mmol) was treated under acidic conditions in a similar manner as described in the step (3) of Example 1-1 to

give 7-(2-hydroxyphenyl)-5-(3-piperidinyl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-one hydrochloride. (0.005 g, yield; 98%)

Molecular weight: 360.85

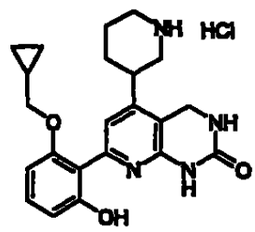
Mass spectrometry: 325 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: B

^{1}H-NMR (500 MHz, DMSO-d6): 1.76 – 1.93 (4H, m), 2.88 – 3.37 (5H, m), 4.47 (2H, dd, J = 15.4, 24.3 Hz), 6.87 – 6.92 (2H, m), 7.26 – 7.30 (2H, m), 7.63 (1H, s), 8.00 (1H, d, J = 8.2 Hz), 8.57 (1H, br), 9.01 (1H, br), 10.08 (1H, s), 12.78 (1H, br).

Example 22-2



With the use of the starting compound 1G, 2B and other materials, 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-3,4-dihydro-1H-pyrido[2,3-d]-pyrimidin-2-one hydrochloride was prepared in a similar manner as that of Example 22-1.

Molecular weight: 430.94

Mass spectrometry: 395 $(M+H)^+$

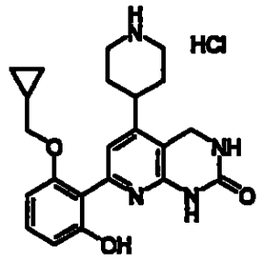
In vitro activity grade: A

Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.34 (2H, m), 0.57 (2H, m), 1.27 (1H, m), 1.73 – 1.87 (4H, m), 2.82 – 2.90 (2H, m), 3.14 (1H, m), 3.29 – 3.33 (2H, m), 3.80 – 3.88

(2H, m), 4.49 (2H, s), 6.52 (2H, d, J = 8.2 Hz), 7.16 (1H, t, J = 8.2 Hz), 7.75 (1H, s), 9.11 (1H, br), 9.26 (1H, br), 9.92 (1H, s).

Example 22-3



With the use of the starting compound 1G and tert-butyl 4-formyl-piperidine-1-carboxylic acid and other materials, 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(4-piperidinyl)-3,4-dihydro-1H-pyrido[2,3-d]pyrimidin-2-one hydrochloride was prepared in a similar manner as that of Example 22-1.

Molecular weight: 430.94

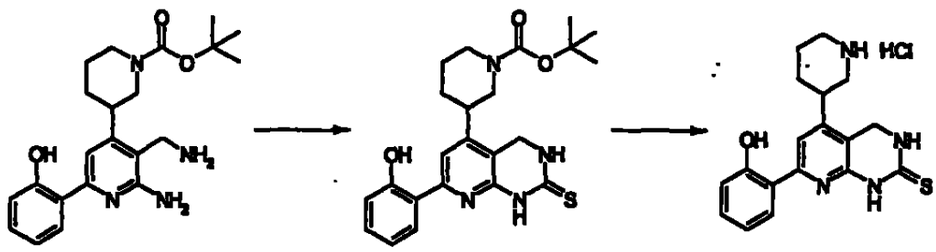
Mass spectrometry: 395 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.32 (2H, d, J = 4.5 Hz), 0.57 (2H, d, J = 1.7 Hz), 1.33 – 1.38 (1H, m), 1.80 – 1.91 (4H, m), 2.96 – 3.05 (3H, m), 3.34 – 3.39 (3H, m), 4.47 (2H, s), 6.51 (2H, dd, J = 3.8, 8.3 Hz), 7.15 (1H, t, J = 7.9 Hz), 7.24 (1H, s), 7.74 (1H,s), 9.86 (1H, s).

Example 22-4



With the use of tert-butyl 3-[2-amino-3-(aminomethyl)-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate obtained in the step (2) of Example 22-1, 7-(2-hydroxyphenyl)-5-(3-piperidinyl)-3,4-dihydro-1H-pyrido[2,3-d]pyrimidine-2-thione hydrochloride was prepared in a similar manner as that of Example 22-1 or 22-2.

Molecular weight: 447.00

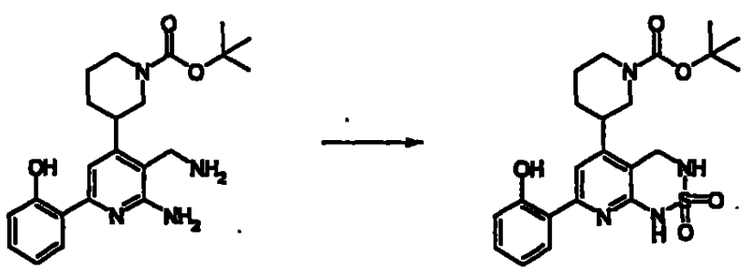
Mass spectrometry: 411 $(M+H)^+$

In vitro activity grade:

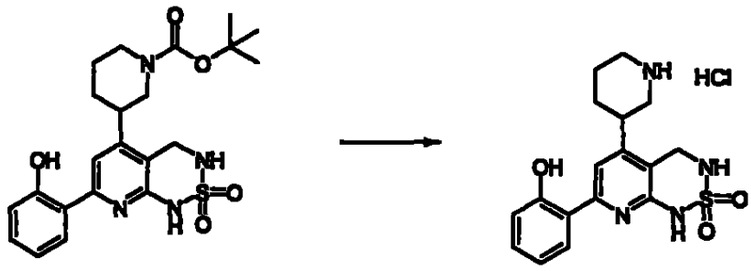
Cellular activity grade: (A549)-

^{1}H-NMR (500 mHz, DMSO-d6): 0.33 – 0.36 (2H, m), 0.57 – 0.59 (2H, m), 1.28 (1H, m), 1.72 – 1.81 (2H, m), 1.89 – 1.90 (2H, m), 2.82 – 2.89 (2H, m), 3.00 (1H, m), 3.27 – 3.34 (2H, m), 3.82 – 3.85 (2H, m), 4.54 – 4.56 (2H, m), 6.52 (2H, d, J = 8.2 Hz), 7.16 (1H, t, J = 8.2 Hz), 7.83 (1H, s), 8.73 (1H, br), 9.08 (2H, br), 11.13 (1H, s).

Example 22-5



A mixture of tert-butyl 3-[2-amino-3-(aminomethyl)-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.060 g, 0.151 mmol), which was obtained in the step (2) of Example 22-1, sulfamine (0.022 g, 0.226 mmol) and pyridine (2.0 mL) was stirred at reflux overnight. After cooled to room temperature, the mixture was partitioned between ethyl acetate and water. The separated organic phase was washed with 0.5N HCl solution, water and brine successively, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane: ethyl acetate, 1: 1) to give tert-butyl 3-[7-(2-hydroxyphenyl)-2,2-dioxido-3,4-dihydro-1H-pyrido[2,3-c][1,2,6]thiadiazin-5-yl]-1-piperidinecarboxylate as a pale yellow foam (0.059 g, yield; 85%).



Then the tert-butyl carbamate was treated in a similar manner as that of the step (3) of Example 1-1 to give 2-[2,2-dioxido-5-(3-piperidinyl)-3,4-dihydro-1H-pyrido-[2,3-c][1,2,6]thiadiazin-7-yl]phenol hydrochloride.

Molecular weight: 396,90

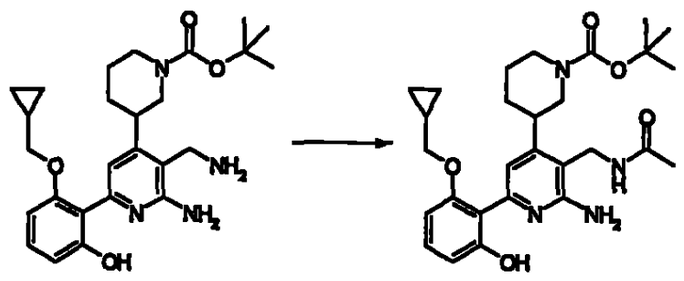
Mass spectrometry: 361 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-B

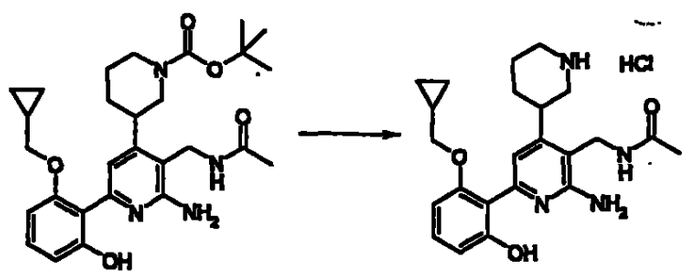
^{1}H-NMR'(500 MHz, DMSO-d6): 1.82 – 1.91 (4H, m), 2.86 – 2.93 (1H, m), 3.18 – 3.36 (4H, m), 4.52 (2H, s), 6.90 – 6.93 (2H, m), 7.30 (1H, dt, J = 1.6, 8.5 Hz), 7.65 (1H, br s), 8.00 (1H, d, J = 7.6 Hz), 8.97 (1H, br), 9.32 (1H, br).

Example 23-1



(1) With the use of the starting compounds 1G, 2B,and similar processes as those of the step (1) and (2) of Example 22-1, tert-butyl 3-{2-amino-3-(aminomethyl)-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-pyridinyl}-1-piperidinecarboxylate was prepared.

(2) To a cold (0 °C) solution of tert-butyl 3-{2-amino-3-(aminomethyl)-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-pyridinyl}-1-piperidinecarboxylate (1.9 g, 4.055 mmol) and triethylamine (1.13 mL, 8.109 mmol) in tetrahydrofuran (40.0 mL) was added acetic anhydride (0.457 mL, 4.865 mmol). The mixture was stirred at 0 °C for 4 hrs. After quenched by water, the mixture was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue (yellow solid) was purified by recrystallization from ethyl acetate/diisopropyl ether to give tert-butyl 3-{3-(acetylamino-methyl)-2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-pyridinyl}-1-piperidinecarboxylate (1.13 g, yield; 55%).



(3) The tert-butyl carbamate was treated in a similar manner as that of the step (3) of Example 1-1 to give N-{[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methyl}acetamide hydrochoride.

Molecular weight: 446.98

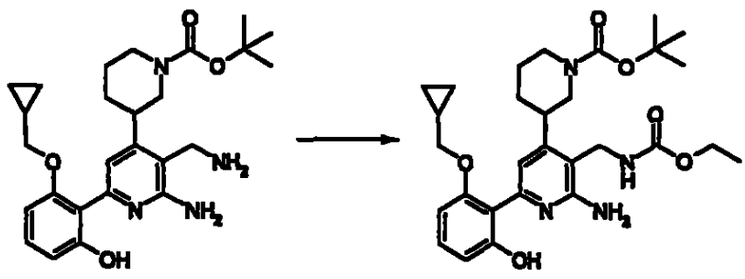
Mass spectrometry: 411 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

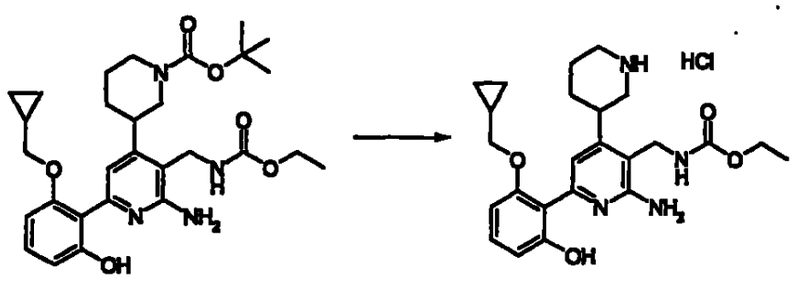
^{1}H-NMR (500 MHz, DMSO-d6): 0.28 – 0.30 (2H, m), 0.47 – 0.50 (2H, m), 1.13 (1H, m), 1.85 – 1.90 (4H, m), 1.93 (3H, s), 2.88 (1H, m), 3.06 (1H, m), 3.23 (1H, m), 3.33 (1H, m), 3.73 (1H, m), 3.80 (2H, m), 4.32 – 4.39 (2H, dd, J = 5.6, 15.5 Hz), 6.58 (1H, d, J = 8.5 Hz), 6.65 (1H, d, J = 8.2 Hz), 7.09 (1H, s), 7.27 (1H, t, J = 8.2 Hz), 7.80 (1H, br), 8.98 (2H, br), 9.29 (1H, br), 13.63 (1H, br).

Example 23-2



(1) To a cold (0 °C) solution of tert-butyl 3-{2-amino-3-(aminomethyl)-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-pyridinyl}-1-piperidinecarboxylate (0.300 g, 0.640 mmol), which was obtained in the step (1) of Example 23-1, and triethylamine (0.067 mL, 0.704 mmol) in tetrahydrofuran (30 mL) was added ethyl chloroformate (0.134 mL, 0.960 mmol) under an argon atmosphere. The mixture was allowed to warm to room temperature, and the stirring was continued for 4 hrs. After quenched by water, the mixture was extracted with ethyl acetate. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered, then concentrated under reduced pressure. The resulting residue was purified by column chromato-

graphy on Silica-gel (hexane / ethyl acetate = 1/1) to give tert-butyl 3-(2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-{[(ethoxycarbonyl)amino]methyl}-4-pyridinyl)-1-piperidinecarboxylate as a pale yellow form (0.246 g, yield; 71%).



(2) Then the tert-butyl carbamate was treated in a similar manner as that of the step (3) of Example 1-1 to give ethyl [2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methylcarbamate hydrochloride.

Molecular weight: 477.01

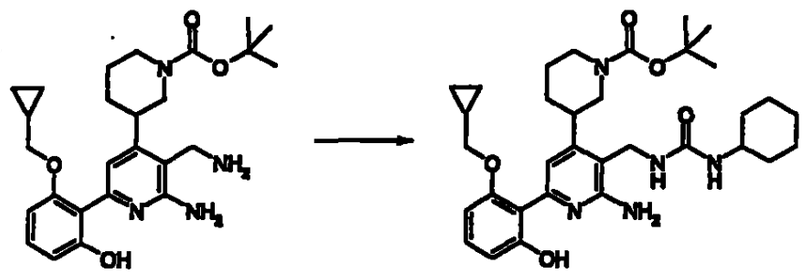
Mass spectrometry: 441 $(M+H)^+$

In vitro activity grade: A

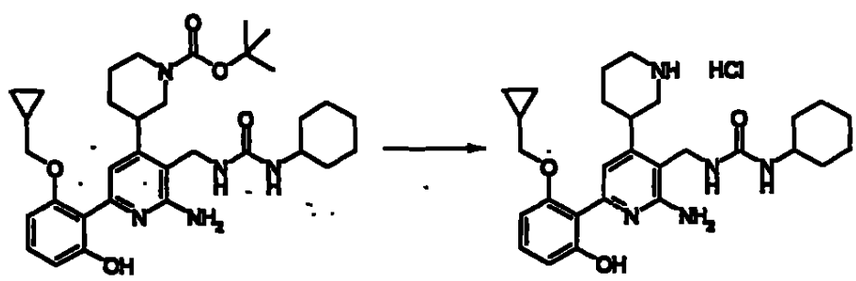
Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.28 – 0.30 (2H, m), 0.48 – 0.51 (2H, m), 1.17 (3H, t, J = 7.1 Hz), 1.22 (1H, m), 1.82 – 1.89 (5H, m), 2.88 (1H, m), 3.03 (1H, m), 3.25 (1H, m), 3.69 (1H, m), 3.84 (2H, m), 4.03 (2H, q, J = 6.9 Hz), 4.28 (2H, dd, J = 5.4, 15.1 Hz), 6.59 (1H, d, J = 8.2 Hz), 6.65 (1H, d, J = 8.2 Hz), 7.11 (1H, s), 7.27 (1H, t, J = 8.2 Hz), 7.64 (1H, s), 7.86 (1H, s), 8.80 (1H, s), 9.27 (1H, s).

Example 23-3



(1) To a solution of tert-butyl 3-{2-amino-3-aminomethyl}-6-[2-(cyclopropyl-methoxy)-6-hydroxyphenyl]-4-pyridinyl}-1-piperidinecarboxylate (0.150 g, 0.320 mmol), which was obtained in the step (1) of Example 23-1, in tetrahydrofuran (10.0 mL) was added cyclohexyl isocyanate (0.044 g, 0.352 mmol). The mixture was stirred at room temperature for 1.5hrs and concentrated under reduced preasure. The resulting residue was purified by preparative TLC (ethyl acetate) to give tert-butyl 3-[2-amino-3[(3-cyclohexyl-ureido)-methyl]-6-[2-(cyclopropylmethoxy)-6-hydroxy-phenyl]-4-pyridinyl}-1-piperidinecarboxylate as a yellow form (0.113 g, yield; 60%).



(2) Then the tert-butyl carbamate was treated in a similar manner as that of the step (3) of Example 1-1 to give N-{[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxy-phenyl]-4-(3-piperidinyl)-3-pyridinyl]methyl}-N'-cyclohexylurea hydrochloride.

Molecular weight: 530.12

Mass spectrometry: 494 $(M+H)^+$

In vitro activity grade: A

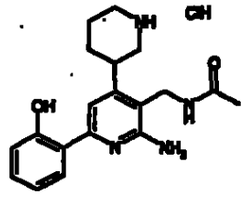
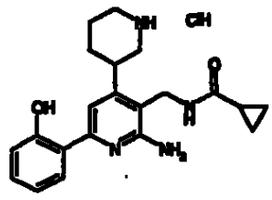
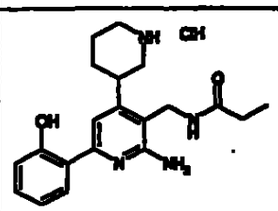
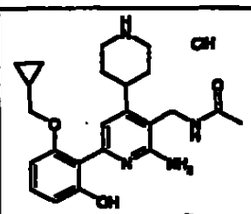
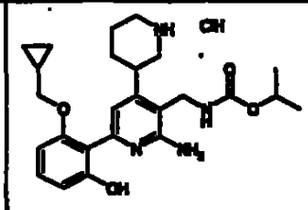
Cellular activity grade: (A549)-A

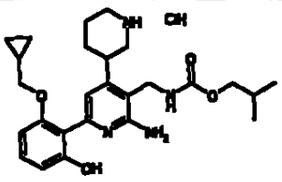
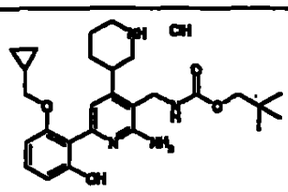
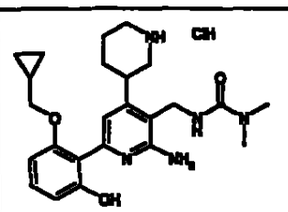
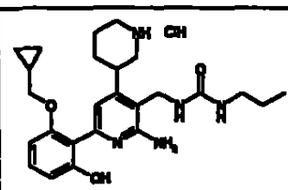
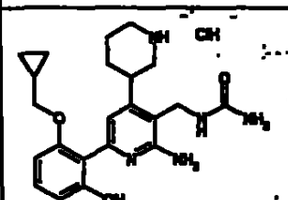
^{1}H-NMR (500 MHz, DMSO-d6): 0.27 – 0.28 (2H, m), 0.47 – 0.49 (2H, m), 1.10 - 1.14 (4H, m), 1.22 – 1.27 (3H, m), 1.51 (1H, m), 1.62 – 1.65 (2H, m), 1.73 – 1.74 (3H, m), 1.83 – 1.89 (5H, m), 2.88 (1H, m), 3.01 (1H, m), 3.72 (1H, m), 3.78 – 3.85 (2H, m), 4.29 – 4.32 (2H, m), 6.59 (1H, d, J = 8.5 Hz), 6.66 (1H, d, J = 8.2 Hz), 7.05 (1H, s), 7.27 (1H, t, J = 8.2 Hz), 8.98 (1H, s), 9.25 (1H, s), 10.3 (1H, s), 13.5 (1H,s).

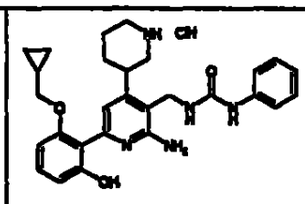
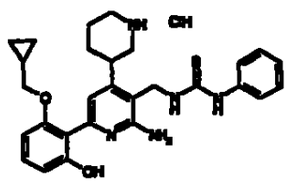
Examples 23-4 to 23-15

According to the similar synthetic procedure of Examples 23-1 to 23-3, compounds shown in Table 6 were prepared.

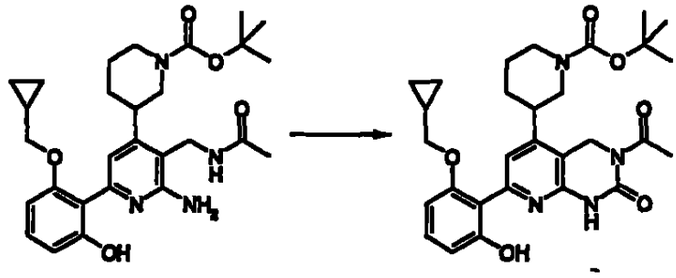
Table 6

Ex. No	Structure	Mol weight	Mass	In vitro	A549	NMR
23-04		376.89	341	A	A	(500 MHz, DMSO-d6): 1.80 - 1.95 (4H, m), 2.90 - 2.95 (1H, m), 3.13 - 3.34 (2H, m), 4.26 (1H, dd, J = 5.8, 15.2 Hz), 4.34 (1H, dd, J = 5.8, 15.2 Hz), 6.95 (1H, t, J = 7.3 Hz), 6.96 (1H, d, J = 8.2 Hz), 7.22 (1H, s), 7.35 (1H, t, J = 8.2 Hz), 7.87 (1H, br s), 8.61 (1H, br), 8.93 (1H, br), 9.26 (1H, br), 13.66 (1H, br).
23-05		402.93	367	A	A	(500 MHz, DMSO-d6): 0.78 (4H, m), 1.88 (1H, m), 1.88 (4H, m), 1.99 (1H, m), 3.05 (2H, dd, J = 11. 4, 23.9 Hz), 3.38 (2H, m), 3.49 (1H, m), 4.34 (2H, ddd, J = 6.0, 13.5, 44.4 Hz), 6.94 (1H, t, J = 7.6 Hz), 7.00 (1H, d, J = 8.2 Hz), 7.23 (1h, S), 7.35 (1H, t, J = 8.2 Hz), 7.70 (1H, br), 8.90 (1H, br), 9.02 (1H, br), 9.21 (1H, br), 13.7 (1H, br).
23-06		390.92	355	B	B	(500 MHz, DMSO-d6): 1.03 (3H, t, J = 7.6 Hz), 1.85 (2H, d, J = 13.3Hz), 1.99 (1H, m), 2.18 (2H, q, J = 7.6 Hz), 3.05 (2H, dd, J = 11. 4, 23.9 Hz), 3.38 (2H, m), 3.49 (1H, m), 4.33 (2H, d, J = 6.0 Hz), 6.97 (2H, t, J = 7.9 Hz), 7.07 (1H, m), 7.37 (1H, t, J = 7.9 Hz), 7.56 (1H, br s), 7.88 (1H, br), 8.75 (1H, br), 8.96 (1H, m), 13.6 (1H, br).
23-07		446.98	411	A	A	(500 MHz, DMSO-d6): 0.28 - 0.31 (2H, m), 0.47 - 0.50 (2H, m), 1.18 (1H, m), 1.85 - 1.91 (3H, m), 1.92 (3H, s), 1.94 - 2.00 (2H, m), 3.04 - 3.09 (2H, m), 3.49 - 3.57 (2H, m), 3.83 (2H, d, J = 6.9 Hz), 4.35 (2H, d, J = 5.7 Hz), 6.60 (1H, d, J = 8.5 Hz), 6.68 (1H, d, J = 8.2 Hz), 6.83 (1H, m), 7.27 (1H, dd, J = 8.2, 8.5 Hz), 7.84 (1H, br s), 8.96 (3H, m), 10.4 (1H, br s), 13.6 (1H, br s).
23-08		491.04	455	A	A	(300 MHz, DMSO-d6): 0.23 - 0.35 (2H, m), 0.41 - 0.57 (2H, m), 1.19 (6H, d, J = 6.4 Hz), 1.06 - 1.26 (1H, m), 1.70 - 1.96 (4H, m), 2.76 - 3.15 (2H, m), 3.15 - 3.60 (2H, m), 3.60 - 3.75 (1H, m), 3.75 - 3.90 (2H, m), 4.15 - 4.45 (2H, m), 4.70 - 4.90 (1H, m), 6.59 (1H, d, J = 8.3 Hz), 6.66 (1H, d, J = 8.3 Hz), 7.11 (1H, br s), 7.27 (1H, t, J = 8.3 Hz), 7.81 (1H, br), 7.80 (1H, br s), 8.85 - 8.95 (1H, m), 9.15 - 9.40 (1H, m), 10.38 (1H, br), 13.64 (1H, br).

23-09		505.08	469	A	A	(300 MHz, DMSO-d6): 0.22 - 0.35 (2H, m), 0.41 - 0.56 (2H, m), 0.88 (6H, d, J = 6.8 Hz), 1.02 - 1.25 (1H, m), 1.70 - 2.00 (5H, m), 2.75 - 3.15 (2H, m), 3.15 - 3.85 (2H, m), 3.85 - 3.97 (5H, m), 4.15 - 4.44 (2H, m), 6.59 (1H, d, J = 8.3 Hz), 6.67 (1H, d, J = 8.3 Hz), 7.10 (1H, br s), 7.27 (1H, t, J = 8.3 Hz), 7.69 (1H, br), 7.92 (1H, br s), 8.94 (1H, br), 9.41 (1H, br), 10.41 (1H, br), 13.68 (1H, br).
23-10		519.09	483	A	A	(300 MHz, DMSO-d6): 0.24 - 0.35 (2H, m), 0.40 - 0.57 (2H, m), 0.89 (9H, s), 1.06 - 1.25 (1H, m), 1.70 - 2.00 (4H, m), 2.75 - 3.15 (2H, m), 3.15 - 3.50 (2H, m), 3.72 (2H, s), 3.67 - 3.90 (3H, m), 4.24 (1H, dd, J = 5.7, 15.5 Hz), 4.37 (1H, dd, J = 5.7, 15.5 Hz), 6.58 (1H, d, J = 8.3 Hz), 6.67 (1H, d, J = 8.3 Hz), 7.11 (1H, br s), 7.26 (1H, t, J = 8.3 Hz), 7.67 (1H, br), 7.91 (1H, br s), 8.95 (1H, br), 9.39 (1H, br), 10.39 (1H, br), 13.66 (1H, br).
23-11		476.02	440	A	A	(500 MHz, DMSO-d6): 0.28 - 0.29 (2H, m), 0.47 - 0.49 (2H, m), 1.13 (1H, m), 1.85 - 1.90 (5H, m), 2.86 (6H, s), 3.01 (1H, m), 3.25 - 3.27 (2H, m), 3.78 - 3.84 (2H, m), 3.98 (1H, m), 4.31 (2H, d, J = 5.0 Hz), 6.59 (1H, d, J = 7.9 Hz), 6.64 (1H, d, J = 7.0 Hz), 7.04 (1H, s), 7.27 (1H, t, J = 7.5 Hz), 8.00 (1H, s), 9.09 (2H, s), 10.35 (1H, s).
23-12		490.05	454	A	A	(500 MHz, DMSO-d6): 0.28 - 0.29 (2H, m), 0.47 - 0.49 (2H, m), 0.82 (3H, t, J = 7.4 Hz), 1.13 (1H, m), 1.37 - 1.42 (2H, m), 1.84 - 1.89 (4H, m), 2.90 (1H, m), 3.00 - 3.01 (3H, m), 3.02 - 3.05 (2H, m), 3.78 - 3.85 (3H, m), 4.30 - 4.36 (2H, m), 6.58 (1H, d, J = 8.5 Hz), 6.67 (1H, d, J = 8.2 Hz), 7.04 (1H, s), 7.18 (1H, s), 7.26 (1H, t, J = 8.2 Hz), 8.06 (2H, s), 9.05 (1H, s), 9.39 (1H, s), 10.39 (1H, s), 13.80 (1H, s).
23-13		447.97	412	A	A	(500 MHz, DMSO-d6): 0.28 - 0.29 (2H, q), 0.47-0.49 (2H, q), 1.14(1H, br s), 1.85 - 1.89 (4H, m), 2.88 (1H, m), 3.02 (1H, m), 3.25 - 3.33 (2H, m), 3.71 (1H, m), 3.78 - 3.86 (2H, m), 4.28 - 4.34 (2H, m), 5.95 (1H, br), 6.58 (1H, d, J = 8.2 Hz), 6.67 (1H, d, J = 8.2 Hz), 7.04 (1H, s), 7.26 (1H, t, J = 8.2 Hz), 8.09 (2H, br), 8.04 (1H, br), 9.40 (1H, br), 10.40 (1H, br), 13.35 (1H, s).

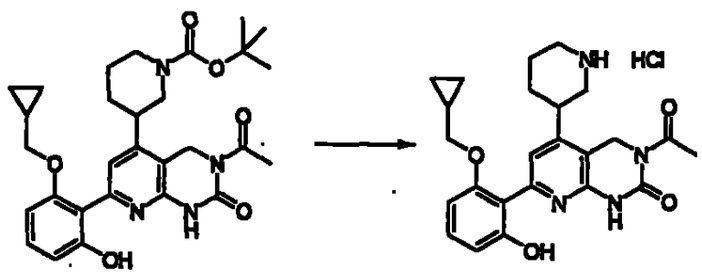
23-14		524.07	488	A	A	(500 MHz, DMSO-d6): 0.27 - 0.28 (2H, m), 0.47-0.48 (2H, m), 1.12 (1H, m), 1.88 - 1.90 (4H, m), 2.89 - 3.09 (2H, m), 3.35 - 3.38 (3H, m), 3.70 - 3.85 (2H, m), 4.38 - 4.45 (2H, m), 6.58 (1H, d, J = 8.8 Hz), 6.66 (1H, d, J = 8.2 Hz), 6.91 - 7.00 (1H, m), 7.10 (1H, s), 7.25 (3H, t, J = 7.8 Hz), 7.40 (2H, d, J = 7.8 Hz), 7.82 (1H, s), 8.85 (1H, s), 9.28 (2H, s), 10.37 (1H, s).
23-15		540.13	504	A	A	(500 MHz, DMSO-d6): 0.29 - 0.31 (2H, m), 0.48 - 0.50 (2H, m), 1.14 (1H, m), 1.81 - 1.92 (4H, m), 2.89 (1H, m), 3.08 (1H, m), 3.59 - 3.60 (2H, m), 3.81 (1H, m), 3.82 (2H, dd, J = 6.2, 10.1 Hz), 4.85 (2H, dd, J = 5.4, 15.8 Hz), 6.59 (1H, d, J = 8.5 Hz), 6.85 (1H, d, J = 8.2 Hz), 7.12 (1H, t, J = 7.5 Hz), 7.14 (1H, s), 7.27 (1H, t, J = 8.5 Hz), 7.32 (2H, t, J = 7.8 Hz), 7.49 (2H, d, J = 7.8 Hz), 7.70 (1H, br), 8.71 (2H, br), 9.25 (1H, br), 10.23 (1H, br).

Example 24-1



To a cold (0 °C) solution of tert-butyl 3-{3-[(acetylamino)methyl]-2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-pyridinyl}-1-piperidinecarboxylate (1.134 g, 2.220 mmol), which was obtained in the step (1) of Example 23-1, and triethylamine (1.871 mL, 13.320 mmol) in tetrahydrofuran (150 mL) was added dropwise a solution of triphosgene (0.652 g, 2.220 mmol) in tetrahydrofuran (150 mL) under an argon atmosphere. After stirred overnight, the reaction mixture was quenched by water. The mixture was extracted with ethyl acetate. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue (yellow solid) was purified by column

chromatography on silica gel (hexane / ethyl acetate =1/1) to give tert-butyl 3-{3-acetyl-7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidin-5-yl}-1-piperidinecarboxylate as a white form (0.569 g, yield; 48%).



Then the tert-butyl carbamate was treated in a similar manner as that of the step (3) of Example 1-1 to give 3-acetyl-7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-one hydrochloride.

Molecular weight: 472.98

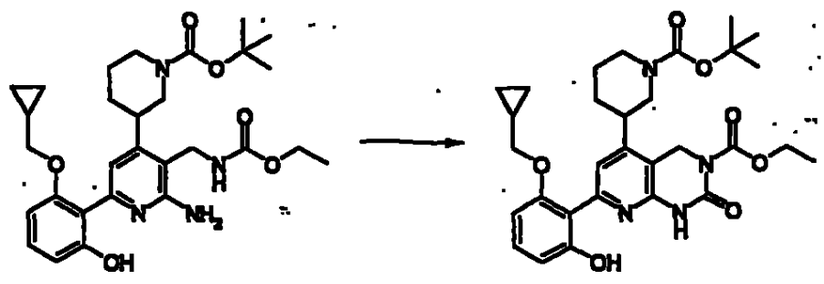
Mass spectrometry: 437 $(M+H)^+$

In vitro activity grade: A

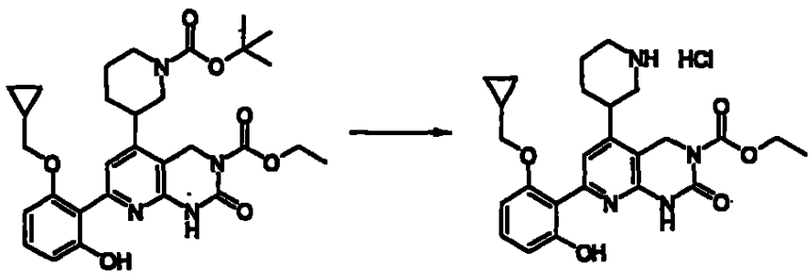
Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.31 – 0.34 (2H, m), 0.56 – 0.59 (2H, m), 1.26 (1H, m), 1.74-1.79 (2H, m), 1.81 – 1.93 (2H, m), 2.47 (H, s), 2.85 – 2.98 (2H, m), 3.21 – 3.34 (3H, m), 3.81 – 3.86 (2H, m), 4.93 (2H, s), 6.52 (2H, d, J = 8.2 Hz), 7.16 (1H, t, J = 8.2 Hz), 7.78 (1H, s), 8.79 (1H, br), 9.30 (1H, br), 10.95 (1H, s).

Example 24-2



To a cooled (0 °C) solution of tert-butyl 3-(2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-{[(ethoxycarbonyl)amino]methyl}-4-pyridinyl)-1-piperidine-carboxylate (0.145 g, 0.268 mmol), which was obtained in the step (1) of Example 23-2, and triethylamine (0.226 mL, 1.609 mmol) in tetrahydrofuran(30 mL) was added triphosgene (0.079 g, 0.268 mmol) in tetrahydrofuran (10 mL) under an argon atmosphere. The mixture was allowed to warm to room temperature, and the stirring was continued for 3 hrs. After quenched by water, the mixture was extracted with ethyl acetate. The separated organic phase was washed with water and brine successively, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (hexane / ethyl acetate = 1/1) to give ethyl 5-[1-(tert-butoxycarbonyl)-3-piperidinyl]-7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxylate as a white solid (0.904 g, yield; 60%).



Then the tert-butyl ester was treated in a similar manner as that of the step (3) of Example 1-1 to give ethyl 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxylate hydrochloride.

Molecular weight: 503.00

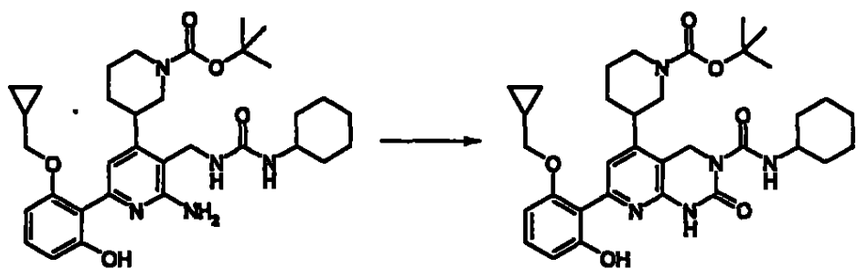
Mass spectrometry: 467 $(M+H)^+$

In vitro activity grade: A

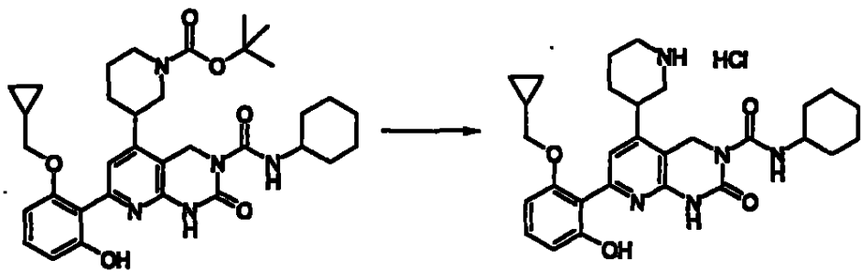
Cellular activity grade: (A549)-A

^{1}H-NMR(500 MHz, DMSO-d6): 0.31 – 0.34 (2H, m), 0.55 – 0.59 (2H, m), 1.26 – 1.28 (1H, br s), 1.27 (3H, t, J = 7.3 Hz), 1.74 – 1.85 (3H, m), 2.85 – 2.95 (2H, m), 3.22 – 3.25 (1H, m), 3.30 – 3.32 (2H, m), 3.79 – 3.87 (1H, m), 4.22 – 4.25 (2H, m), 4.91 (2H, s), 6.52 (2H, d, J = 8.2 Hz), 7.16 (1H, t, J = 8.2 Hz), 7.78 (1H, s), 8.91 (1H, br s), 9.29 (1H, br), 10.86 (1H, s).

Example 24-3



To a cooled (0 °C) solution of tert-butyl 3-{2-amino-3-({[(cyclohexylamino)-carbonyl]amino}methyl)-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-pyridinyl}-1-piperidinecarboxylate(0.039 g, 0.065 mmol), which was obtained in the step (1) of Example 23-3, and triethylamine (15.0 mL, 0.389 mmol) in tetrahydrofuran (10.0 mL) was added dropwise a solution of triphosgene (0.019 g, 0.065 mmol) in tetrahydrofuran (5.0 mL) under an argon atmosphere. The mixture was stirred at 0 °C for 2 hrs. After quenched by water, the mixture was extracted with ethyl acetate. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue (white solid) was triturated with diisopropyl ether, collected by filtration, washed with diisopropyl ether, and dried under reduced pressure to give tert-butyl 3-{3-[(cyclohexylamino)carbonyl]-7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-5-yl}-1-piperidinecarboxylate (0.021 g, yield; 52%).



Then the tert-butyl carbamate was treated in a similar manner as that of the step (3) of Example 1-1 to give N-cyclohexyl-7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxamide hydrochloride.

Molecular weight: 556.11

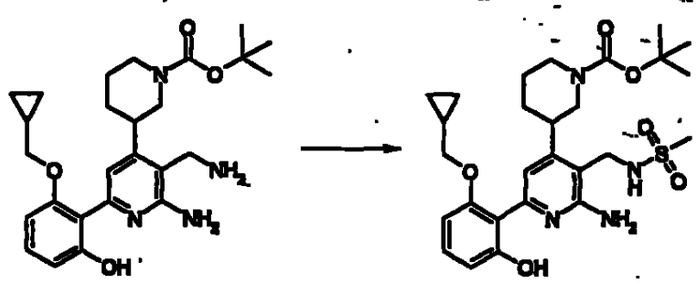
Mass spectrometry: 520 $(M + H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

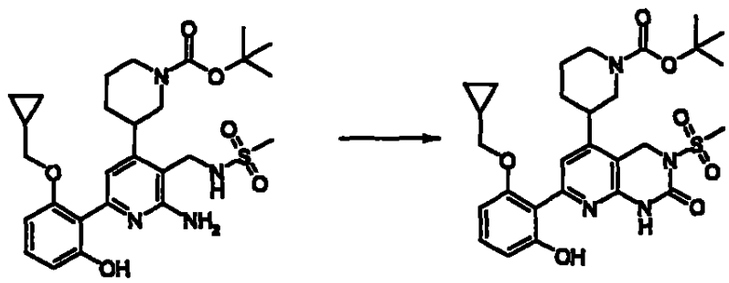
^{1}H-NMR (500 MHz, DMSO-d6): 0.32 – 0.34 (2H, m), 0.55 – 0.59 (2H, m), 1.24 – 1.35 (8H, m), 1.64 (1H, m), 1.75 – 1.78 (2H, m), 1.82 – 1.84 (4H, m), 1.91 – 1.93 (2H, m), 2.86 (1H, m), 2.96 (1H, m), 3.16 (1H, m), 3.62 (1H, m), 3.63 – 3.88 (2H, dd, J = 6.9, 9.8 Hz), 4.98 (2H, s), 6.52 (2H, d, J = 8.2 Hz), 7.16 (1H, t, J = 8.5 Hz), 7.77 (1H, s), 9.00 (1H, s), 10.82 (1H, s), 11.73 (1H, s).

Example 24-4

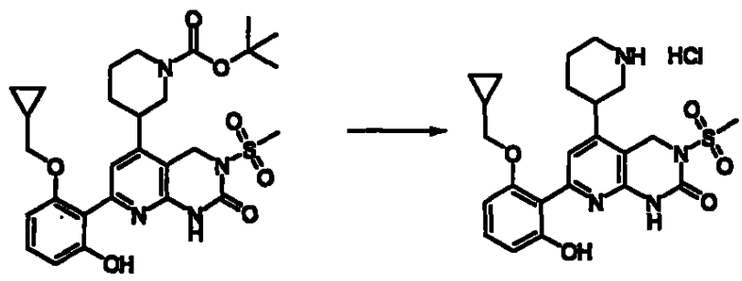


To a cold (0 °C) solution of tert-butyl 3-{2-amino-3-(aminomethyl)-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-pyridinyl}-1-piperidinecarboxylate (0.150 g,

0.320 mmol), which was obtained in the step (1) of Example 23-1, and triethylamine (0.067 mL, 0.480 mmol) in tetrahydrofuran (9 mL) was added methanesulfonyl chloride (0.027 mL, 0.352 mmol) under an argon atmosphere. The stirring was continued at 0 °C for 1 hr. After quenched by water, the mixture was extracted with ethyl acetate. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting yellow residue was purified by recrystallization from diisopropyl ether / dichloromethane to give tert-butyl 3-(2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-{[(methylsulfonyl)amino]methyl}-4-pyridinyl)-1-piperidinecarboxylate as a yellow solid (0.097 g, yield; 56%).



To a cooled (0 °C) solution of tert-butyl 3-(2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-{[(methylsulfonyl)amino]methyl}-4-pyridinyl)-1-piperidinecarboxylate (0.050 g, 0.091 mmol) and triethylamine (0.077 mL, 0.549 mmol) in tetrahydrofuran (15 mL) was added to a solution of triphosgene (0.027 g, 0.091 mmol) in tetrahydrofuran(5 mL) under an argon atmosphere. The mixture was allowed to warm to room temperature, and the stirring was continued for 3 hrs under an argon atmosphere. After quenched by water, the mixture was extracted with ethy acetate. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting yellow solid was triturated with diisopropyl ether and collected by filtration to give tert-butyl 3-[7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-(methylsulfonyl)-2-oxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-5-yl]-1-piperidinecarboxylate as a yellow solid (0.028 g, yield; 55%).



Then the tert-butyl carbamate was treated in a similar manner as that of the step (3) of Example 1-1 to give 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-(methylsulfonyl)-5-(3-piperidinyl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-one hydrochloride.

Molecular weight: 509.03

Mass spectrometry: 473 $(M+H)^+$

In vitro activity grade: A

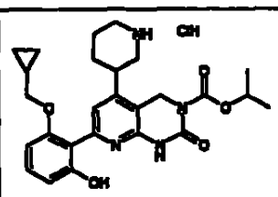
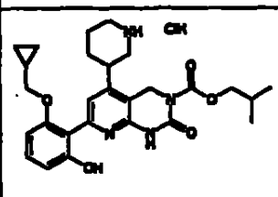
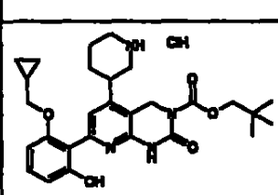
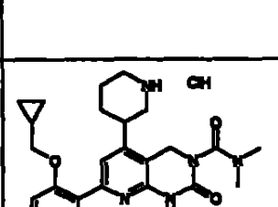
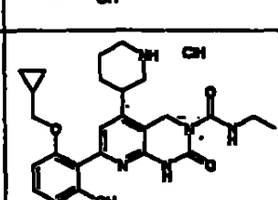
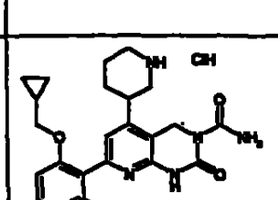
Cellular activity grade: (A549)-A

^{1}H-NMR '(500 MHz, DMSO-d6): 0.30 – 0.33 (2H, m), 0.54 – 0.58 (2H, m), 1.26 (1H, m), 1.73 – 1.78 (2H, m), 1.88 – 1.93 (2H, m), 2.88 (1H, m), 2.99 (1H, m), 3.13 (1H, m), 3.30 – 3.35 (2H, m), 3.50 (3H, s), 3.83 (2H, dd, J = 6.9, 7.2 Hz), 4.97 (2H, s), 6.53 (2H, d, J = 8.2 Hz), 7.17 (1H, t, J = 8.5 Hz), 7.75 (1H, s), 8.67 (1H, s), 9.11 (1H,s), 11.02 (1H, s).

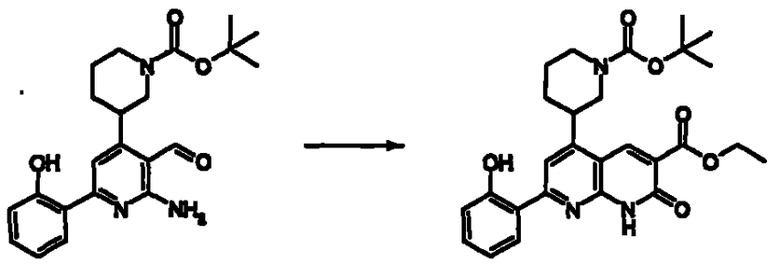
Examples 24-5 to 24-10

According to the similar synthetic procedure of Examples 24-1 to 24-4, compounds shown in Table 7 were prepared.

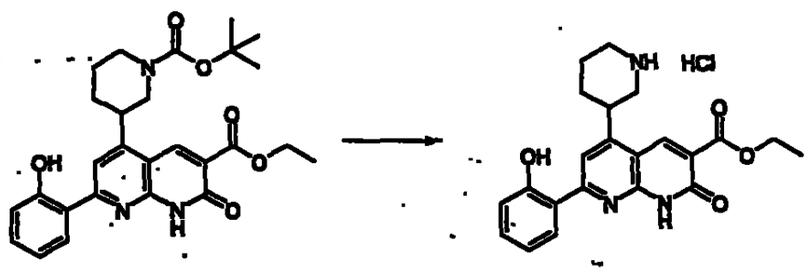
Table 7

Ex. No	Structure	Mol weight	Mass	In vitro	A549	EMS
24-05		517.03	481	A	A	(300 MHz, DMSO-d6): 0.25 - 0.38 (2H, m), 0.50 - 0.64 (2H, m), 1.29 (6H, d, J = 6.0 Hz), 1.20 - 1.32 (1H, m), 1.80 - 2.00 (4H, m), 2.75 - 3.05 (2H, m), 3.15 - 3.40 (3H, m), 3.75 - 3.92 (2H, m), 4.89 (2H, s), 4.90 - 5.04 (1H, m), 6.53 (2H, d, J = 8.3 Hz), 7.17 (1H, t, J = 8.3 Hz), 7.78 (1H, s), 8.92 (1H, br), 9.25 (1H, br), 10.82 (1H, s).
24-06		531.06	495	A	A	(300 MHz, DMSO-d6): 0.25 - 0.38 (2H, m), 0.51 - 0.64 (2H, m), 0.85 (6H, d, J = 6.4 Hz), 1.17 - 1.35 (1H, m), 1.83 - 2.05 (5H, m), 2.75 - 3.10 (2H, m), 3.10 - 3.45 (3H, m), 3.75 - 3.92 (2H, m), 3.99 (2H, d, J = 8.3 Hz), 4.88 (1H, d, J = 15.8 Hz), 4.95 (1H, d, J = 15.8 Hz), 6.53 (2H, d, J = 8.3 Hz), 7.17 (1H, t, J = 8.3 Hz), 7.78 (1H, br), 8.85 - 9.20 (1H, m), 9.20 - 9.75 (1H, m), 10.84 (1H, s).
24-07		545.08	509	A	A	(300 MHz, DMSO-d6): 0.25 - 0.37 (2H, m), 0.52 - 0.63 (2H, m), 0.97 (9H, s), 1.17 - 1.35 (1H, m), 1.80 - 2.00 (4H, m), 2.75 - 3.10 (2H, m), 3.10 - 3.40 (2H, m), 3.78 - 3.92 (3H, m), 3.80 (2H, s), 4.89 (1H, d, J = 15.8 Hz), 4.96 (1H, d, J = 15.8 Hz), 6.53 (2H, d, J = 8.3 Hz), 7.17 (1H, t, J = 8.3 Hz), 7.77 (1H, s), 8.85 - 9.05 (1H, m), 9.25 - 9.60 (1H, m), 10.83 (1H, s).
24-08		502.02	466	A	A	(500 MHz, DMSO-d6): 0.33 - 0.35 (2H, m), 0.56 - 0.58 (2H, m), 1.26 (1H, m), 1.76 - 1.80 (2H, m), 1.90 - 1.92 (2H, m), 2.84 - 2.91 (10H, m), 3.14 (1H, m), 3.83 - 3.85 (2H, m), 4.64 - 4.70 (2H, m), 6.51 - 6.54 (2H, m), 7.16 (1H, t, J = 8.2 Hz), 7.80 (1H, s), 8.47 (1H, s), 8.97 (1H, s), 10.68 (1H, s).
24-09		502.02	466			(500 MHz, DMSO-d6): 0.32 - 0.33 (2H, m), 0.55 - 0.56 (2H, m), 1.10 (3H, t, J = 7.3 Hz), 1.27 (1H, m), 1.72 - 1.91 (4H, m), 2.85 - 2.95 (2H, m), 3.18 (1H, m), 3.22 - 3.27 (2H, m), 3.31 - 3.33 (2H, m), 3.82 - 3.86 (2H, m), 4.99 (2H, s), 6.52 (2H, d, J = 8.2 Hz), 7.17 (1H, t, J = 8.2 Hz), 7.78 (1H, s), 8.96 (1H, br), 9.17 (1H, br), 10.84 (1H, s).
24-10		473.98	438	A	A	(300 MHz, DMSO-d6): 0.32 - 0.33 (2H, m), 0.56 - 0.58 (2H, m), 1.26 (1H, m), 1.73 - 1.85 (3H, m), 2.85 - 2.97 (3H, m), 3.19 - 3.34 (4H, m), 3.78 - 3.86 (2H, m), 4.98 (2H, s), 6.53 (2H, d, J = 7.9 Hz), 7.16 (1H, t, J = 8.3 Hz), 7.46 (1H, br), 7.78 (1H, s), 8.33 (1H, br), 8.87 (1H, br), 9.12 (1H, br), 10.80 (1H, s).

Example 25-1



To a suspension of tert-butyl 3-[2-amino-3-formyl-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.86 g, 2.16 mmol) in ethanol (25 mL) were added diethyl malonate (6.93 g, 43.27 mmol) and piperidine (2.14 mL, 21.64 mmol) and, and the mixture was heated at reflux overnight. The mixture was allowed to cool to room temperature, and then diluted with ethanol. The resulting precipitate was collected by filtration, washed with ethanol and dried under reduced pressure to give ethyl 5-[1-(tert-butoxycarbonyl)-3-piperidinyl]-7-(2-hydroxyphenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate as a yellow solid (0.752 g, yield; 71%).



Then the tert-butyl carbamate was treated in a similar manner as that of the step (3) of Example 1-1 to give ethyl 7-(2-hydroxyphenyl)-2-oxo-5-(3-piperidinyl)-1,2-dihydro-1,8-naphthyridine-3-carboxylate hydrochloride.

Molecular weight: 429.91

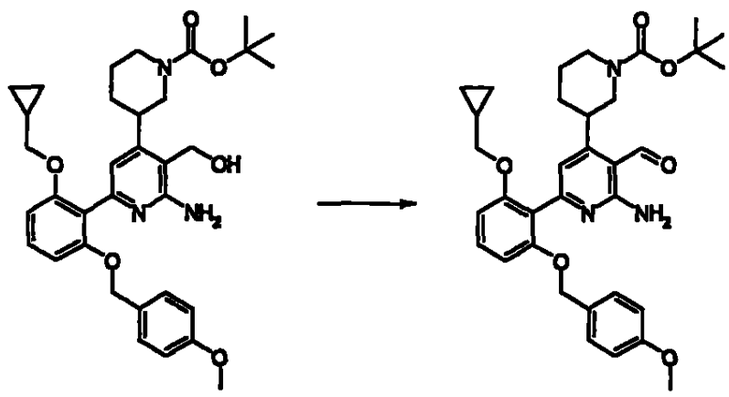
Mass spectrometry: 394 $(M+H)^+$

In vitro activity grade: A

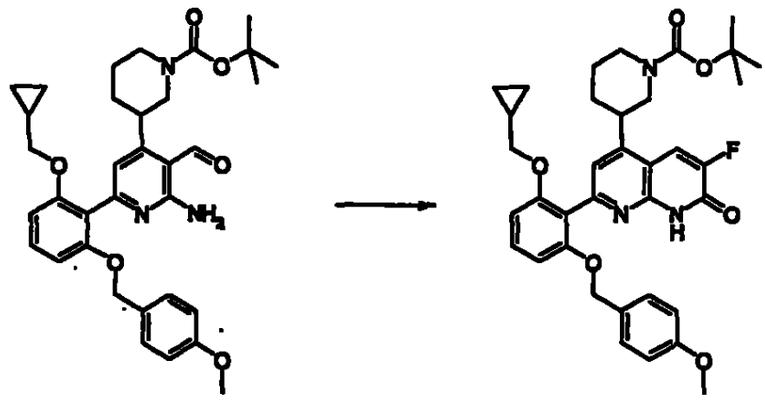
Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 1.34 (3H, t, J = 7.1 Hz), 1.89 – 2.07 (4H, m,), 2.92 – 3.00 (1H, m), 3.40 – 3.44 (1H, m, 3.77 (1H, br), 4.32 (2H, q, J = 7.1 Hz), 6.97 – 7.01 (2H, m), 7.41 (1H, t, J = 7.25 Hz), 8.01 (1H, s), 8.21 (1H, d, J = 7.25 Hz), 8.62 (1H, s), 8.83 (1H, br), 9.18 (1H, br), 12.69 (1H, s), 12.96 (1H, br s).

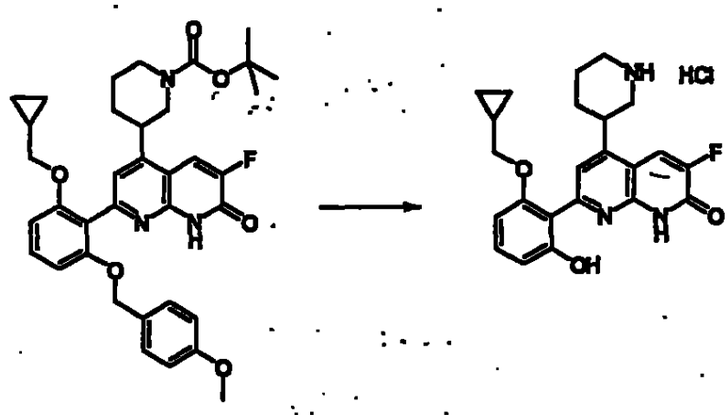
Example 25-2



(1) To a stirred solution of tert-butyl 3-[2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-(hydroxymethyl)-4-pyridinyl]-1-piperidine-carboxylate (1.100 g, 1.863 mmol), which was obtained in the step (2) of Example 17-1, in dichloromethane (50 mL) was added manganese dioxide (3.240 g, 37.261 mmol). The mixture was stirred at room temperature for 3 hrs and filtered on Celite®. The filtrate was concentrated under reduced pressure to give tert-butyl 3-(2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-formyl-4-pyridinyl)-1-piperidinecarboxylate (0.978 g, yield; 89%).



(2) To a stirred solution of tert-butyl 3-(2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-formyl-4-pyridinyl)-1-piperidinecarboxylate (0.500 g, 0.851 mmol), triethyl-2-fluoro-2-phosphonoacetate (0.350 mL, 1.701 mmol) and anhydrous lithium chloride (0.072 g, 1.701 mmol) in acetonitrile (20 mL) was added 1,8-diazabicyclo[5,4,0]undec-7-ene (0.250 mL, 1.701 mmol). The mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. The residue was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue (liquid) was purified by column chromatography on silica gel (hexane / ethyl acetate = 2/1-1/1) to give tert-butyl 3-(2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-6-fluoro-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1-piperidinecarboxylate as a form (0.261 g, 49%).



Then the *tert*-butyl carbamate was treated in a similar manner as that of the step (2) of Example 21-1 to give 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-fluoro-5-(3-piperidinyl)-1,8-naphthyridin-2(1H)-one hydrochloride.

Molecular weight: 445.93

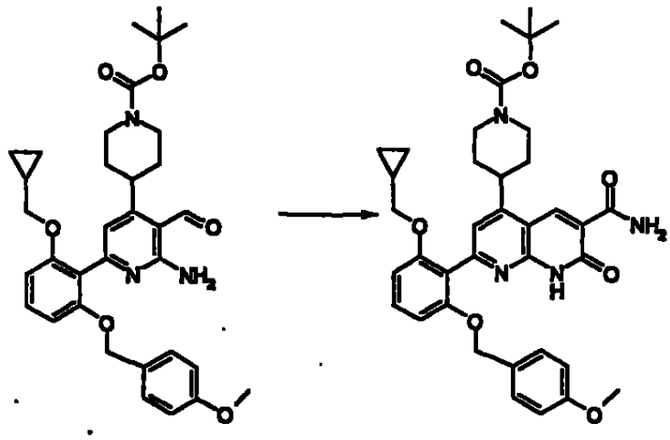
Mass spectrometry: 410 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

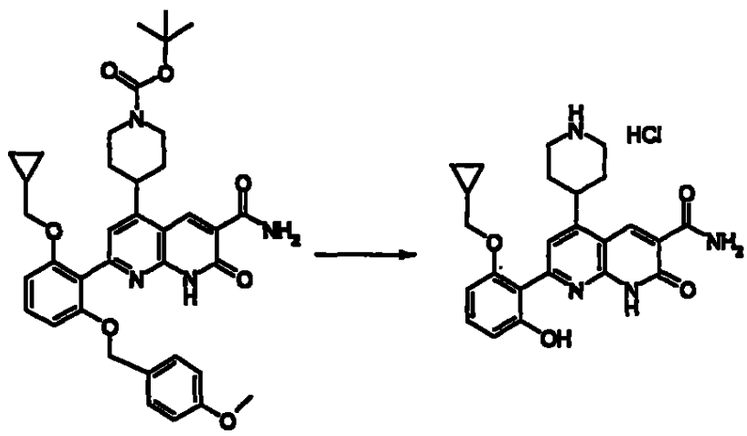
^{1}H-NMR (500 MHz, DMSO-d6): 0.32 (2H, m), 0.55 (2H, m), 1.25 (1H, m), 1.94 (4H, m), 2.95 (2H, m), 3.65 (1H, br), 6.58 (2H, d, J = 8.2 Hz), 7.23 (1H, t, J = 8.2 Hz), 7.97 (1H, s), 8.15 (1H, d, J = 11.4 Hz), 8.64 (1H, br), 9.01 (1H, br), 11.66 (1H, br), 13.02 (1H, d, J = 5.4 Hz).

Example 25-3



(1) With the use of the starting compound 1G and tert-butyl 4-formyl piperidine-1-carboxylic acid, tert-butyl 4-(2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-formyl-4-pyridinyl)-1-piperidinecarboxylate was prepared in a similar manner as that of the step (1) of Example 25-2. To a solution of tert-butyl 4-(2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-formyl-4-pyridinyl)-1-piperidinecarboxylate (0.400 g, 0.681 mmol) in ethyl alcohol (5.0 mL) was added ethyl malonate monoamine (1.780 g, 13.612 mmol) and piperidine

(0.580 g, 6.806 mmol). The mixture was refluxed 12hrs. The reaction mixture was extracted with ethyl acetate and water. The separated organic phase was washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue (liquid) was purified by column chromatography on silica gel (hexane / ethyl acetate = 1 / 1 and ethylacetate 100%) to give tert-butyl 4-(6-(aminocarbonyl)-2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1-piperidinecarboxylate as a yellow form. (0.455 g, yield; quant.)



(2) Then the tert-butyl carbamate was treated in a similar manner as that of the step (2) of Example 21-1 to give 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(4-piperidinyl)-1,2-dihydro-1,8-naphthyridine-3-carboxamide hydrochloride.

Molecular weight: 470.96

Mass spectrometry: 435 $(M+H)^+$

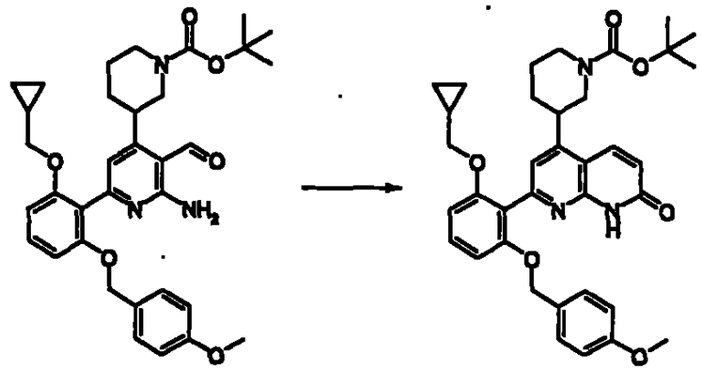
In vitro activity grade: A

Cellular activity grade: (A549)-B

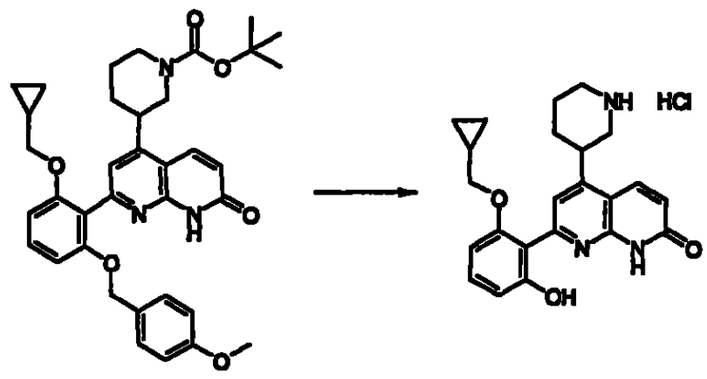
^{1}H-NMR(500 MHz, DMSO-d6): 0.32 (2H, d, J = 4.7 Hz), 0.57 (2H, d, J = 7.9 Hz), 1.32 – 1.35 (1H, m), 1.91 – 2.01 (5H, m), 3.23 – 3.26 (3H, m), 3.70 – 3.80 (2H, m), 3.90 (2H, d, J = 6.9 Hz), 6.59 (2H, dd, J = 1.7, 8.3 Hz), 7.26 (1H, t, J = 8.2 Hz), 7.87

(1H, d, J = 3.5 Hz), 8.01 (1H, s), 8.70 (1H, d, J = 12.3 Hz), 8.87 (1H, d, J = 10.7 Hz), 8.99 (1H, d, J = 3.4 Hz), 9.06 (1H, s), 13.05 (1H, s).

Example 25-4



(1) To a solution of ethyl (diphenoxyphosphoryl)acetate (1.090 g, 3.403 mmol) in THF (15 mL) were added 1,8-diazabicyclo[5,4,0]undec-7-ene (0.520 g, 3.403 mmol) and NaI (0.510 g, 3.403 mmol) followed by a solution of tert-butyl 3-(2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]-phenyl}-3-formyl-4-pyridinyl)-1-piperidinecarboxylate (1.000 g, 1.701 mmol), obtained in the step (1) of Example 25-2, in THF (5 mL). The mixture was stirred at 0 °C for 1.5 hrs and quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ethyl acetate, and the extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3:2 to 1:2) to give tert-butyl 3-(2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1-piperidinecarboxylate as an amorphous solid (0.276 g, 27%).



(2) To a stirred solution of tert-butyl 3-(2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1-piperidine-carboxylate (0.260 g, 0.425 mmol) in 1,4-dioxane (2 mL) was added 4 N HCl in dioxane (2 mL). The mixture was stirred at room temperature overnight, and diluted with ethyl acetate. The resulting precipitate was collected by filtration, washed with ethanol, and dried under reduced pressure to give 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-1,8-naphthyridin-2(1H)-one hydrochloride as a yellow solid (0.146 g, 80%).

Molecular weight: 427.93

Mass spectrometry: 392 $(M+H)^+$

In vitro activity grade: A

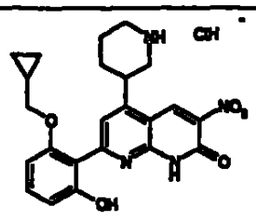
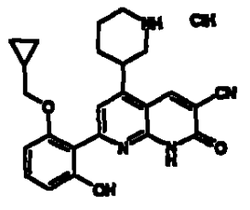
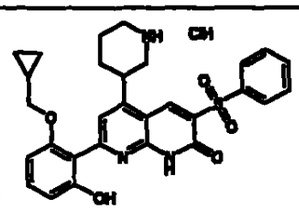
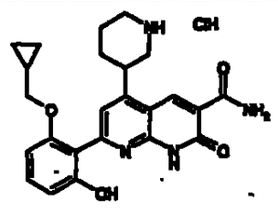
Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.34 (2H, m), 0.58 (2H, m), 1.28 (1H, m), 1.91 (4H, m), 2.89 (1H, br d, J = 6.6 Hz), 3.00 (1H, dd, J = 10.4, 12.3 Hz), 3.37 (2H, dd, J = 12.3, 12.6 Hz), 6.57 (2H, d, J = 8.2 Hz), 6.67 (1H, d, J = 9.8 Hz), 7.23 (1H, t, J = 8.2 Hz), 7.99 (1H, s), 8.21 (1H, d, J = 9.8 Hz), 9.02 (1H, br), 9.14 (1H, br), 12.45 (1H, br s).

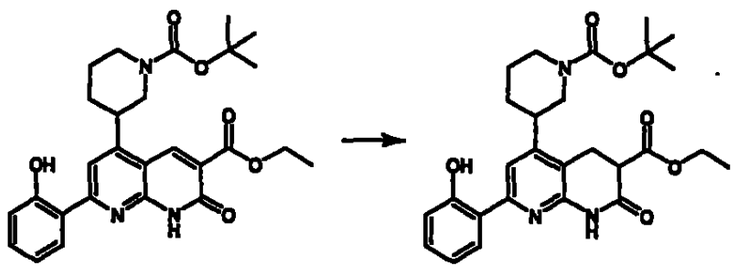
Examples 25-5 to 25-8

According to the similar synthetic procedure of Examples 25-1 to 25-4, compounds shown in Table 8 were prepared.

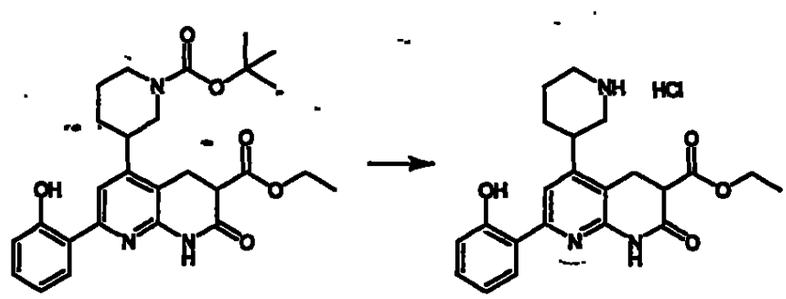
Table 8

Ex. No	Structure	Mol weight	Mass	In vitro	A549	NMR
25-06		472.93	437	A	B	(500 MHz, DMSO-d6): 0.33 (2H, dd, J = 4.7, 9.1 Hz), 0.56 (2H, m), 1.25 (1H, m), 1.94 (4H, m), 2.90 (1H, br), 3.00 (1H, t, J = 12.3 Hz), 3.40 (2H, br d, J = 12.3 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.27 (1H, t, J = 8.2 Hz), 8.03 (1H, s), 9.02 (1H, s), 11.57 (1H, s), 13.32 (1H, br).
25-08		452.94	417	A	A	(500 MHz, DMSO-d6): 0.32 (2H, dd, J = 4.7, 9.1 Hz), 0.57 (2H, m), 1.25 (1H, m), 1.93 (4H, m), 2.88 (1H, br d, J = 7.3 Hz), 2.97 (1H, dd, J = 11.4, 11.7 Hz), 3.39 (2H, t, J = 14.5 Hz), 6.58 (2H, d, J = 8.5 Hz), 7.26 (1H, t, J = 8.5 Hz), 8.00 (1H, s), 8.81 (1H, br), 9.01 (1H, s), 9.26 (1H, br), 11.66 (1H, s), 13.13 (1H, s).
25-07		566.10	532	A	A	(500 MHz, DMSO-d6): 0.32 (2H, m), 0.57 (2H, m), 1.25 (1H, m), 1.95 (4H, m), 2.93 (1H, br d, J = 11.0 Hz), 3.06 (1H, dd, J = 11.0, 12.0 Hz), 6.58 (2H, dd, J = 2.5, 8.2 Hz), 7.25 (1H, t, J = 8.2 Hz), 7.64 (2H, t, J = 7.6 Hz), 7.74 (1H, t, J = 7.6 Hz), 8.04 (3H, m), 8.85 (1H, br), 9.01 (1H, s), 9.35 (1H, br), 11.47 (1H, br), 12.93 (1H, s).
25-08		470.96	435	A	A	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.58 (2H, m), 1.28 (1H, m), 1.90 (4H, m), 2.91 (1H, d, J = 11.3 Hz), 3.06 (1H, dd, J = 11.3, 12.3 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.28 (1H, t, J = 8.2 Hz), 7.90 (1H, d, J = 3.5 Hz), 8.06 (1H, s), 8.81 (1H, br), 9.00 (1H, d, J = 3.5 Hz), 9.02 (1H, s), 9.31 (1H, br), 11.80 (1H, br), 13.07 (1H, s).

Example 26-1



(1) To a cold (0 °C) suspension of ethyl 5-[1-(tert-butoxycarbonyl)-3-piperidinyl]-7-(2-hydroxyphenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (0.050 g, 0.101 mmol) in THF (2.0 mL) under an argon atmosphere was added $LiBH_4$ (0.004 g, 0.20 mmol). The mixture was allowed to warm to room temperature, and the stirring was continued for 3 hrs. The resulting mixture was quenched with water, and partitioned between ethyl acetate and a saturated ammonium chloride solution. The separated organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 3:2) to give Ethyl 5-[1-(tert-butoxycarbonyl)-3-piperidinyl]-7-(2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate. (0.027 g, yield; 54%)



(2) Ethyl 5-[1-(tert-butoxycarbonyl)-3-piperidinyl]-7-(2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate (0.024 g, 0.048 mmol) was treated under acidic conditions in a similar manner as described in Example 1-1 to

give ethyl 7-(2-hydroxyphenyl)-2-oxo-5-(3-piperidinyl)-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate. (0.019 g, yield; 91%)

Molecular weight: 431.92

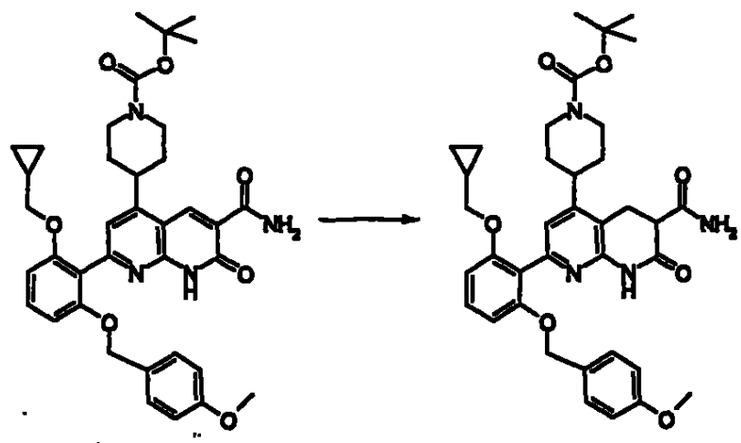
Mass spectrometry: 396 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

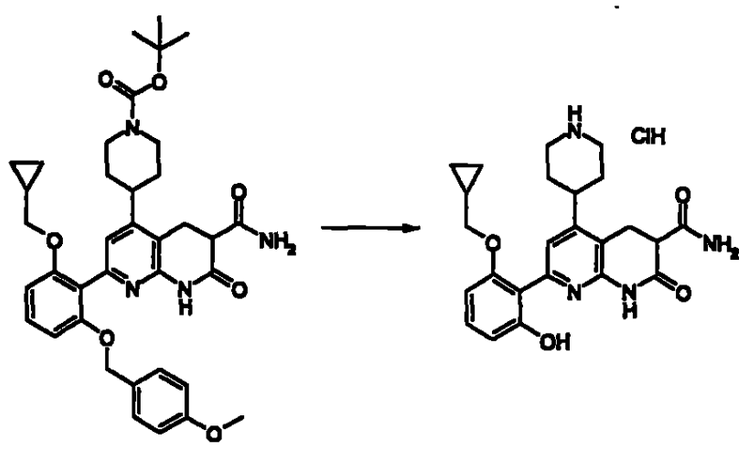
^{1}H-NMR '(500 MHz, DMSO-d6): 1.16 – 1.21 (3H, m), 1.83 – 1.95 (4H, m), 2.87 – 2.94 (1H, m), 3.18 – 3.37 (6H, m), 4.12 – 4.17 (2H, m), 6.90 – 6.93 (2H, m), 7.29 (1H, t, J = 7.88 Hz), 7.73 (1H, s), 8.03 (1H, d, J = 7.88 Hz), 8.81 – 8.90 (1H, m), 9.23 – 9.30 (1H, m), 11.33 (1H, s).

Example 26-2



To a cold (0 °C) solution of 4-(6-(aminocarbonyl)-2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1-piperidinecarboxylate (0.200 g, 0.305 mmol), which was obtained in the step (1) of Example 25-3, in methyl alcohol (5.0 mL) under an argon atmosphere was added $NaBH_4$ (0.010 g, 0.367 mmol). The mixture was allowed to warm to room temperature, and the stirring was continued for 12 hrs. The reaction mixture was quenched with water, and extracted with ethyl acetate. The separated organic phase was washed with

brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give tert-butyl 4-(6-(aminocarbonyl)-2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)-oxy]phenyl}-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)-1-piperidinecarboxy-late. (0.133 g, yield; 67 %)



To a stirred solution of tert-butyl 4-(6-(aminocarbonyl)-2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)-1 piperidinecarboxylate (0.120 g, 0.187 mmol) in 1,4-dioxane (3 mL) was added 4N HCl in dioxane (1 mL). The mixture was stirred at room temperature for 2 hrs. The resulted precipitate was collected by filtration, washed with acetonitrile, and dried under reduced pressure to give 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(4-piperidinyl)-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxamide hydrochloride. (0.080 g, yield 90 %).

Molecular weight: 472.98

Mass spectrometry: 437 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

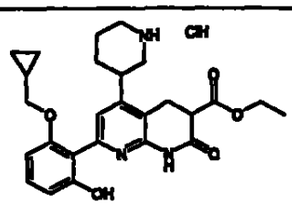
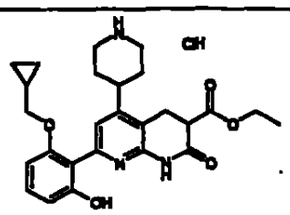
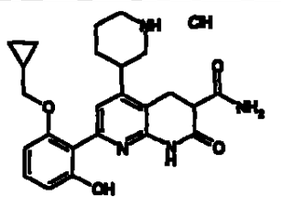
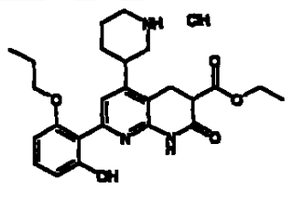
^{1}H-NMR (500 MHz, DMSO-d6): 0.33 (2H, d, J = 4.4 Hz), 0.60 (2H, d, J = 6.3 Hz), 1.33 – 1.39 (1H, m), 1.77 – 1.91 (5H, m), 3.06 – 3.10 (2H, m), 3.20 (3H, d, J = 8.2

Hz), 3.86 (2H, dd, J = 2.2, 7.1 Hz), 6.53 (2H, dd, J = 8.2, 7.0 Hz), 7.16 (1H, t, J = 8.2 Hz), 7.20 (1H, s), 7.56 (1H, s), 7.84 (1H, s), 11.02 (1H, s).

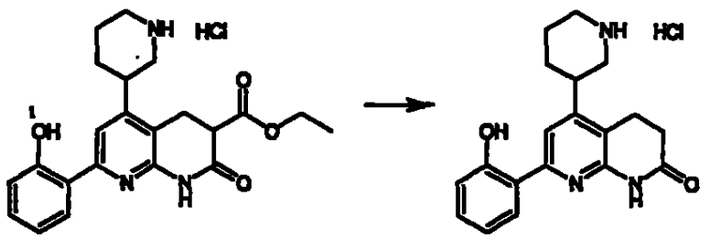
Examples 26-3 to 26-6

According to the similar synthetic procedure of Examples 26-1 to 26-2, compounds shown in Table 9 were prepared.

Table 9

Ex. No	Structure	Mol weight	Mass	In vitro	A549	NMR
26-03		502.02	466	A	A	(300 MHz, DMSO-d6): 0.31 - 0.36 (2H, m), 0.56 - 0.60 (2H, m), 1.17 (3H, t, J = 7.2 Hz), 1.26 (1H, m), 1.82 - 1.90 (4H, m), 2.84 - 2.89 (2H, m), 3.23 - 3.39 (6H, m), 3.80 - 3.89 (2H, m), 4.16 (2H, q, J = 7.2 Hz), 6.52 (2H, d, J = 8.3 Hz), 7.16 (1H, t, J = 8.3 Hz), 7.85 (1H, s), 9.17 (1H, br), 9.39 (1H, br), 11.17 (1H, s).
26-04		502.02	466	A	A	(500 MHz, DMSO-d6): 0.30 - 0.33 (2H, m), 0.56 - 0.59 (2H, m), 1.17 (3H, t, J = 7.2 Hz), 1.36 (1H, m), 1.86 - 1.92 (4H, m), 3.06 - 3.09 (2H, m), 3.18 - 3.23 (2H, m), 3.30 - 3.38 (3H, m), 3.80 (1H, m), 3.85 - 3.87 (2H, d, J = 7.0 Hz), 4.12 (2H, q, J = 7.2 Hz), 6.51 (1H, d, J = 8.2 Hz), 6.53 (1H, d, J = 8.2 Hz), 7.16 (1H, t, J = 8.2 Hz), 7.83 (1H, s), 8.98 (1H, br), 9.03 (1H, br), 11.16 (1H, s).
26-05		472.98	437	A	A	(500 MHz, DMSO-d6): 0.36 (2H, m), 0.60 (2H, m), 1.30 (1H, m), 1.73 - 1.94 (4H, m), 2.94 (2H, m), 6.52, 6.53 (2H, d x 2, J = 8.2 Hz), 7.16 (1H, t, J = 8.2 Hz), 7.22, 7.23 (1H, br x 2), 7.54, 7.59 (1H, br s x 2), 7.85, 7.87 (1H, s x 2), 8.86 1H, br), 9.15 (1H, br), 11.04, 11.04 (1H, s x 2).
26-06		490.00	454	A	A	(500 MHz, DMSO-d6): 0.93 (3H, t, J = 7.3 Hz), 1.17 (3H, td, J = 3.5, 7.2 Hz), 1.74 - 1.79 (3H, m), 1.85 - 1.91 (3H, m), 2.87 - 2.89 (2H, m), 3.34 - 3.40 (3H, m), 3.80 - 3.85 (1H, m), 3.93 - 3.97 (2H, m), 4.14 (2H, q, J = 7.2 Hz), 6.52 (1H, d, J = 8.2 Hz), 6.57 (1H, d, J = 8.5 Hz), 7.17 (1H, t, J = 8.2 Hz), 7.85 (1J, s), 8.88 (1H, br), 9.15 (1H, br), 11.13 (1H, s).

Example 27-1



A solution of ethyl 7-(2-hydroxyphenyl)-2-oxo-5-(3-piperidinyl)-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate hydrochloride (0.012 g, 0.023 mmol), which was obtained in the step(2) of Example 26-1, in 2.5N HCl (3.0 mL) was heated at reflux for 4 hrs. After being cooled to room temperature, the mixture was concentrated under reduced pressure. The residue was washed with acetonitrilee and dried under reduced pressure to give 7-(2-hydroxyphenyl)-5-(3-piperidinyl)-3,4-dihydro-1,8-naphthyridin-2(1H)-one hydrochloride. (0.007 g, yield; 70%)

Molecular weight: 359.86

Mass spectrometry: 324 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

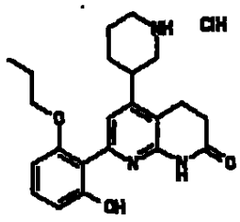
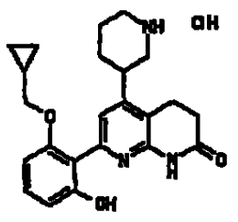
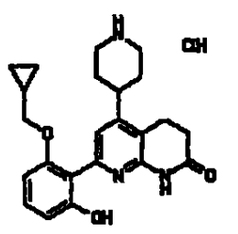
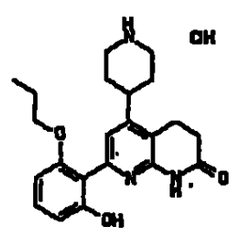
^{1}H-NMR (500 MHz, DMSO-d6): 1.83 – 1.94 (4H, m), 2.57 – 2.64 (2H, m), 2.89 – 3.01 (3H, m), 3.19 – 3.37 (4H, m), 6.88 – 6.93 (2H, m), 7.28 (1H, t, J = 8.2 Hz), 7.69 (1H, s), 8.01 (1H, d, J.= 7.9 Hz), 8.90 (1H, br), 9.16 (1H, br), 10.99 (1H, s).

Examples 27-2 to 27-5

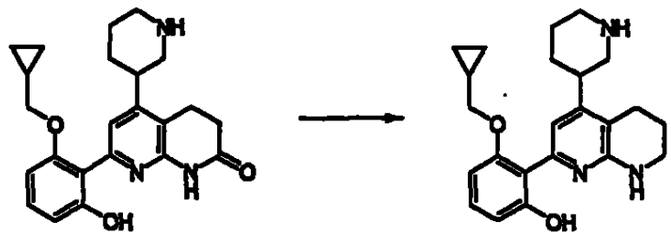
In similar manners as described in Example 27-1 above, compounds in Examples 27-2 to 27-5 were synthesized.

According to the similar synthetic procedure of Example 27-1 , compounds shown in Table 10 were prepared.

Table 10

Ex. No	Structure	Mol weight	Mass	In vitro	A549	NMR
27-02		417.94	382	A	A	(500 MHz, DMSO-d6): 0.94 (3H, t, J = 7.5 Hz), 1.72 - 1.80 (2H, m), 1.87 - 1.89 (4H, m), 2.59 - 2.61 (2H, m), 2.88 - 2.91 (2H, m), 2.99 - 3.02 (2H, m), 3.26 - 3.33 (2H, m), 3.43 (1H, m), 3.95 (2H, m), 6.54 (1H, d, J = 8.2 Hz), 6.59 (1H, d, J = 7.9 Hz), 7.18 (1H, t, J = 7.4 Hz), 7.84 (1H, s), 9.26 (1H, br), 10.84 (1H, s).
27-03		429.95	394	A	A	(300 MHz, DMSO-d6): 0.32 - 0.37(2H,m), 0.58 - 0.62 (2H, m), 1.29 (1H, m), 1.75 - 1.83 (4H, m), 2.57 - 2.61 (2H, m), 2.88 (1H, m), 2.96 - 3.01 (2H, m), 3.33 - 3.38 (4H, m), 3.82 - 3.87 (2H, m), 6.52 (2H, d, J = 7.9 Hz), 7.15 (1H, t, J = 7.9 Hz), 7.83 (1H, s), 9.07 (1H, br), 10.81 (1H, s).
27-04		429.95	394	A	A	(500 MHz, DMSO-d6): 0.31 - 0.34 (2H, m), 0.57 - 0.60 (2H, m), 1.33 (1H, m), 1.81 - 1.85 (2H, m), 1.90 - 1.93 (2H, m), 2.57 (2H, t, J = 7.2 Hz), 2.99 (2H, t, J = 7.2 Hz), 3.05 - 3.08 (2H, m), 3.18 (1H, m), 3.39 - 3.40 (2H, m), 3.95 (2H, d, J = 6.9 Hz), 6.52 (2H, d, J = 7.9 Hz), 7.15 (1H, t, J = 8.2 Hz), 7.90 (1H, s), 8.52 (1H, br), 8.77 (1H, br), 10.80 (1H, s).
27-05		417.94	382	A	A	(500 MHz, DMSO-d6): 0.93 (3H, t, J = 7.3 Hz), 1.80 - 1.84 (2H, m), 2.57 - 2.59 (2H, m), 2.89 - 3.09 (4H, m), 3.12 (1H, m), 3.38 - 3.39 (2H, m), 3.97 (2H, t, J = 7.7 Hz), 6.52 (1H, d, J = 8.2 Hz), 6.57 (1H, d, J = 8.5 Hz), 7.18 (1H, t, J = 8.2 Hz), 7.59 (1H, s), 9.03 (2H, br), 10.80 (1H, s).

Example 28-01



To a stirred solution of 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-3,4-dihydro-1,8-naphthyridin-2(1H)-one (0.029 g, 0.074 mmol), which was obtained in the Example 27-3, in THF (1.5 mL) was added dropwise Vitride® (70% toluene solution, 0.500 mL). The mixture was stirred at 65 °C for 1 hr. After cooled to room temperature, the mixture was quenched with saturated aqueous potassium sodium tartrate solution. The mixture was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (chloroform / methanol = 4/1) to give 3-(cyclopropylmethoxy)-2-[4-(3-piperidinyl)-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl]phenol. (0.003 g, yield; 11%)

Molecular weight: 379.51

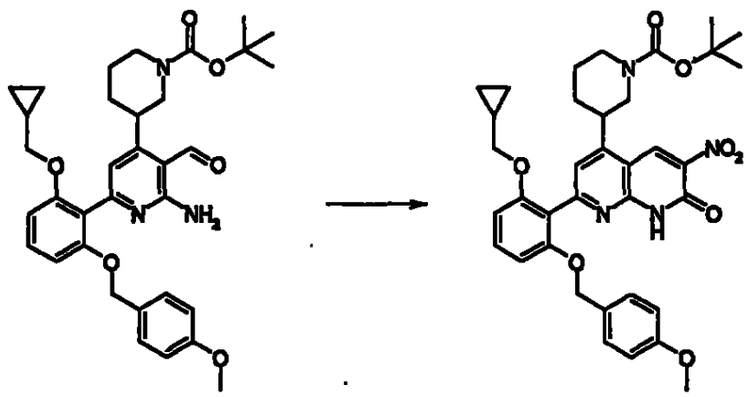
Mass spectrometry: 380 $(M+H)^+$

In vitro activity grade: A

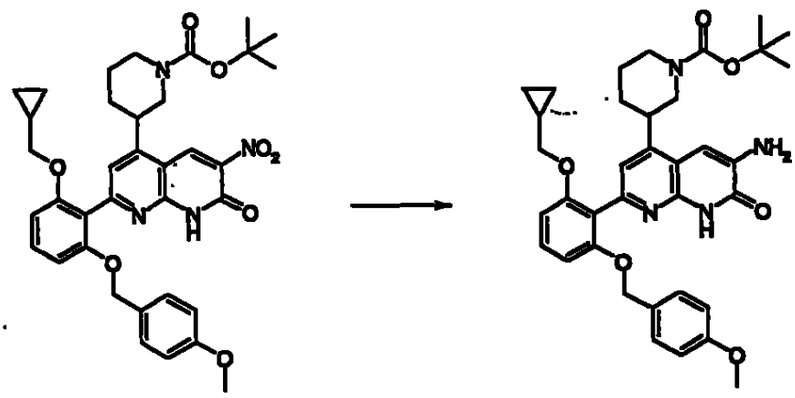
Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, CDCl3): 0.42 (2H, m), 0.68 (2H, m), 1.35 (1H, m), 1.91 (1H, d, J = 12.0 Hz), 1.98 (2H, m), 2.63 (1H, dt, J = 2.8, 12. Hz), 2.77 (3H, m), 2.86 (1H, m), 3.11 (2H, dd, J = 2.3, 10.5 Hz), 3.40 (2H, dt, J = 2.8, 5.4 Hz), 3.83 (2H, d, J = 6.9 Hz), 4.75 (1H, br s), 6.38 (1H, dd, J = 1.3, 8.2 Hz), 6.59 (1H, dd, J = 1.3, 8.2 Hz), 7.09 (1H, t, J = 8.2 Hz), 7.78 (1H, s), 14.69 (1H, br).

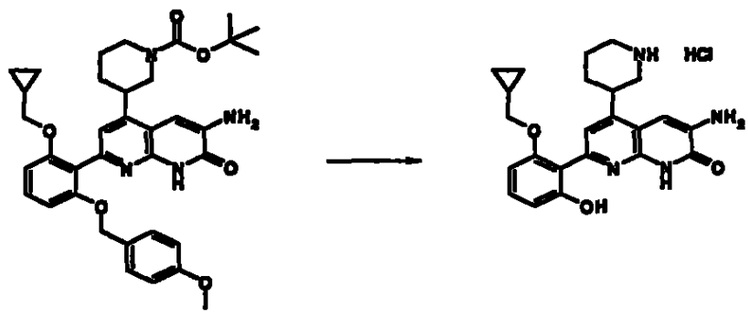
Example 29-01



(1) To a stirred solution of tert-butyl 3-(2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-formyl-4-pyridinyl)-1-piperidinecarboxylate (0.100 g, 0.170 mmol), which was obtained in the step (1) of Example 25-2, and ethyl nitroacetate (0.060 mL, 0.510 mmol) in ethanol (5 mL) was added piperidine (0.050 mL, 0.510 mmol). The mixture was stirred at 75 °C for 18 hrs, and concentrated under reduced pressure. The residue was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue (liquid) was purified by column chromatography on silica gel (hexane / ethyl acetate = 3/1-3/2) to give tert-butyl 3-(2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-6-nitro-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1- piperidinecarboxylate (0.105 g, yield; 94%).



(2) To a stirred mixture of tert-butyl 3-(2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-6-nitro-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1- piperidinecarboxylate (0.085 g, 0.129 mmol), iron powder (0.300 g), ethanol (4.5 mL) and water (0.5 mL) was added ammonium chloride (0.100 g). The mixture was stirred at 85 °C for 30 min. After cooled to room temperature, the mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give tert-butyl 3-(6-amino-2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]-phenyl}-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1-piperidinecarboxylate (0.068 g, yield; 84%).



(3) Then benzyl moiety and tert-butyl carbamate were removed in a similar manner as described in the step (2) of Example 25-4, to give 3-amino-7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-1,8-naphthyridin-2(1H)-one hydrochloride.

Molecular weight: 442.95

Mass spectrometry: 407 $(M+H)^+$

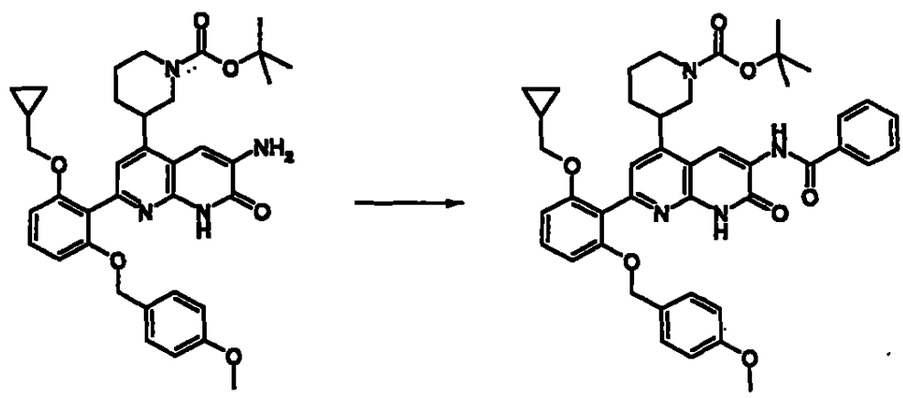
In vitro activity grade: A

Cellular activity grade: (A549)-A

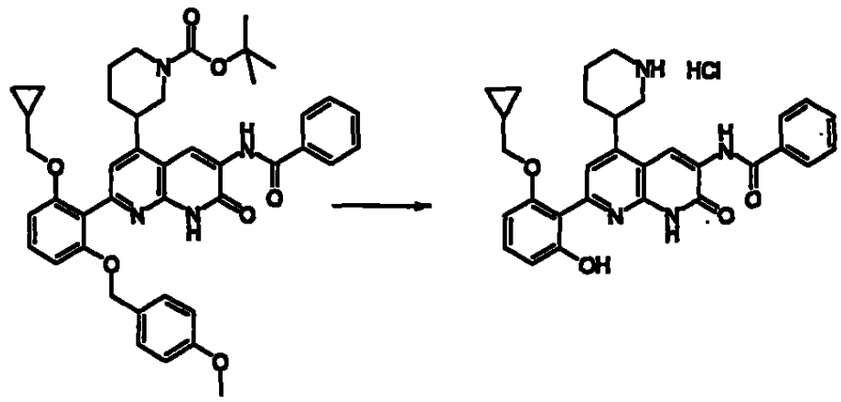
^{1}H-NMR (500 MHz, DMSO-d6): 0.35 (2H, m), 0.62 (2H, m), 1.32 (1H, m), 1.73 (1H, ddd, J = 4.1, 8.2, 8.2 Hz), 1.93 (3H, m), 2.90 (1H, dd, J = 11.7, 12.3 Hz), 3.11

(1H, dd, J = 11.0, 11.7 Hz), 6.54 (2H, d, J = 8.2 Hz), 6.93 (1H, s), 7.17 (1H, t, J = 8.2 Hz), 7.99 (1H, s), 9.10 (1H, br), 9.28 (1H, br), 12.55 (1H, s).

Example 29-2



To a stirred solution of tert-butyl 3-(6-amino-2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1-piperidine-carboxylate (0.068 g, 0.109 mmol), which was obtained in the step (2) of Example 29-1, and triethyl amine (0.05 mL, 0.327 mmol) in methylene chloride (3 mL) were added benzoyl chloride (0.01 mL, 0.109 mmol) and 4-dimethylaminopyridine (0.001 g, 0.011 mmol). The mixture was stirred at room temperature for 19 hrs, and poured into water. The mixture was extracted with ethyl acetate. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced. The resulting residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 5/1-3/2) to give tert-butyl 3-{2-{2-(cyclopropylmethoxy)-6-[(4-methoxy-benzyloxy]phenyl}-7-oxo-[(1-phenyl-methanoyl)-amino]-7,8-dihydro-1,8-naphthyridin-4-yl)-1-piperidinecarboxylate (0.022 g, yield; 28%).



Then benzyl moiety and tert-butyl carbamate were removed in a similar manner as described in the step (2) of Example 25-4 to give N-[7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,2-dihydro-1,8-naphthyridin-3-yl]benzamide hydrochloride.

Molecular weight: 547.06

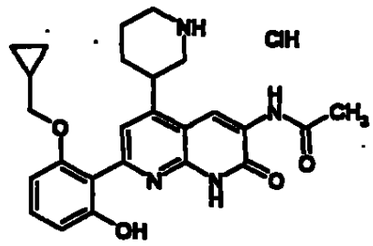
Mass spectrometry: 511 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 0.34 (2H, m), 0.59 (2H, m), 1.29 (1H, m), 1.80 – 2.08 (4H, m), 2.96 (1H, br), 3.18 (1H, dd, J = 11.4, 11.7 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.23 (1H, t, J = 8.2 Hz), 7.61 (2H, t, J = 7.9 Hz), 7.68 (1H, m), 8.01 (2H, m), 8.04 (1H, s), 8.80 (1H, br), 9.03 (2H, s), 9.61 (1H, s), 13.13 (1H, s).

Example 29-3



In a similar manner as that of Example 29-2, N-[7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,2-dihydro-1,8-naphthyridin-3-yl]acetamide hydrochloride was prepared.

Molecular weight: 484.99

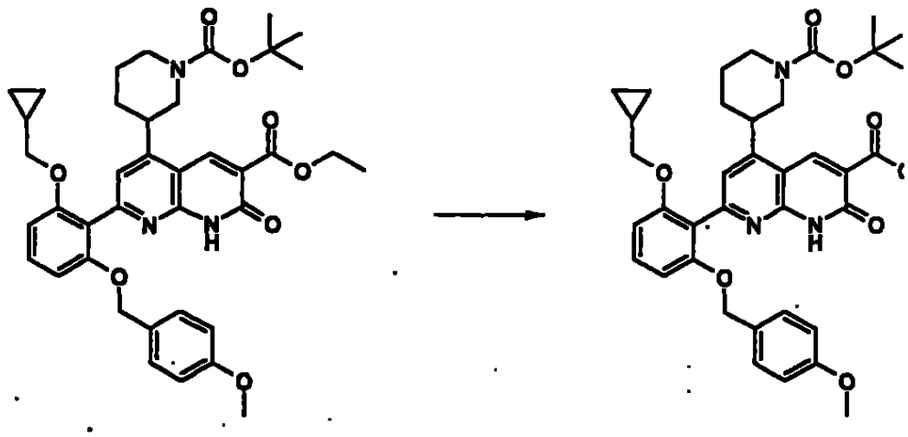
Mass spectrometry: 449 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

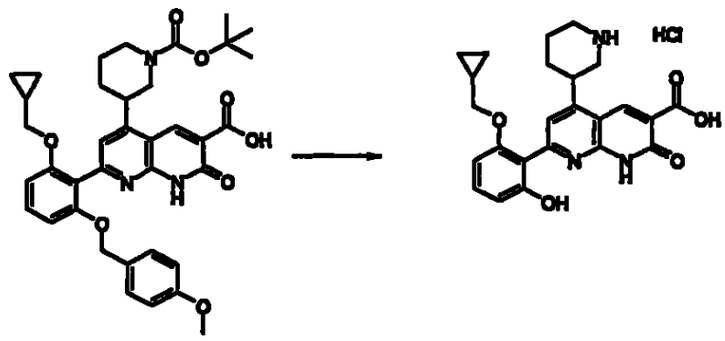
(500 MHz, DMSO-d6): 0.33 (2H, m), 0.59 (2H, m), 1.28 (1H, m), 1.76 (1H, m), 1.89 (1H, m), 1.98 (1H, m), 2.92 (1H, dd, J = 11.4, 12.0 Hz), 3.17 (1H, dd J = 11.0, 12.0 Hz), 6.57 (2H, d, J = 8.5 Hz), 7.21 (1H, t, J = 8.5 Hz), 7.99 (1H, s), 8.78 (1H, br), 8.94 (1H, s), 9.02 (1H, br), 9.69 (1H, s), 11.92 (1H, br), 12.93 (1H, s).

Example 30-1



(1) To a stirred solution of ethyl 5-[1-(tert-butoxycarbonyl)-3-piperidinyl]-7-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (0.276 g, 0.403 mmol), which was obtained in a similar manner as that of the step (1) of Example 29-1 using diethyl malonate instead of ethyl nitroacetate, in tetrahydrofuran (4 mL) and water (1 mL) was added lithium hydroxide monohydrate (0.015 g, 0.605 mmol). The mixture was stirred at room temperature for 18 hrs and acidified (pH 3-4) with aqueous 1N hydrochloric acid solution. The mixture was extracted with ethyl acetate. The separated organic phase

was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 5-[1-(tert-butoxycarbonyl)-3-piperidinyl]-7-{2-(cyclopropyl-methoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylic acid (0.259 g, yield; 98%).



(2) Then benzyl moiety and tert-butyl carbamate were removed in a similar manner as described in the step (2) of Example 25-4 to give 7-(2-cyclopropylmethoxy-6-hydroxy-phenyl)-2-oxo-5-piperidin-3-yl-1,2-dihydro-[1,8]naphthyridine-3-carboxylic acid hydrochloride.

Molecular weight: 471.94

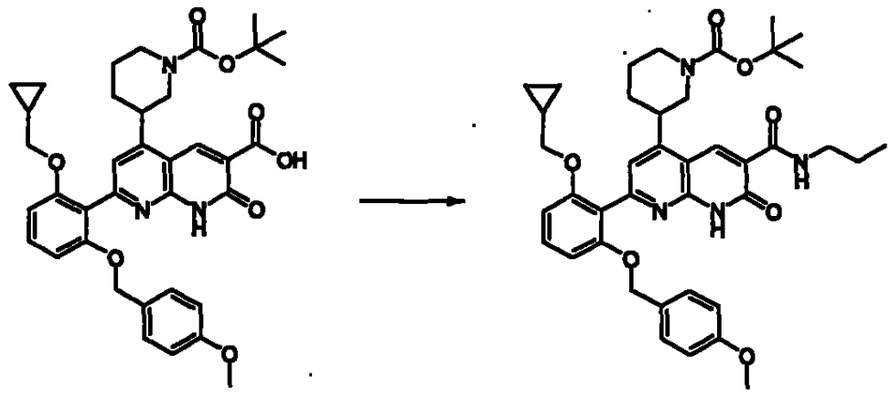
Mass spectrometry: 436 $(M+H)^+$

In vitro activity grade: A

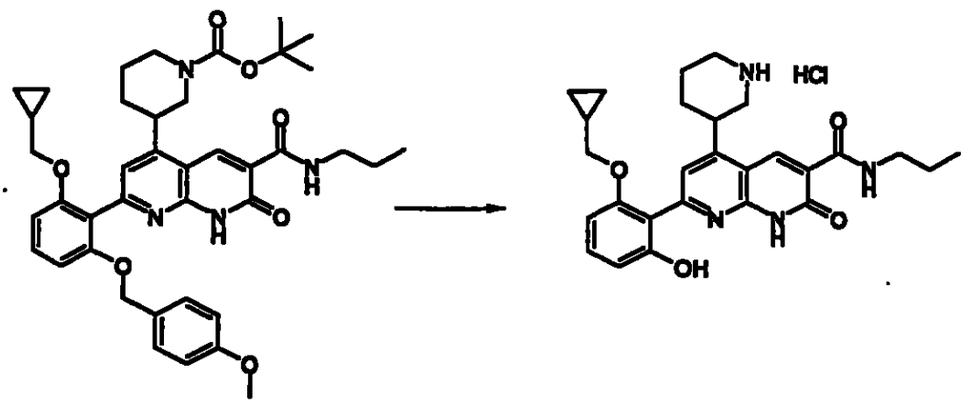
Cellular activity grade: (A549)-B

'(500 MHz, DMSO-d6): 0.30 – 0.33 (2H, m), 0.54 – 0.55 (2H, m), 1.23 (1H, m), 1.92 – 1.98 (4H, m), 2.91 (1H, m), 3.04 (1H, m), 3.39-3.41 (3H, m), 3.86 – 3.89 (3H, m), 6.61 (2H, d, J = 8.5 Hz), 7.27 (1H, t, J = 8.2 Hz), 8.07 (1H, s), 8.72 (1H, s), 9.24 (1H, s), 13.74 (1H, s), 14.43 (1H, s).

Example 31-1



(1) To a stirred solution of 5-[1-(tert-butoxycarbonyl)-3-piperidinyl]-7-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylic acid (0.200 g, 0.305 mmol), which was obtained in the step (1) of Example 30-1, and 1-hydroxybenzotriazole hydrate (0.062 g, 0.457 mmol) in dimethylformamide (4 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.070 g, 0.366 mmol). The mixture was stirred at room temperature for 18 hrs, and then extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 1/1) to give tert-butyl 3-{2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-7-oxo-6-[(propylamino)-carbonyl]-7,8-dihydro-1,8-naphthyridin-4-yl}-1-piperidinecarboxylate (0.129 g, yield; 61%).



(2) Then benzyl moiety and tert-butyl carbamate were removed in a similar manner as described in the step (2) of Example 25-4 to give 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-N-propyl-1,2-dihydro-1,8-naphthyridine-3-carboxamide.

Molecular weight: 513.04

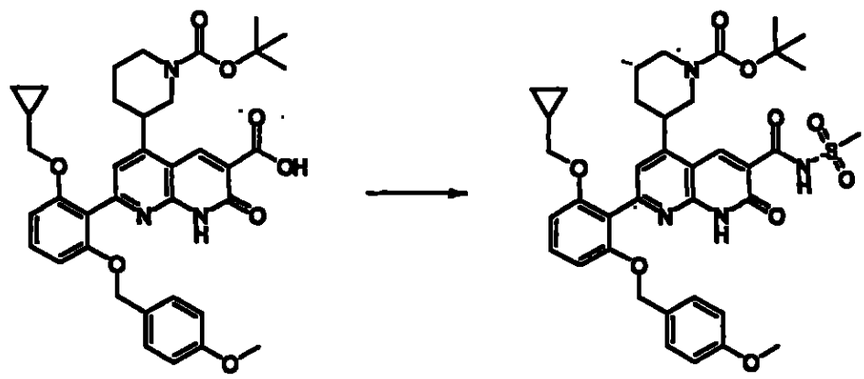
Mass spectrometry: 477 $(M+H)^+$

In vitro activity grade: A

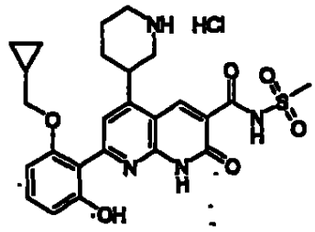
Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.33 (2H, m), 0.57 (2H, m), 0.94 (3H, t, J = 7.3 Hz), 1.27 (1H, m), 1.58 (2H, tq, J = 7.3, 7.3 Hz), 1.92 (4H, m), 2.90 (1H, m), 3.06 (1H, t, J = 12.3 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 8.07 (1H, s), 9.01 (1H, s), 9.69 (1H, t, J = 6.0 Hz), 11.80 (1H, s).

Reaction 31-2



To a stirred solution of methanesulfonamide (0.026 g, 0.268 mmol) and triethylamine (0.030 mL, 0.229 mmol) in toluene (2 mL) was added trimethylsilyl chloride (0.020 mL, 0.152 mmol). The mixture was stirred at 90 °C for 1 hr, and then concentrated under reduced pressure. To the residue diluted with dichloromethane (2 mL) were added triethylamine (0.020 mL, 0.152 mmol), 4,4-dimethylaminopyridine (0.002 g, 0.015 mmol), benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (0.040 g, 0.091 mmol) and 5-[1-(tert-butoxycarbonyl)-3-piperidinyl]-7-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylic acid (0.050 g, 0.076 mmol) successively. The mixture was stirred at room temperature for 6 hrs. The mixture was extracted with ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (hexane / ethyl acetate = 1/1 x 2) to give tert-butyl 3-(2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-6-{[(methylsulfonyl)-amino]carbonyl}-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1-piperidinecarboxylate (0.024 g, yield; 43%).



Then the benzyl moiety and tert-butyl carbamate were removed in a similar manner as described in the step (2) of Example 25-4 to give N-{[7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,2-dihydro-1,8-naphthyridin-3-yl]carbonyl}methanesulfonamide hydrochloride.

Molecular weight: 549.05

Mass spectrometry: 513 $(M+H)^+$

In vitro activity grade: A

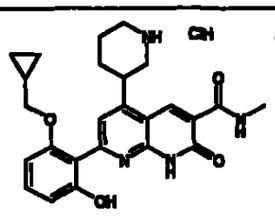
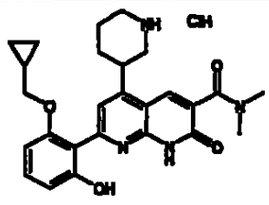
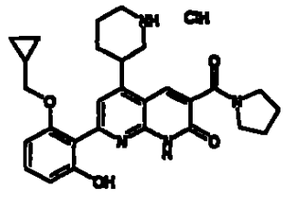
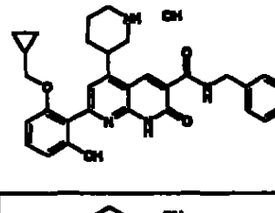
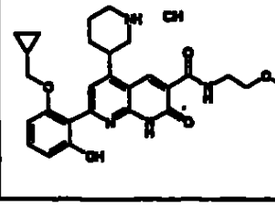
Cellular activity grade: (A549)-B

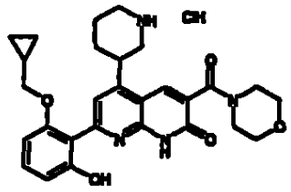
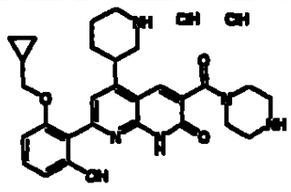
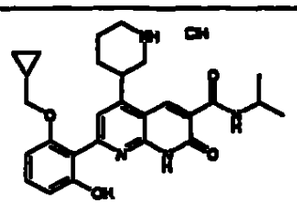
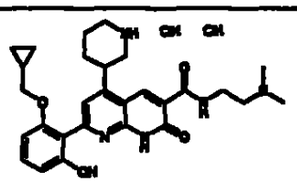
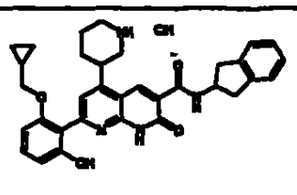
^{1}H-NMR (500 MHz, DMSO-d6): 0.33 (2H, m), 0.55 (2H, m), 1.25 (1H, m), 1.95 (4H, m), 2.92 (1H, br), 3.06 (1H, t, J = 12.0 Hz), 3.40 (2H, t, J = 11.7 Hz), 3.45 (3H, s), 6.61 (2H, d, J = 8.2 Hz), 7.28 (1H, t, J = 8.2 Hz), 8.09 (1H, s), 8.74 (1H, br), 9.08 (1H, s), 11.62 (1H, br), 12.72 (1H, br), 13.56 (1H, br).

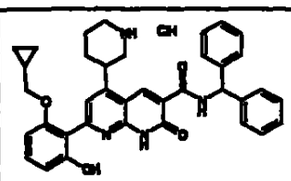
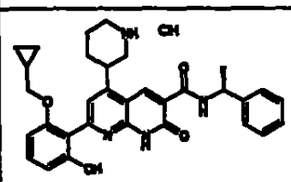
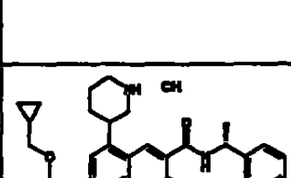
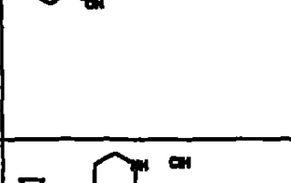
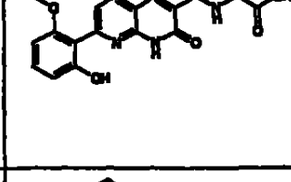
Example 31-3 to 31-27

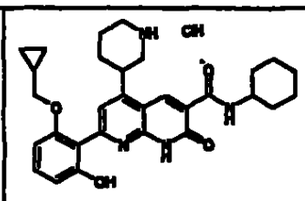
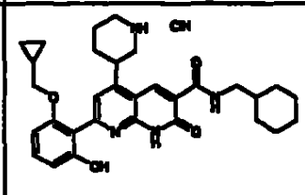
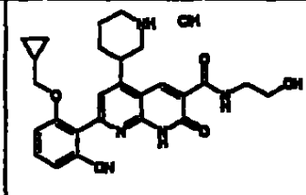
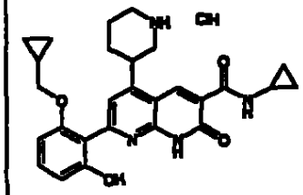
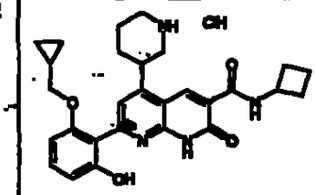
According to the similar synthetic procedure of Example 31-1 to 31-2, compounds shown in Table 11 were prepared.

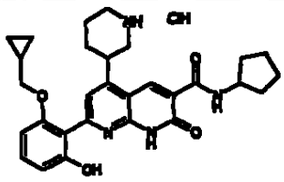
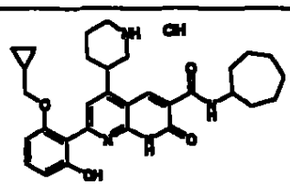
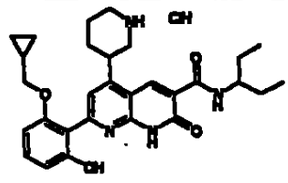
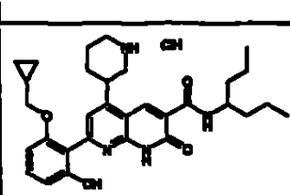
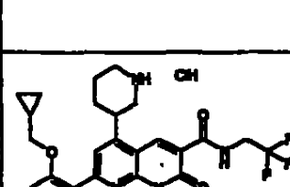
Table 11

Ex. No	Structure	Mol weight	Mass	In vitro	A549	NMR
31-03		484.99	449	A	A	(500 MHz, DMSO-d6): 0.34 (2H, m), 0.57 (2H, m), 1.27 (1H, m), 1.92 (4H, m), 2.91 (3H, d, J = 4.7 Hz), 3.05 (1H, t, J = 12.3 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 8.06 (1H, s), 9.00 (1H, s), 9.53 (1H, q, J = 4.7 Hz), 11.79 (1H, s).
31-04		499.01	463	A	B	(500 MHz, DMSO-d6): 0.34 (2H, m), 0.57 (2H, m), 1.27 (1H, m), 1.94 (4H, m), 2.92 (3H, s), 3.00 (3H, s), 6.58 (2H, d, J = 8.2 Hz), 7.24 (1H, t, J = 8.2 Hz), 8.00 (1H, s), 8.19 (1H, s), 8.58 (1H, br), 9.10 (1H, br), 11.84 (1H, br), 12.72 (1H, s).
31-05		525.05	489	A	B	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.57 (2H, m), 1.25 (1H, m), 1.89 (8H, m), 2.90 (1H, m), 2.98 (1H, dd, J = 11.4, 12.8 Hz), 6.58 (2H, d, J = 8.2 Hz), 7.24 (1H, t, J = 8.2 Hz), 8.00 (1H, s), 8.22 (1H, d, J = 2.5 Hz), 8.46 (1H, br), 9.05 (1H, br), 11.82 (1H, br), 12.74 (1H, s).
31-06		561.09	525	A	A	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.57 (2H, m), 1.27 (1H, m), 1.92 (4H, m), 2.91 (1H, m), 3.06 (1H, t, J = 12.3 Hz), 4.61 (2H, d, J = 6.0 Hz), 6.59 (2H, d, J = 8.5 Hz), 7.26 (2H, m), 7.37 (4H, m), 8.08 (1H, s), 9.05 (1H, s), 10.07 (1H, t, J = 6.0 Hz), 11.80 (1H, s).
31-07		529.04	493	A	A	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.57 (2H, m), 1.27 (1H, m), 1.92 (4H, m), 2.91 (1H, m), 3.07 (1H, t, J = 12.3 Hz), 3.50 (2H, m), 3.55 (2H, m), 6.60 (2H, d, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 8.07 (1H, s), 9.02 (1H, s), 9.78 (1H, m), 11.80 (1H, s).

31-08		541.05	505	A	B	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.57 (2H, m), 1.28 (1H, m), 1.93 (4H, m), 2.90 (1H, m), 2.98 (1H, dd, J = 11.3, 12.0 Hz), 3.73 (1H, br), 3.88 (2H, m), 6.58 (2H, d, J = 8.2 Hz), 7.24 (1H, t, J = 8.2 Hz), 8.00 (1H, s), 8.83 (1H, br), 9.06 (1H, br d, J = 10.7 Hz), 11.85 (1H, br), 12.73 (1H, s).
31-09		578.53	504	A	C	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.57 (2H, m), 1.28 (1H, m), 1.94 (4H, m), 2.90 (1H, m), 2.98 (1H, dd, J = 10.7, 11.4 Hz), 3.18 (4H, br s), 3.88 (5H, m), 6.58 (2H, d, J = 8.2 Hz), 7.24 (1H, t, J = 8.2 Hz), 8.00 (1H, s), 8.38 (1H, s), 9.03 - 9.21 (4H, br), 11.81 (1H, br), 12.78 (1H, s).
31-10		513.04	477	A	A	(500 MHz, DMSO-d6): 0.34 (2H, m), 0.57 (2H, m), 1.23 (6H, d, J = 6.6 Hz), 1.88 - 1.99 (4H, m), 2.91 (1H, m), 3.07 (1H, dd, J = 11.0, 12.0 Hz), 4.11 (1H, dq, J = 6.6, 7.8 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 8.07 (1H, s), 8.72 (1H, br), 9.01 (1H, s), 9.59 (1H, d, J = 7.8 Hz), 11.80 (1H, br), 13.13 (1H, s).
31-11		578.54	506	A	A	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.56 (2H, m), 1.28 (1H, m), 1.88 - 1.99 (4H, m), 2.85 (6H, s), 3.11 (1H, dd, J = 11.0, 12.3 Hz), 3.75 (2H, t, J = 5.7 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.27 (1H, t, J = 8.2 Hz), 8.07 (1H, s), 8.83 (1H, br), 9.01 (1H, s), 9.14 (1H, br), 9.86 (1H, br), 9.83 (1H, t, J = 6.0 Hz), 11.75 (1H, s), 13.16 (1H, s).
31-12		557.12	551	A	A	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.57 (2H, m), 1.28 (1H, m), 1.88 - 1.99 (4H, m), 2.92 (3H, dd, J = 5.4, 10.7 Hz), 3.07 (1H, t, J = 12.3 Hz), 4.74 (1H, ddd, J = 6.9, 6.9, 12.6 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.19 (2H, m), 7.28 (3H, m), 8.06 (1H, s), 8.03 (1H, s), 9.91 (1H, d, J = 6.9 Hz), 11.76 (1H, s), 13.09 (1H, br).

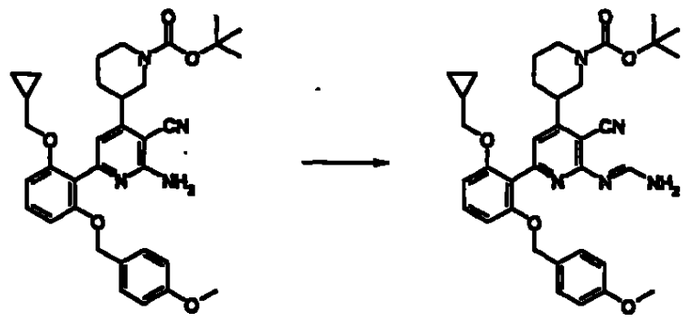
31-13		637.18	601	A	A	(500 MHz, DMSO-d6): 0.32 (2H, m), 0.56 (2H, m), 1.25 (1H, m), 1.86 - 1.97 (4H, m), 2.90 (1H, m), 3.05 (1H, t, J = 12.3 Hz), 6.33 (1H, d, J = 7.9 Hz), 6.60 (2H, d, J = 8.2 Hz), 7.26 (3H, m), 7.38 (6H, m), 8.04 (1H, s), 9.03 (1H, s), 10.07 (1H, d, J = 7.9 Hz), 11.69 (1H, s), 13.20 (1H, br).
31-14		575.11	539	A	A	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.56 (2H, m), 1.26 (1H, m), 1.53 (3H, d, J = 6.9 Hz), 1.86 - 1.96 (4H, m), 2.91 (1H, m), 3.06 (1H, m), 5.19 (1H, dq, J = 6.9, 7.3 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.28 (2H, m), 7.39 (4H, m), 8.06 (1H, d, J = 2.9 Hz), 8.71 (1H, br t, J = 11.7 Hz), 9.01 (1H, d, J = 2.9 Hz), 9.09 (1H, br t, J = 11.7 Hz), 10.11 (1H, dd, J = 5.7, 7.6 Hz), 11.78 (1H, br), 13.16 (1H, s).
31-15		575.11	539	A	A	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.56 (2H, m), 1.26 (1H, m), 1.53 (3H, d, J = 6.9 Hz), 1.86 - 1.98 (4H, m), 2.91 (1H, m), 3.06 (1H, m), 5.19 (1H, dq, J = 6.9, 7.3 Hz), 6.59, 6.59 (2H, d x 2, J = 8.2 Hz), 7.28 (2H, m), 7.39 (4H, m), 8.06 (1H, d, J = 2.9 Hz), 8.73 (1H, br t, J = 11.7 Hz), 9.00 (1H, d, J = 2.9 Hz), 9.16 (1H, br t, J = 11.4 Hz), 10.11 (1H, dd, J = 5.7, 7.6 Hz), 11.78 (1H, br), 13.16 (1H, s).
31-16		543.02	507	A	B	(500 MHz, DMSO-d6): 0.34 (2H, m), 0.57 (2H, m), 1.28 (1H, m), 1.44 (3H, d, J = 7.3 Hz), 1.88 - 1.99 (4H, m), 2.92 (1H, m), 3.07 (1H, dd, J = 11.4, 12.0 Hz), 4.53 (1H, m), 6.59, 6.61 (2H, d x 2, J = 8.2 Hz), 7.27 (1H, t, J = 8.2 Hz), 8.08 (1H, s), 8.79 (1H, br), 9.02 (1H, s), 9.28 (1H, br), 10.07, 10.08 (1H, d x 2, J = 6.9 Hz), 13.17 (1H, s).
31-17		575.11	539	A	B	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.56 (2H, m), 1.26 (1H, m), 1.86 - 1.99 (4H, m), 2.86 (2H, t, J = 7.3 Hz), 3.07 (1H, dd, J = 11.7, 12.0 Hz), 3.63 (2H, dt, J = 6.3, 7.3 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.21-7.33 (6H, m), 8.05 (1H, s), 8.69 (1H, br), 8.99 (1H, br d, J = 5.1 Hz), 9.01 (1H, s), 9.73 (1H, t, J = 6.3 Hz), 11.74 (1H, br s), 13.11 (1H, s).

31-18		553.11	517	A	A	(500 MHz, CDCl3): 0.41 - 0.47 (2H, m), 0.65 - 0.77 (2H, m), 0.77 - 0.92 (1H, m), 1.32 - 1.42 (1H, m), 1.76 - 1.84 (1H, m), 1.84 - 1.97 (2H, m), 2.15 - 2.24 (1H, m), 2.72 (1H, dd, J = 2.8, 12.0 Hz), 2.80 - 2.88 (m, 1H), 3.16 - 3.26 (1H, m), 3.34 - 3.46 (2H, m), 3.91 (2H, d, J = 6.9 Hz), 5.95 (2H, br s), 6.42 (1H, dd, J = 1.0, 8.2 Hz), 6.73 (1H, dd, J = 1.0, 8.2 Hz), 7.23 - 7.26 (1H, m), 8.63 (1H, s), 8.69 (1H, s), 15.00 (1H, br).
31-19		567.13	531	A	C	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.56 (2H, m), 1.02 (2H, m), 1.14 - 1.26 (4H, m), 1.53 (1H, br'), 1.64 (1H, br d, J = 11.4 Hz), 1.72 (4H, m), 1.93 (4H, m), 2.82 (1H, br), 3.07 (1H, t, J = 12.0 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 8.05 (1H, s), 8.90 (1H, br), 9.00 (1H, br'), 9.01 (1H, s), 9.73 (1H, d, J = 11.7 Hz), 11.74 (1H, s), 13.12 (1H, br).
31-20		515.01	479	A	B	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.56 (2H, m), 1.27 (1H, m), 1.93 (4H, m), 2.91 (1H, m), 3.07 (1H, t, J = 12.0 Hz), 3.39 (2H, br), 3.44 (2H, dd, J = 5.7, 6.0 Hz), 3.56 (2H, dd, J = 5.4, 5.7 Hz), 6.59 (2H, d, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 8.07 (1H, s), 9.02 (1H, s), 9.79 (1H, d, J = 5.4 Hz), 11.82 (1H, s), 13.13 (1H, br).
31-21		511.03	475	A	A	(500 MHz, DMSO-d6): 0.34 (2H, m), 0.58 (2H, m), 0.79 (2H, m), 1.28 (1H, m), 1.91 (4H, m), 2.93 (2H, m), 3.07 (1H, t, J = 12.0 Hz), 6.60 (2H, d, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 8.06 (1H, s), 8.89 (1H, s), 8.96 (1H, d, J = 4.4 Hz), 11.78 (1H, s), 13.13 (1H, br).
31-22		525.05	489	A	A	(500 MHz, DMSO-d6): 0.33 (2H, m), 0.56 (2H, m), 1.26 (1H, m), 1.74 (2H, m), 1.87 - 2.05 (6H, m), 2.91 (1H, m), 3.05 (1H, t, J = 12.3 Hz), 4.46 (1H, m), 6.59 (2H, d, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 8.06 (1H, s), 8.89 (1H, s), 8.94 (1H, d, J = 7.8 Hz), 11.79 (1H, s), 13.13 (1H, br).

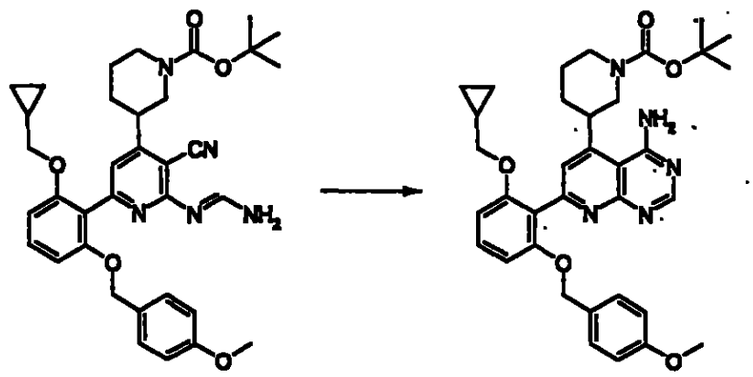
31-23		539.08	503	A	A	(500 MHz, DMSO-d6): 0.34 (2H, m), 0.56 (2H, m), 1.26 (1H, m), 1.50 (2H, m), 1.62 (2H, m), 1.71 (2H, m), 1.88 -1.99 (6H, m), 2.92 (1H, m), 3.06 (1H, t, J = 12.0 Hz), 6.58 (2H, d, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 8.06 (1H, s), 9.01 (1H, s), 9.72 (1H, d, J = 8.9 Hz), 11.77 (1H, s), 13.12 (1H, br).
31-24		567.13	531	A	A	(500 MHz, DMSO-d6): 0.34 (2H, m), 0.56 (2H, m), 1.26 (1H, m), 1.59 (10H, m), 1.87 -1.99 (5H, m), 2.90 (1H, m), 3.06 (1H, t, J = 11.7 Hz), 4.07 (1H, m), 6.59 (2H, d, J = 8.5 Hz), 7.26 (1H, t, J = 8.5 Hz), 8.06 (1H, s), 9.01 (1H, s), 9.78 (1H, d, J = 7.9 Hz), 11.76 (1H, s), 13.12 (1H, br).
31-25		541.10	505	A	A	(500 MHz, DMSO-d6): 0.34 (2H, m), 0.56 (2H, m), 0.90 (6H, t, J = 8.2 Hz), 1.27 (1H, m), 1.51 (2H, m), 1.81 (2H, m), 1.88 -1.99 (4H, m), 2.92 (1H, m), 3.07 (1H, t, J = 12.0 Hz), 6.60 (2H, d, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 8.07 (1H, s), 8.67 (1H, br), 8.96 (1H, br), 9.03 (1H, s), 9.54 (1H, d, J = 8.8 Hz), 11.76 (1H, s), 13.12 (1H, br).
31-26		569.15	533	A	A	(500 MHz, DMSO-d6): 0.34 (2H, m), 0.56 (2H, m), 0.90 (6H, t, J = 7.3 Hz), 1.25 - 1.54 (9H, m), 1.88 -1.99 (4H, m), 2.92 (1H, m), 3.06 (1H, t, J = 12.3 Hz), 4.07 (1H, m), 6.59 (2H, d, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 8.07 (1H, s), 8.69 (1H, br), 9.00 (1H, br), 9.03 (1H, s), 9.51 (1H, d, J = 9.1 Hz), 11.76 (1H, s), 13.11 (1H, br).
31-27		552.99	517	A	A	(500 MHz, DMSO-d6): 0.34 (2H, m), 0.57 (2H, m), 1.27 (1H, m), 1.88 -1.99 (4H, m), 2.92 (1H, m), 3.06 (1H, t, J = 12.3 Hz), 4.28 (2H, m), 6.60 (2H, d, J = 8.2 Hz), 7.27 (1H, t, J = 8.2 Hz), 8.08 (1H, s), 9.07 (1H, s), 10.12 (1H, d, J = 6.6 Hz), 11.76 (1H, s), 13.26 (1H, br).

Example 32-1

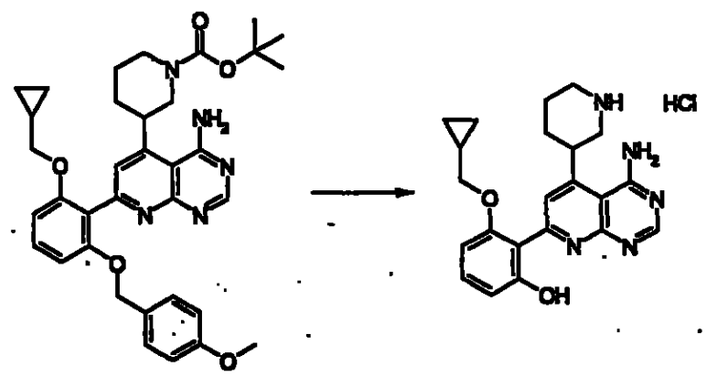
With the use of the starting compound 1G, 2B, and other materials, tert-butyl 3-(2-amino-3-cyano-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-4-pyridinyl)-1-piperidinecarboxylate was prepared in a similar manner as that of the step (1) of Example 1-1.



To a solution of tert-butyl 3-(2-amino-3-cyano-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-4-pyridinyl)-1-piperidinecarboxylate (0.580 g, 0.999 mmol) in triethyl orthoformate (1.2 mL) was added ammonium sulfate (0.004 g, 0.030 mmol), and the mixture was stirred at 150 °C for 2 hrs. After cooled to room temperature, EtOH (1.5 mL) and a solution of NH_3 in EtOH (8.6 N, 0.5 mL) were added successively. The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was triturated with hexane and isopropyl ether, and dried under reduced pressure to give tert-butyl 3-(2-{[(1E)-aminomethylidene]amino}-3-cyano-6-{2-(cyclopropyl-methoxy)-6-[(4-methoxy-benzyl)oxy]phenyl}-4-pyridinyl)-1-piperidinecarboxylate as a brown solid (0.543 g, yield; 89%).



To a solution of tert-butyl 3-(2-{[(1E)-aminomethylidene]amino}-3-cyano-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-4-pyridinyl)-1-piperidinecarboxylate (0.180 g, 0.289 mmol) in MeOH (5 mL) and toluene (5 mL) was added trifluoroacetic acid (0.01 mL). The mixture was allowed to stand for 20 days and concentrated under reduced pressure. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH 50:1 to 20:1) gave tert-butyl 3-(4-amino-7-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]-phenyl}pyrido[2,3-d]pyrimidin-5-yl)-1-piperidinecarboxylate as a colorless oil (0.026 g, yield; 15%).



Then the benzyl moiety and tert-butyl carbamate were removed in a similar manner as described in the step (2) of Example 25-4 to give 2-[4-amino-5-(3-piperidinyl)pyrido[2,3-d]pyrimidin-7-yl]-3-(cyclopropylmethoxy)phenol hydrochloride as a yellow powder (0.004 g, 24%).

Molecular weight: 391.48

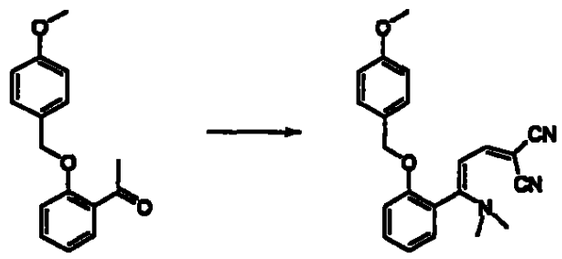
Mass spectrometry: 392 $(M+H)^+$

In vitro activity grade: C

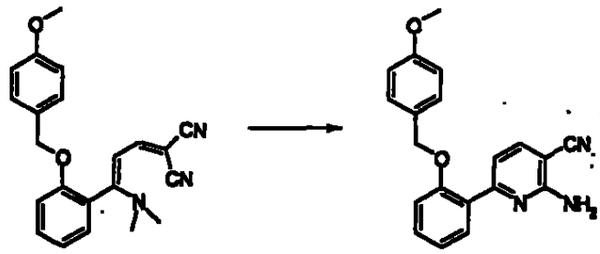
Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, CDCl3): 0.41 – 0.47 (2H, m), 0.65 – 0.77 (2H, m), 0.77 – 0.92 (1H, m), 1.32 – 1.42 (1H, m), 1.78 – 1.84 (1H, m), 1.84 – 1.97 (2H, m), 2.15 – 2.24 (1H, m), 2.72 (1H, dd, J = 2.8, 12.0 Hz), 2.80 – 2.88 (m, 1H), 3.16 – 3.26 (1H, m), 3.34 – 3.46 (2H, m), 3.91 (2H, d, J = 6.9 Hz), 5.95 (2H, br s), 6.42 (1H, dd, J = 1.0, 8.2 Hz), 6.73 (1H, dd, J = 1.0, 8.2 Hz), 7.23 – 7.26 (1H, m), 8.63 (1H, s), 8.69 (1H, s), 15.00 (1H, br).

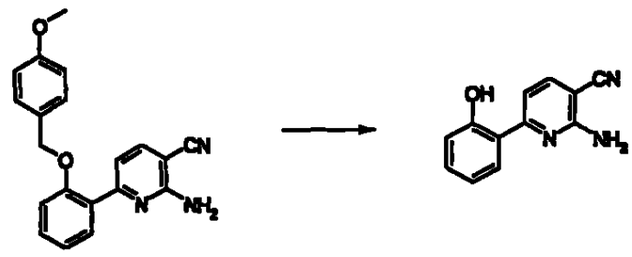
Example 33-1



To a solution of oxalyl chloride (3.63 g, 28.6 mmol) in acetonitrile (5.00 mL) at room temperature was added DMF (5.00 mL). After 10 minutes, a solution of 2-(4-methoxyphenylmethoxy)acetophenone (3.33 g, 13.0 mmol)(starting compound 1D) in DMF (50 mL) was added, and the stirring was continued overnight. To the reaction mixture were adde malononitrile (1.03 g, 15.6 mmol) and Et_3N (7.25 mL, 52.0 mmol) successively, and the stirring was continued overnight. The reaction mixture was poured into water, and then extracted with ether. The separated organic phase was washed with brine, and dried over $MgSO_4$, filtetred and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$) to give 2-((2Z)-3-(dimethylamino)-3-{2-[(4-methoxybenzyl)-oxy]phenyl}-2-propenylidene)malononitrile (1.27 g yield; 27%).



To a cold (-78 °C) solution of 2-((2Z)-3-(dimethylamino)-3-{2-[(4-methoxybenzyl)oxy]phenyl}-2-propenylidene)malononitrile (1.26 g, 3.51 mmol) in MeOH was added liquid NH_3, and the mixture was heated at 120 °C in a sealed tube overnight. After cooled to room temperature, the reaction mixture was poured into water and the resulting mixture was extracted with ethyl acetate. The separated organic phase was washed with brine, and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (hexane:ethyl acetate, 70:30) to give 2-amino-6-({2-[(4-methoxybenzyl)oxy]phenyl}nicotinonitrile (0.050 g, yield; 4.3%).



A mixture of 2-amino-6-({2-[(4-methoxybenzyl)oxy]phenyl}nicotinonitrile (0.050 g, 0.151 mmol), trifluoroacetic acid (3.00 mL), anisole (0.50 mL) and water (0.50 mL) was stirred at room temperature overnight. The reaction mixture was diluted with toluene, and concentrated under reduced pressure. The residue was dissolved in THF, and then hexane was added to give precipitates. The precipitates were collected by filtration and washed with hexane, and then dried under reduced pressure to give 2-amino-6-(2-hydroxyphenyl)nicotinonitrile. (0.026 g, yield; 82%)

Molecular weight: 211.23

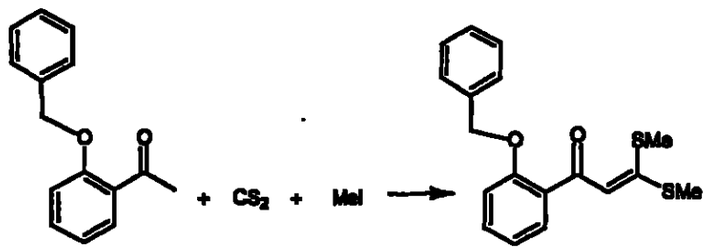
Mass spectrometry: 212 $(M + H)^+$

In vitro activity grade: B

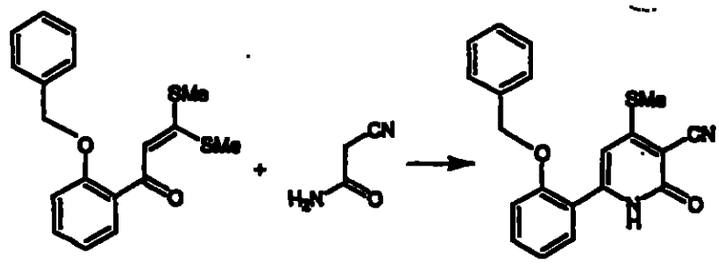
Cellular activity grade: (A549)-B

^{1}H-NMR (500 MHz, DMSO-d6): 6.87 – 6.92 (2H, m), 7.31 – 7.39 (4H, m), 7.94 (1H, d, J = 8.3 Hz), 8.01 (1H, d, J = 8.3 Hz), 13.38 (1H, br s).

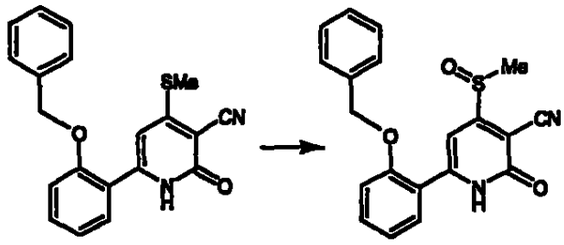
Example 34-1



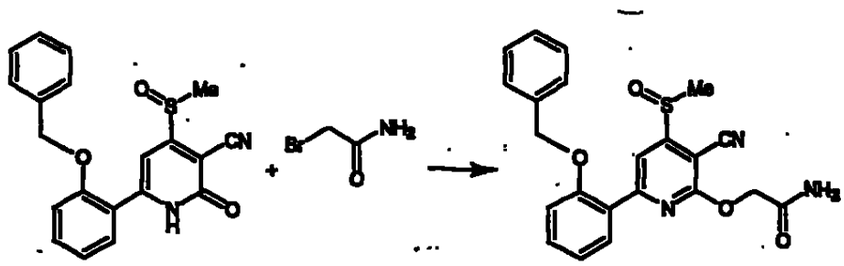
(1) To a solution of 2-(benzyloxy)acetophenone (5.66 g, 25 mmol)(starting compound 1A) in toluene (40 mL) were added carbon disulfide (6.0 mL, 99.8 mmol) and methyl iodide (10 mL, 245 mmol). To the mixture, sodium hydride (60% suspension, 2.00 g, 50 mmol) and N,N-dimethylacetamide (10 mL) were added. The resulting mixture was stirred at room temperature for 1 hr, and refluxed for 2 hrs. After cooled to room temperature, the reaction mixture was partitioned between CH_2Cl_2 and water. The organic phase was separated and washed with water, dried, and concentrated under reduced pressure. The residual solid was triturated with diisopropyl ether to give 1-[2-(benzyl)phenyl]-3,3-bis(methylthio)-2-propene-1-one as a light yellow solid (5.17 g, yield; 63%).



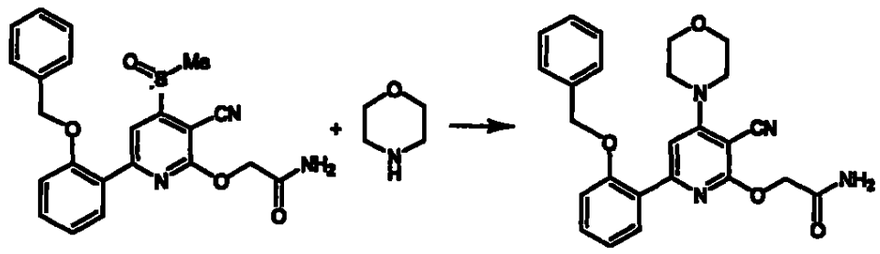
(2) To a suspension of cyanoacetamide (1.27 g, 15.1 mmol) in 2-propanol (50 mL) was added sodium hydride (60% suspension, 0.605 g, 15.1 mmol). The mixture was stirred at room temperature for 10 min. To this mixture, 1-[2-(benzyl)phenyl]-3,3-bis(methylthio)-2-propene-1-one (5.00 g, 15.1 mmol) was added in one portion. The resulting mixture was refluxed for 4 hrs. After being cooled to room temperature, the mixture was diluted with 1N HCl. The resulting precipitates were collected by filtration and washed with EtOH to give 6-[2-(benzyloxy)phenyl]-4-(methylthio)-2-oxo-1,2-dihydro-nicotinonitrile as a yellow crystalline solid (4.43 g, yield; 84%).



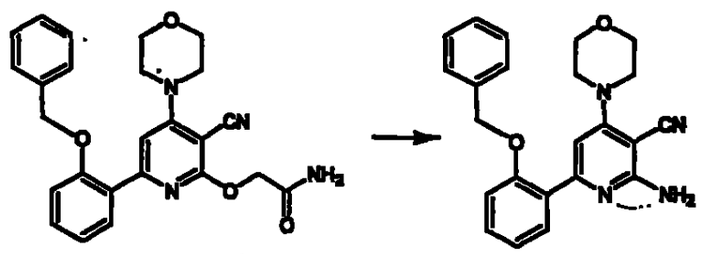
(3) To a cold (0 °C) solution of 6-[2-(benzyloxy)phenyl]-4-(methylthio)-2-oxo-1,2-dihydro-nicotinonitrile (4.00 g, 11.5 mmol) in CH_2Cl_2 was added m-chloroperbenzoic acid (mCPBA) (69%, 3.45 g, 13.8 mmol) in one portion. The reaction mixture was stirred at 0 °C to room temperature for 1 hr, quenched with saturated $NaHCO_3$ solution (80 mL) including $Na_2S_2O_3 \cdot 5H_2O$ (5 g), and diluted with CH_2Cl_2. The separated organic phase was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual solid was triturated with diisopropyl ether to give 6-[2-(benzyloxy)phenyl]-4-(methylsulfinyl)-2-oxo-1,2-dihydro-nicotinonitrile as a yellow solid (4.00 g, yield; 96%).



(4) A mixture of 6-[2-(benzyloxy)phenyl]-4-(methylsulfinyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile (2.97 g, 8.16 mmol), bromoacetamide (1.27 g, 9.21 mmol), and K_2CO_3 (1.43 g, 10.4 mmol) in DMF (30 mL) was stirred at 60 °C for 1.5 hrs. The reaction mixture was poured into water, and the resulting precipitates were collected by filtration. The solid obtained was washed with acetone to give 2-{[6-[2-(benzyloxy)phenyl]-3-cyano-4-(methylsulfinyl)-2-pyridinyl]oxy}acetamide as a solid (2.09 g, yield; 61%).

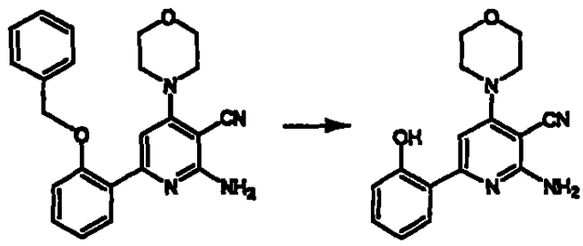


(5) A mixture of 2-{[6-[2-(benzyloxy)phenyl]-3-cyano-4-(methylsulfinyl)-2-pyridinyl]oxy}acetamide (300 mg, 0.71 mmol) and morpholine (1.0 mL) was stirred at 130 °C for 1 hr, and then water was added. The resulting precipitates were collected by filtration and dried under reduced pressure to give 2-{[6-[2-(benzyloxy)phenyl]-3-cyano-4-(4-morpholinyl)-2-pyridinyl]oxy}acetamide as a yellow solid (304 mg, yield; 96%).



(6) To a solution of 2-{[6-[2-(benzyloxy)phenyl]-3-cyano-4-(4-morpholinyl)-2-pyridinyl]oxy}acetamide (318 mg, 0.72 mmol) in DMF (1 mL) was added K_2CO_3 (198 mg, 1.43 mmol), and the mixture was stirred at 130 °C for 24 hrs. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with

brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/ethyl acetate = 3/1 to 2/1) followed by trituration with diisopropyl ether gave 2-amino-6-[2-(benzyloxy)phenyl]-4-(4-morpholinyl)nicotinonitrile as a white solid (141 mg, yield; 51%).



(7) Then the benzyl moiety was removed in a same manner as described in the step (2) of Example 1-1. The residue was triturated with Et_2O and dried under reduced pressure to give 2-amino-6-(2-hydroxyphenyl)-4-(4-morpholinyl)nicotinonitrile as a solid (68 mg, yield; 76%).

Molecular weight: 296.33

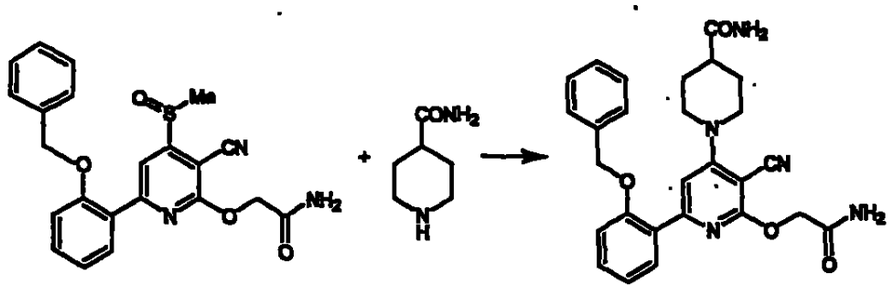
Mass spectrometry: 297 $(M+H)^+$

In vitro activity grade: B

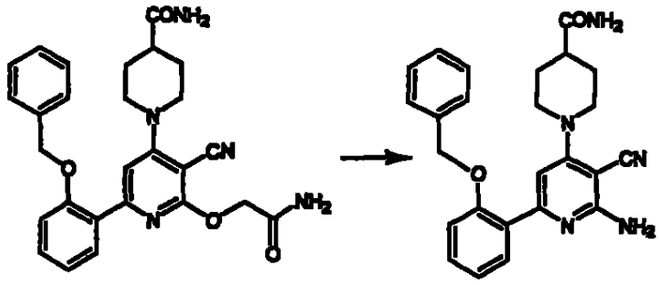
Cellular activity grade: (A549)-C

^{1}H-NMR (300 MHz, DMSO-d6): 3.44 – 3.54 (4H, m), 3.68 – 3.78 (4H, m), 6.77 – 6.90 (3H, m), 7.08 (2H, br s), 7.25 – 7.35 (1H, m), 7.92 – 8.00 (1H, m), 13.77 (1H, s).

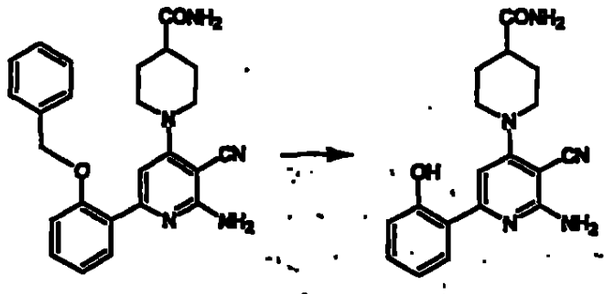
Example 34-2



A mixture of 2-{[6-[2-(benzyloxy)phenyl]-3-cyano-4-(methylsulfinyl)-2-pyridinyl]-oxy}acetamide (500 mg, 1.19 mmol), which was obtained in the step (4) of Example 34-1, and isonipecotamide (228 mg, 1.78 mmol) in DMF (2 mL) was stirred at 130 °C for 5 hrs. After cooled to room temperature, the mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give 1-{2-(2-amino-2-oxoethoxy)-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-4-piperidinecarboxamide as a solid (485 mg, yield; 84%).



A mixture of 1-{2-(2-amino-2-oxoethoxy)-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-4-piperidinecarboxamide (485 mg, 1.00 mmol) and K_2CO_3 (280 mg, 2.03 mmol) in DMF (2.5 mL) was stirred at 130 °C for 28 hrs. After cooled to room temperature, the mixture was diluted with water, and the resulting precipitates were collected by filtration. The precipitates were washed with EtOH and CH_2Cl_2 to give 1-{2-amino-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}-4-piperidinecarboxamide as a solid (119 mg, yield; 28%).



Then the benzyl moiety was removed in a similar manner as that of the step (2) of Example 1-1 to give 1-[2-amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]-4-piperidinecarboxamide as a solid (19 mg, yield; 36%).

Molecular weight: 337.38

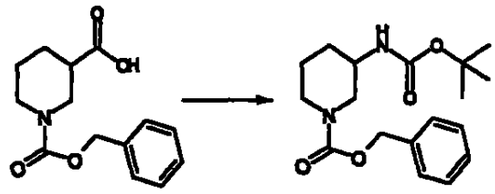
Mass spectrometry: 338 $(M+H)^+$

In vitro activity grade: B

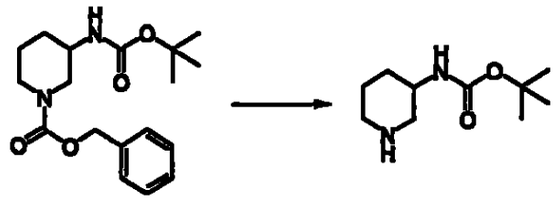
Cellular activity grade: (A549)-C

^{1}H-NMR (300 MHz, DMSO-d6): 1.58 – 1.77 (2H, m), 1.77 – 1.90 (2H, m), 2.30 – 2.46 (1H, m), 2.98 – 3.15 (2H, m), 3.97 (2H, d, J = 12.8 Hz), 6.73 – 6.90 (4H, m), 7.10 (2H, s), 7.22 – 7.36 (2H, m), 7.94 (1H, d, J = 7.2 Hz), 13.85 (1H, s).

Example 34-3

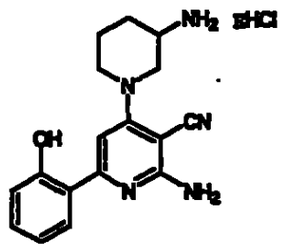


To a solution of 1-[(benzyloxy)carbonyl]-3-piperidinecarboxylic acid (3.00 g, 11.4 mmol) and Et_3N (1.56 mL, 11.4 mmol) in t-BuOH (30 mL) was added diphenyl phosphoryl azide(DPPA) (2.46 mL, 11.4 mmol), and the mixture was refluxed for 21 hrs. After cooled to room temperature, the mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and a saturated aqueous $NaHCO_3$ solution. The organic phase was washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/ethyl acetate = 4/1 to 3/1) gave benzyl 3-[(tert-butoxycarbonyl)amino]-1-piperidinecarboxylate as a solid (2.22 g, yield; 58%).



A mixture of benzyl 3-[(tert-butoxycarbonyl)amino]-1-piperidinecarboxylate (2.25 g, 6.73 mmol) and 10% Pd/C (0.229 g) in EtOH (20 mL) was stirred at room temperature under a hydrogen atmosphere (1 atm) for 14 hrs. The catalyst was removed by filtration through Celite®, and the filtrate was concentrated under reduced pressure to give tert-butyl 3-piperidinylcarbamate as a solid (1.22 g, yield; 91%).

The resulting tert-butyl 3-piperidinylcarbamate and 2-{[6-[2-(benzyloxy)phenyl]-3-cyano-4-(methylsulfinyl)-2-pyridinyl]oxy}acetamide were used as starting materials to prepare 2-amino-4-(3-amino-1-piperidinyl)-6-(2-hydroxyphenyl)nicotinonitrile hydrochloride in a similar manner as described in Example 34-1.



Molecular weight: 345.83

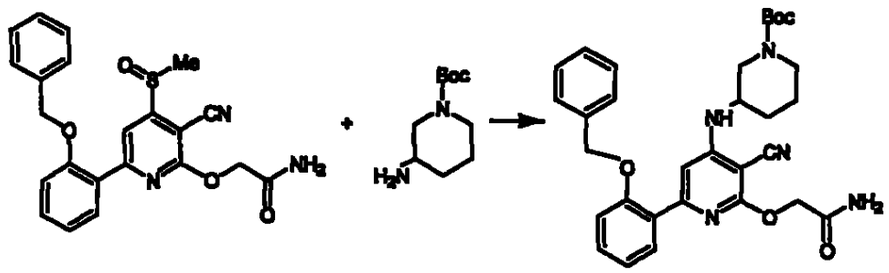
Mass spectrometry: 310 $(M+H)^+$

In vitro activity grade: B

Cellular activity grade: (A549)-B

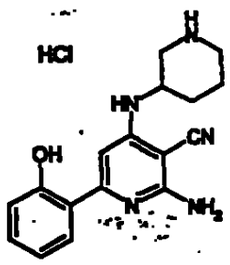
^{1}H-NMR (500 MHz, DMSO-d6): 1.59 – 1.76 (2H, m), 1.82 – 1.95 (1H, m), 2.02 – 2.14(1H, m), 3.27 – 3.50 (3H, m), 3.90 – 4.05 (1H, m), 4.08 – 4.22 (1H, m), 6.80 (1H, s), 6.92 (1H, t, J = 7.6 Hz), 6.96 – 7.06 (1H, m), 7.37 (1H, t, J = 6.9 Hz), 7.79 (3H, br s), 8.39 (3H, br s), 13.25 (1H, br s).

Example 34-4



A mixture of 2-{[6-[2-(benzyloxy)phenyl]-3-cyano-4-(methylsulfinyl)-2-pyridinyl]-oxy}acetamide (500 mg, 1.19 mol), which was obtained in the step (4) of Example 34-1, and tert-butyl 3-amino-1-piperidinecarboxylate (555 mg, 2.77 mmol) in DMF (0.6 mL) was stirred at 130 °C for 24 hrs. After cooled to room temprature, the mixture was partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/ethyl acetate = 1/1) gave tert-butyl 3-({2-(carbamoylmethoxy)-6-[2-(benzyloxy)phenyl]-3-cyano-4-pyridinyl}amino)-1-piperidinecarboxylate as a foam (360 mg, yield; 64%).

With the use of the resulting compound, 2-amino-6-(2-hydroxyphenyl)-4-(3-piperidinylamino)nicotinonitrile hydrochloride was prepared in a similar manner as described in Example 34-2.



Molecular weight: 345.83

Mass spectrometry: 310 $(M + H)^+$

In vitro activity grade: A

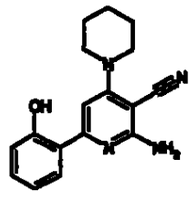
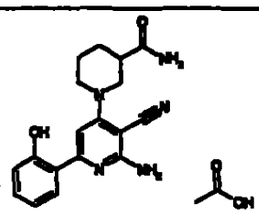
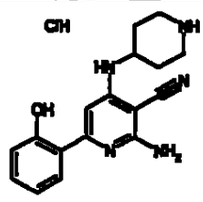
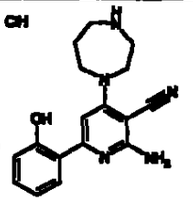
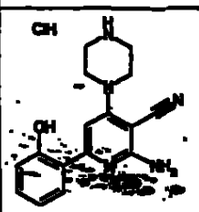
Cellular activity grade: (A549)-A

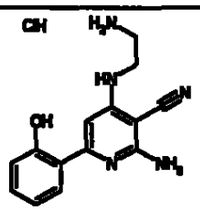
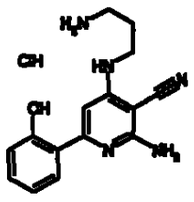
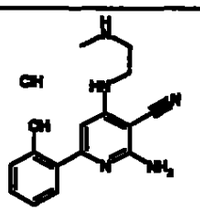
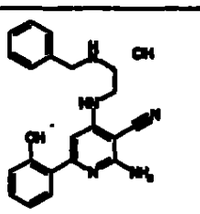
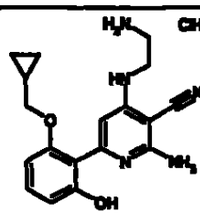
^{1}H-NMR (300 MHz, DMSO-d6): 1.68 – 2.06 (4H, m), 2.66 – 2.96 (2H, m), 3.17 – 3.38 (2H, m), 4.23 (1H, br s), 6.73 (1H, s), 6.92 (1H, t, J = 7.5 Hz), 7.01 (1H, d, J = 7.5 Hz), 7.37 (1H, t, J = 7.5 Hz), 7.55 (3H, br), 7.78 (1H, d, J = 7.5 Hz), 9.20 (2H, br s), 13.20 (1H, br).

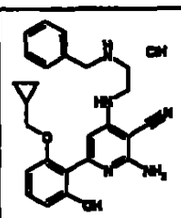
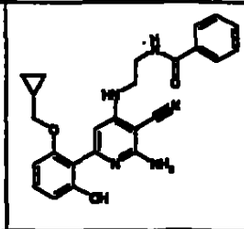
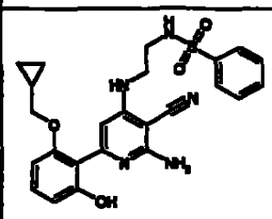
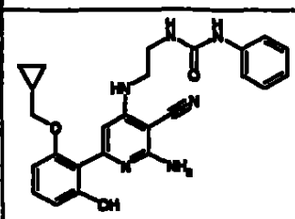
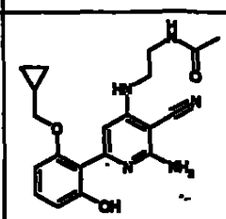
Example 34-5 to 34-19

According to the similar synthetic procedure of Example 34-1 to 34-4, compounds shown in Table 12 were prepared.

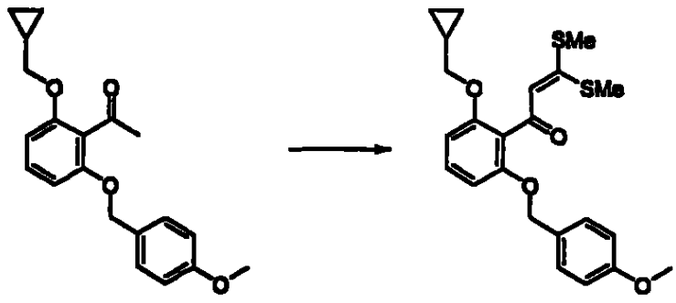
Table 12

Ex. No	Structure	Mol weight	Mass	In vitro	A549	NMR
34-05		294.36	295	D		(300 MHz, DMSO-d6): 1.64 (6H, br s), 3.48 (4H, br s), 6.76 (1H, s), 6.78 - 6.89 (2H, m), 6.98 (1H, br s), 7.28 (1H, t, J = 7.2 Hz), 7.93 (1H, d, J = 7.2 Hz), 13.86 (1H, br s).
34-06		397.44	338	C	C	(300 MHz, DMSO-d6): 1.49 - 1.71 (2H, m), 1.71 - 1.87 (1H, m), 1.91 (3H, s), 1.87 - 2.02 (1H, m), 2.37 - 2.54 (1H, m), 2.94 - 3.08 (1H, m), 3.09 (1H, dd, J = 11.3, 12.8 Hz), 3.88 - 4.04 (2H, m), 6.78 - 6.92 (4H, m), 7.01 (2H, s), 7.24 - 7.33 (1H, m), 7.34 (1H, br s), 7.95 (1H, d, J = 7.2 Hz), 11.92 (1H, br).
34-07		345.83	310	A	B	(500 MHz, DMSO-d6): 1.90 (2H, br s), 1.98 (2H, br s), 2.98 (2H, br s), 3.31 (2H, br s), 4.07 (1H, br s), 6.67 - 6.75 (1H, m), 6.90 - 6.99 (1H, m), 7.04 (1H, br s), 7.30 - 7.47 (1H, m), 7.63 (1H, br s), 7.81 (3H, br), 8.54 (1H, br s), 9.09 (1H, br s), 12.94 (1H, br).
34-08		345.83	310	B	B	(500 MHz, DMSO-d6): 2.20 (2H, br s), 3.24 (2H, br s), 3.36 (2H, br s), 3.91 (2H, br s), 4.09 (2H, br s), 6.69 (1H, s), 6.94 (1H, t, J = 7.6 Hz), 7.03 (1H, d, J = 7.9 Hz), 7.37 (1H, t, J = 7.9 Hz), 7.66 (1H, d, J = 7.3 Hz), 7.84 (2H, br), 9.36 (2H, br s), 13.15 (1H, br).
34-09		331.81	296	A	B	(500 MHz, DMSO-d6): 3.26 (4H, br s), 3.86 (4H, br s), 6.86 (1H, s), 6.92 (1H, t, J = 7.5 Hz), 6.93 - 7.03 (1H, m), 7.36 (1H, t, J = 7.5 Hz), 7.70 (1H, br), 7.82 (1H, d, J = 7.5 Hz), 9.57 (2H, br).

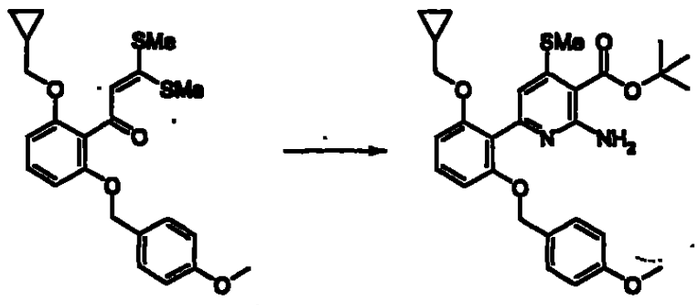
34-10		305.77	270	A	A	(500 MHz, DMSO-d6): 2.92 - 3.07 (2H, m), 3.71(2H, br s), 6.71 (1H, d, J = 2.8 Hz), 6.94 (1H, t, J = 7.8 Hz), 7.03 - 7.11 (1H, m), 7.38 (1H, t, J = 7.8 Hz), 7.71 (1H, br s), 7.95 (3H, br), 8.13 (3H, br s), 12.98 (1H, br).
34-11		319.80	284	A	B	(500 MHz, DMSO-d6): 1.81 - 1.95 (2H, m), 2.79 - 2.91 (2H, m), 3.45 - 3.63 (2H, m), 6.67 (1H, s), 6.92 - 6.96 (1H, m), 7.10 (1H, d, J = 8.2 Hz), 7.35 - 7.43 (1H, m), 7.63 (1H, d, J = 7.8 Hz), 7.85 - 8.55 (6H, m), 12.80 (1H, br).
34-12		319.80	284	A	A	(500 MHz, DMSO-d6): 2.55 - 2.61 (3H, m), 3.08 (2H, br s), 3.77 (2H, br s), 6.73 (1H, s), 6.94 (1H, t, J = 7.8 Hz), 7.02 - 7.11 (1H, m), 7.38 (1H, t, J = 7.8 Hz), 7.74 (1H, br), 7.96 (2H, br), 9.06 (2H, br), 12.99 (1H, br).
34-13		395.90	360	A	A	(500 MHz, DMSO-d6): 3.11 (2H, br s), 3.77 - 3.93 (2H, m), 4.15 - 4.23 (2H, m), 6.78 (1H, s), 6.90 - 6.98 (1H, m), 7.07 (1H, d, J = 8.2 Hz), 7.33 - 7.48 (4H, m), 7.55 - 7.64 (2H, m), 7.66 - 7.79 (1H, m), 7.98 (3H, br), 8.57 (2H, br s), 12.97 (1H, br).
34-14		375.86	340	A		(500 MHz, DMSO-d6): 0.26 - 0.37 (2H, m), 0.44 - 0.55 (2H, m), 1.11 - 1.20 (1H, m), 2.85 (2H, br s), 3.63 (2H, br s), 3.84 (2H, d, J = 6.9 Hz), 6.51 - 6.72 (3H, m), 7.26 (1H, t, J = 8.4 Hz), 7.75 - 8.35 (6H, m), 10.39 (1H, br), 12.89 (1H, br).

34-15		465.99	430	A	A	(500 MHz, DMSO-d6): 0.28 - 0.37 (2H, m), 0.44 - 0.55 (2H, m), 1.10 - 1.22 (1H, m), 3.11 (2H, br s), 3.74 (2H, br s), 3.85 (2H, d, J = 6.6 Hz), 4.18 (2H, br s), 6.50 - 6.74 (3H, m), 7.22 - 7.32 (1H, m), 7.39 - 7.48 (3H, m), 7.52 - 7.58 (2H, m), 7.86 and 8.21 (2H, br), 9.21 and 10.35 (2H, br), 12.81 (1H, br).
34-16		443.51	444	A	A	(500 MHz, DMSO-d6): 0.25 - 0.37 (2H, m), 0.47 - 0.57 (2H, m), 1.22 - 1.33 (1H, m), 3.41 - 3.54 (4H, m), 3.83 (2H, d, J = 6.9 Hz), 6.39 - 6.49 (2H, m), 6.80 - 7.00 (3H, m), 7.14 (1H, t, J = 8.2 Hz), 7.23 (1H, br s), 7.43 (2H, t, J = 7.3 Hz), 7.51 (1H, t, J = 7.3 Hz), 7.80 (2H, d, J = 7.3 Hz), 8.62 (1H, br s), 14.39 (1H, br).
34-17		479.56	480	A	C	(500 MHz, DMSO-d6): 0.25 - 0.36 (2H, m), 0.47 - 0.58 (2H, m), 1.18 - 1.30 (1H, m), 2.98 (2H, q, J = 6.0 Hz), 3.33 (2H, q, J = 6.0 Hz), 3.82 (2H, d, J = 6.9 Hz), 6.40 - 6.48 (2H, m), 6.80 (1H, t, J = 6.0 Hz), 6.76 (2H, s), 7.07 (1H, s), 7.13 (1H, t, J = 8.2 Hz), 7.52 (2H, t, J = 7.3 Hz), 7.59 (1H, t, J = 7.3 Hz), 7.75 (2H, d, J = 7.3 Hz), 7.80 (1H, t, J = 6.0 Hz), 14.28 (1H, br s).
34-18		458.52	459	A	A	(500 MHz, DMSO-d6): 0.28 - 0.37 (2H, m), 0.50 - 0.62 (2H, m), 1.22 - 1.34 (1H, m), 3.35 (4H, br s), 3.83 (2H, d, J = 6.9 Hz), 6.33 (1H, br s), 6.40 - 6.48 (2H, m), 6.80 (2H, br), 6.85 - 6.92 (1H, m), 7.10 - 7.25 (4H, m), 7.37 (2H, d, J = 7.8 Hz), 8.57 (1H, s), 14.44 (1H, br).
34-19		381.44	382	A	A	(300 MHz, CDCl3): 0.31 - 0.41 (2H, m), 0.60 - 0.70 (2H, m), 1.21 - 1.38 (1H, m), 1.98 (3H, s), 3.40 - 3.60 (4H, m), 3.84 (2H, d, J = 7.2 Hz), 5.60 (2H, br s), 6.11 (1H, br s), 6.37 (1H, d, J = 8.3 Hz), 6.53 (1H, d, J = 8.3 Hz), 7.13 (1H, t, J = 8.3 Hz), 7.35 (1H, s), 7.48 (1H, br s), 14.44 (1H, br s).

Example 35-1

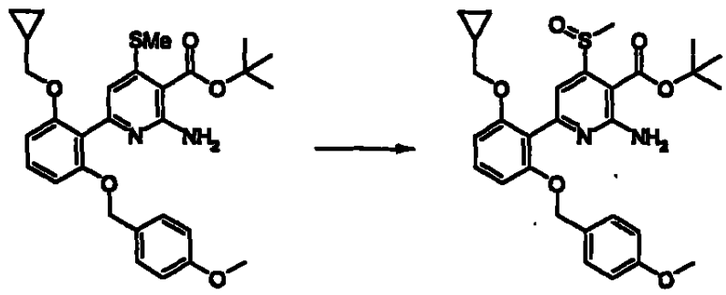


To a suspension of potassium tert-butoxide (0.809 g, 6.128 mmol) in THF (5 mL) was added a solution of 1-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]-phenyl}ethanone (1.00 g, 3.064 mmol)(starting compound 1G) in THF (5 mL) followed by carbon disulfide (0.23 mL, 3.83 mmol) and methyl iodide (0.57 mL, 9.19 mmol) successively. The resulting mixture was stirred at room temperature for 40 min, and then partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/ethyl acetate 4:1 to 3:1) gave 1-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3,3-bis(methylsulfanyl)-2-propene-1-one as a pale yellow oil (0.825 g, yield; 63%).

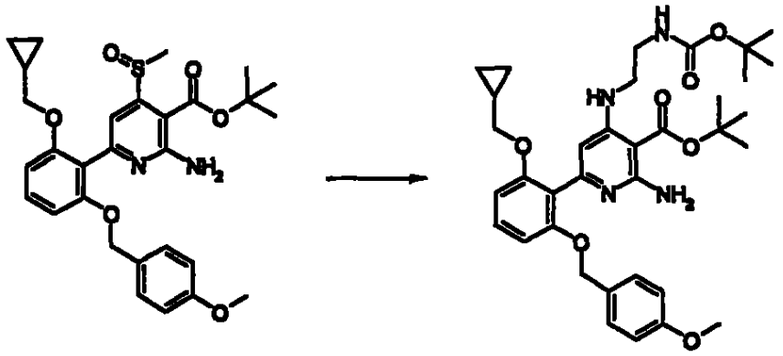


To a suspension of NaH (60%, 0.056 g, 1.39 mmol) in THF (3 mL) was added a solution of t-butyl cyanoacetate (0.197 g, 1.392 mmol) in THF (1 mL) in one portion. After 10 min, a solution of 1-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)-oxy]phenyl}-3,3-bis(methylsulfanyl)-2-propene-1-one (0.500 g, 1.16 mmol) in THF

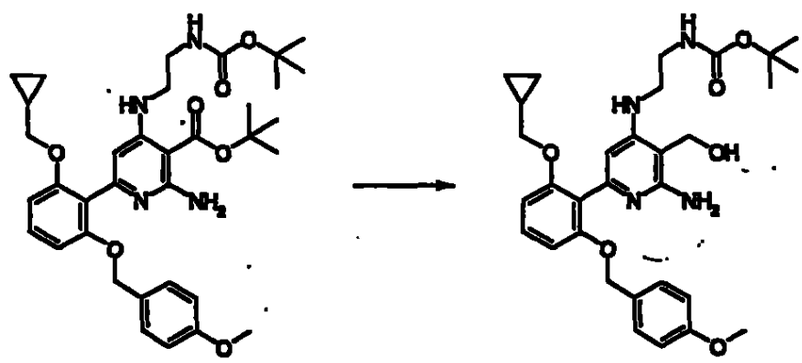
(3 mL) was added followed by dibenzo-18-crown-6 (0.013 g, 0.035 mmol). The resulting mixture was refluxed for 4 hrs. After cooled to room temperature, the mixture was partitioned between 0.1 N acetic acid solution and CH_2Cl_2. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual oil was dissolved in 1,2-dichloroethane (1 mL) and acetic acid (1 mL), and ammonium acetate (1.20 g, 15.57 mmol) was added. The mixture was stirred at 120 °C for 0.5 hrs. After cooled to room temperature, the mixture was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The organic phase was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/ethyl acetate 4:1 to 3:1) gave tert-butyl 2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-4-(methylsulfanyl)nicotinate as an pale yellow oil (0.177 g, yield; 29%).



To a cold (0 °C) solution of tert-butyl 2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-4-(methylsulfanyl)nicotinate (1.72 g, 3.30 mmol) in CH_2Cl_2 (20 mL) was added m-CPBA (69%, 0.82 g, 3.30 mmol). The reaction mixture was stirred at 0 °C for 15 min, quenched with saturated aqueous $NaHCO_3$ solution (20 mL) containing $Na_2S_2O_3$ (1 g). The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/ethyl acetate = 3:2 to 1:1) gave solid, which was triturated with ethyl acetate and diisopropyl ether to give tert-butyl 2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-4-(methylsulfinyl)nicotinate as a white powder (1.112 g, yield; 63%).

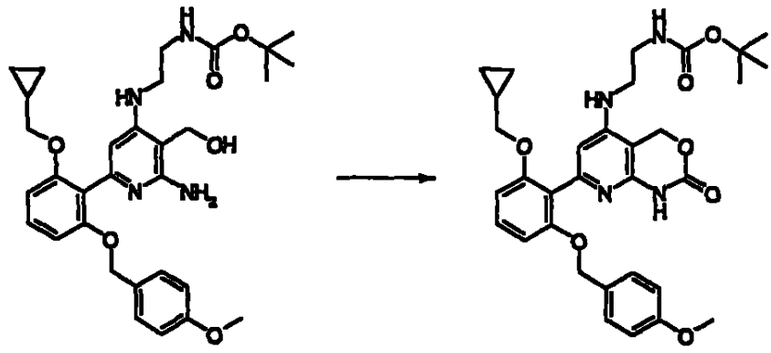


A mixture of tert-butyl 2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-4-(methylsulfinyl)nicotinate (0.118 g, 0.219 mmol) and ethylenediamine (0.29 mL) was stirred at 100 °C for 8 hrs. After cooled to room temperature, the mixture was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL), and di-tert-butyl dicarbonate (0.060 g, 0.275 mmol) was added. The mixture was stirred at room temperature for 2 hrs and concentrated under reduced pressure. The residue was purified by column chromatography to give tert-butyl 2-amino-4-({2-[(tert-butoxycarbonyl)amino]ethyl}amino)-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}nicotinate as a foam (0.121 g, 92%).

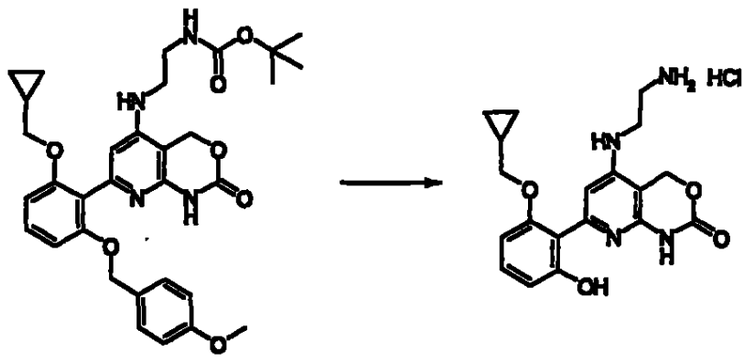


To a cold (0 °C) solution of tert-butyl 2-amino-4-({2-[(tert-butoxycarbonyl)amino]ethyl}amino)-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}nicotinate (0.113 g, 0.178 mmol) in THF (5 mL) was added a solution of Vitride®

(3.4 M, 1.0 mL, 3.4 mmol). The mixture was stirred at 0 °C for 0.5 hrs, quenched with saturated aqueous potassium sodium tartaric acid solution, and then partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a solid, which was triturated with ethyl acetate and diisopropyl ether to give tert-butyl 2-{[2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]-phenyl}-3-(hydroxymethyl)-4-pyridinyl]amino}ethylcarbamate as a pink solid (0.078 g, yield; 78%).



To a cold (0 °C) solution of tert-butyl 2-{[2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-(hydroxymethyl)-4-pyridinyl]amino}ethylcarbamate (0.050 g, 0.089 mmol) and Et_3N (0.074 mL, 0.531 mmol) in THF (10 mL) was added triphosgene (0.013 g, 0.044 mmol) in one portion. The mixture was stirred at 0 °C for 1 hr, and then partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (ethyl acetate) gave tert-butyl 2-[(7-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)-oxy]phenyl}-2-oxo-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-5-yl)amino]ethylcarbamate as colorless oil (0.036 g, yield; 69%).



To a solution of tert-butyl 2-[(7-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)-oxy]phenyl}-2-oxo-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-5-yl)amino]ethyl-carbamate (0.032 g, 0.054 mmol) in 1,4-dioxane (1 mL) was added 4N HCl in 1,4-dioxane (1 mL). The mixture was stirred at room temperature overnight. The resulting precipitate was collected by filtration, washed with ethyl acetate to give 5-[(2-aminoethyl)amino]-7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one hydrochloride as a solid (0.013 g, yield; 59%).

Molecular weight: 406.87

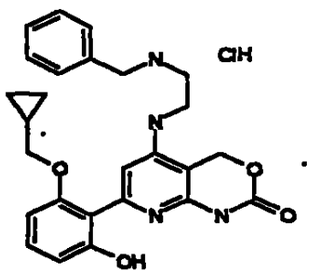
Mass spectrometry: 370 $(M+H)^+$

In vitro activity grade: A

Cellular activity grade: (A549)-A

^{1}H-NMR (500 MHz, DMSO-d6): 0.26 – 0.36 (2H, m), 0.47 – 0.57 (2H, m), 1.15 – 1.25 (1H, m), 2.96 – 3.07 (2H, m), 3.50 – 3.60 (2H, m), 3.85 (2H, d, J = 6.9 Hz), 5.45 (2H, br s), 6.57 (1H, d, J = 8.2 Hz), 6.56 – 6.68 (1H, m), 6.96 (1H, br s), 7.24 (1H, t, J = 8.2 Hz), 7.75 (1H, br), 8.18 (3H, br s), 10.86 (1H, br).

Example 35-2



In a similar manner as that of Example 35-1, 5-(2-benzylamino-ethylamino)-6-(2-cyclopropylmethoxy-6-hydroxy-phenyl)-1,4-dihydro-pyrido[2,3-d][1,3]oxazin-2-one hydrochloride was prepared.

Molecular weight: 497.00

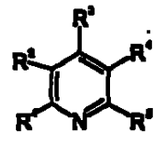
Mass spectrometry: 461 $(M+H)^+$

In vitro activity grade: A

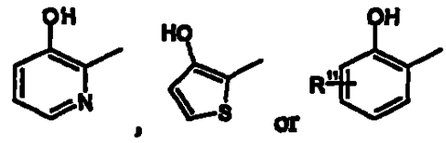
(500 MHz, DMSO-d6): 0.26 – 0.35 (2H, m), 0.45 – 0.58 (2H, m), 1.10 – 1.28 (1H, m), 3.16 (2H, br s), 3.67 (2H, br), 3.85 (2H, d, J = 6.8 Hz), 4.13 – 4.25 (2H, m), 5.43 (2H, br s), 6.50 – 6.65 (2H, m), 7.04 (1H, br s), 7.22 (1H, t, J = 8.3 Hz), 7.35 – 7.50 (4H, m), 7.50 – 7.65 (3H, m), 9.44 (2H, br), 10.74 (1H, br).

CLAIMS

1. A pyridine derivative of the formula (I)



wherein -R^1 represents



in which R^{11} is hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-12} alkoxy, nitro, amino, C_{1-6} alkylsulfonylamino, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di (C_{1-6} alkyl)amino, C_{1-6} alkanoylamino, phenyl C_{1-6} alkylamino, phenylsulfonylamino, or -O-$(CH_2)_n$-R^{111},

wherein n represents an integer selected from 0 to 6, and R^{111} is C_{2-6} alkenyl, benzoyl, diphenylmethyl, di (C_{1-6} alkyl)amino, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, or a 3 to 10 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of S, O and N as heteroatoms and is optionally substituted by C_{1-6} alkyl, mono or di halogen, halogen substituted C_{1-6} alkyl, nitro, ciano, C_{1-6} alkoxycarbonyl, phenyl, hydroxy, amino, C_{1-6} alkylamino, di (C_{1-6} alkyl)amino, C_{1-6} alkanoylamino, C_{1-6} alkoxy, or carbamoyl;

R^2 represents hydrogen or halogen;

R^3 represents hydrogen or 1,2,3,6-Tetrahydro-pyridine,

$-CR^{31}R^{32}R^{33}$,

wherein R^{31} is hydrogen or C_{1-6} alkyl,

R^{32} is hydrogen, α-aminobenzyl, C_{1-6} alkyl optionally substituted by one or two substituents selected from the group consisting of hydroxy, amino, amino substituted phenyl, phenyl, halogen substituted phenyl, and C_{1-6} alkoxysubstituted phenyl, or a 5 to 8 membered saturated ring having 0 to 3 atoms selected from the group consisting of S, O and N as heteroatoms and optionally substituted by C_{1-6} alkyl, and

R^{33} is hydrogen, amino, C_{1-6} alkoxycarbonylamino, C_{2-6} alkenyloxycarbonyl-amino, piperidino-C_{1-6} alkylcarbonylamino, piperidinyl-C_{1-6} alkyl-carbonylamino, or

R^{32} and R^{33} may form, together with the adjacent carbon atom, a 5 to 8 membered saturated ring having 0 to 3 heteroatoms selected from the group consisting of N, O and S as heteroatoms, which ring is optionally substituted by phenyl-C_{1-6} alkyl, C_{1-6} alkoxy substituted phenyl- C_{1-6} alkyl, C_{1-6} alkyl, amino, ciano, hydroxy, carbamoyl, carboxy, C_{1-6} alkylamino, C_{1-6} alkoxycarbonyl, di(C_{1-6} alkyl)amino, benzylamino, C_{1-6} alkylsulfonyl, piperidino C_{1-6} alkyl carbonyl, or optionally fused by benzene;

or

$-NR^{34}R^{35}$,

wherein R^{34} is hydrogen or C_{1-6} alkyl and

R^{35} is hydrogen, a 5 to 8 membered saturated ring having 0 to 3 heteroatoms selected from the group consisting of N, O and S as heteroatoms, or $-(CH_2)_m-NR^{351}R^{352}$(m represents any of integers from 1 to 6)

wherein R^{351} represents hydrogen, C_{1-6} alkyl,

R^{352} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsubstituted phenyl, benzoyl, C_{1-6} alkanoyl, phenylaminocarbonyl, phenylsulfonyl, or

R^{34} and R^{35} may form, together with the adjacent N atom, a 5 to 8 membered saturated heterocyclic ring, and said ring may optionally contain NH, S or O atom other than the adjacent N atom and optionally substituted by carbamoyl, amino, or C_{1-6} alkyl;

R^4 represents hydroxycarbonyl, C_{1-6} alkanoyl, carbamoyl, cyano, nitro, carboxyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, C_{1-6} alkylamino, 5 to 10 membered heteroaryl (hydroxy) methyl, 5 to 10 membered heteroaryl-C_{1-6} alkyl, or methyl substituted by hydroxy and a 5 to 7 membered saturated cyclic ring, C_{1-6} alkyl optionally substituted by one selected from the group consisting of hydroxy, C_{1-6} alkoxy, C_{1-6} alkylsulfonylamino, C_{1-6} alkylcarbonylamino, C_{5-10} aryl, C_{5-10} arylsulfonyl, C_{5-10} arylsulfanyl, C_{5-10} aryloxy, imidazolyl, or dioxo substituted pyrolidino-oxy,

$$-(CH_2)_pNHCOR^{41}, -(CH_2)_pNHC(=S)R^{41}$$

wherein p represents any of integer from 1 to 6 and R^{41} represents C_{1-6} alkoxy, amino, phenylamino, C_{1-6} alkyl, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-10} cycloalkylamino,

R^3 and R^4 may form, together with the carbon atoms in the pyridine ring, 4 to 10 membered monocycloalkyl or bicycloalkyl optionally interrupted by NH and optionally substituted by benzyl, =NH, or =O;

R^5 represents $NR^{51}R^{52}$,

wherein R^{51} is hydrogen, C_{1-6} alkyl,

R^{52} is hydrogen, C_{1-6} alkyl, phenyl, benzyl, C_{1-6} alkanoyl, or NR51 R52 may form saturated 5-6 membered ring optionally contain NH or O as other heteroatom than the adjacent N atom,

or

R^4 and R^5 may form,

$-R^{40}-CO-NH-$,
$-R^{40}-SO_2-NH-$,
$-R^{40}-C(=S)-NH-$
$-R^{40}-CH_2-NH-$,

wherein said $-R^{40}-$ represents $-CHR^{401}-O-$, $-CH_2-N\ R^{401}-$, $-CO-NR^{401}-$, $-CH_2-CHR^{401}-$, $-CH=CR^{401}-$, (in which R^{401} is C_{1-6} alkanoyl, C_{1-6} alkyl, phenyl, C_{1-6} alkylsulfonyl, C_{3-8} cycloalkylaminocarbonyl, hydrogen, halogen, nitro, amino, ciano, benzoylamino, phenylsulfonyl, carbamoyl, hydroxycarbonyl, C_{1-6} alkoxycarbonyl, C_{1-12} alkylaminocarbonyl, halogen substituted C_{1-6} alkylaminocarbonyl, C_{1-6} alkanoylamino, C_{1-6} alkylamino, di(C_{1-6} alkyl)aminocarbonyl, di(C_{1-6} alkyl)aminoC_{1-6} alkylaminocarbonyl, hydroindenylaminocarbonyl, diphenylmethylaminocarbonyl, pyrrolidinocarbonyl, C_{1-6} alkoxy C_{1-6} alkyl amino carbonyl, morpholinocarbonyl, piperazinocarbonyl, phenylC_{1-6}alkylaminocarbonyl, hydroxycarbonylC_{1-6}alkylaminocarbonyl, C_{3-8} cycloalkylaminocarbonyl, C_{3-8} cycloalkylC_{1-6}alkylaminocarbonyl, hydroxyC_{1-6}alkylaminocarbonyl, carboxyethylaminocarbonyl, C_{1-6}alkylsulfonylaminocarbonyl)

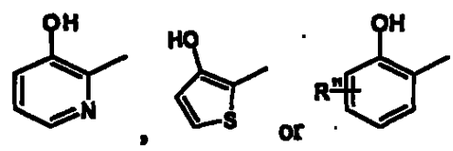
$-CR^{41}=N-NH-$ (R^{41} is hydrogen, amino, or C_{1-6}alkanoylamino),

$-CR^{42}=N-C=N-$ (R^{42} is hydrogen or amino)

or a salt thereof.

2. The compound or a salt thereof as claimed in claim 1, wherein:

$-R^1$ represents



in which R^{11} is hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-12} alkoxy, amino, C_{1-6} alkanoylamino, phenyl C_{1-6} alkylamino, phenylsulfonylamino, or $-O-(CH_2)_n-R^{111}$,

wherein n represents an integer selected from 1 to 6, and R^{111} is C_{2-6} alkenyl, benzoyl, diphenylmethyl, di (C_{1-6} alkyl)amino, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, or a 3 to 10 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of S, O and N as heteroatoms and is optionally substituted by C_{1-6} alkyl, mono or di halogen, halogen substituted C_{1-6} alkyl, nitro, ciano, C_{1-6} alkoxycarbonyl, phenyl;

R^2 represents hydrogen;

R^3 represents hydrogen, 1,2,3,6-tetrahydro-pyridine

$$-CR^{31}R^{32}R^{33},$$

wherein R^{31} is hydrogen or C_{1-6} alkyl,

R^{32} is hydrogen, α-aminobenzyl, C_{1-6} alkyl optionally substituted by one or two substituents selected from the group consisting of hydroxy, amino, amino substituted phenyl, phenyl, halogen substituted phenyl, and C_{1-6} alkoxysubstituted phenyl, or a 5 to 8 membered saturated ring having 0 to 3 atoms selected from the group consisting of S, O and N as heteroatoms and optionally substituted by C_{1-6} alkyl, and

R^{33} is hydrogen, amino, C_{1-6} alkoxycarbonylamino, C_{2-6} alkenyloxycarbonyl-amino, piperidino-C_{1-6} alkylcarbonylamino, or

R^{32} and R^{33} may form, together with the adjacent carbon atom, a 5 to 8 membered saturated ring having 0 to 3 heteroatoms selected from the group consisting of N, O and S as heteroatoms, which ring is optionally substituted by phenyl-C_{1-6} alkyl, C_{1-6} alkoxy substituted phenyl- C_{1-6} alkyl, C_{1-6} alkyl, amino, carboxy, C_{1-6} alkylamino, C_{1-6} alkoxycarbonyl, di(C_{1-6} alkyl)amino, benzylamino, C_{1-6} alkylsulfonyl, piperidino C_{1-6} alkyl carbonyl, or optionally fused by benzene;

or

$$-NR^{34}R^{35},$$

wherein R^{34} is hydrogen and

R^{35} is hydrogen, a 5 to 8 membered saturated ring having 0 to 3 heteroatoms selected from the group consisting of N, O and S as heteroatoms, or $-(CH_2)_m-NR^{351}R^{352}$(m represents any of integers from 1 to 6)

wherein R^{351} represents hydrogen, C_{1-6} alkyl,

R^{352} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsubstituted phenyl, benzoyl, C_{1-6} alkanoyl, phenylaminocarbonyl, phenylsulfonyl, or

R^{34} and R^{35} may form, together with the adjacent N atom, a 5 to 8 membered saturated heterocyclic ring, and said ring may optionally contain NH, S or O atom other than the adjacent Natom and optionally substituted by carbamoyl, amino, or C_{1-6} alkyl;

R^4 represents hydroxycarbonyl, C_{1-6} alkanoyl, carbamoyl, cyano, carboxyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, C_{1-6} alkylamino, 5 to 10 membered heteroaryl (hydroxy) methyl, 5 to 10 membered heteroaryl-C_{1-6} alkyl, or methyl substituted by hydroxy and a 5 to 7 membered saturated cyclic ring, C_{1-6} alkyl optionally substituted by one selected from the group consisting of hydroxy, C_{1-6} alkoxy, C_{1-6} alkylsulfonylamino, C_{1-6} alkylcarbonylamino, C_{5-10} aryl, C_{5-10} arylsulfanyl, C_{5-10} arylsulfenyl, C_{5-10} aryloxy, imidazolyl, or dioxo substituted pyrolidino-oxy,

$$-(CH_2)_pNHCOR^{41}, -(CH_2)_pNHC(=S)R^{41}$$

wherein p represents any of integer from 1 to 6 and R^{41} represents C_{1-6} alkoxy, amino, phenylamino, C_{1-6} alkyl, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-10} cycloalkylamino,

R^3 and R^4 may form, together with the carbon atoms in the pyridine ring, 4 to 10 membered monocycloalkyl or bicycloalkyl optionally interrupted by NH and optionally substituted by benzyl, =NH, or =O;

R^5 represents $NR^{51}R^{52}$,

wherein R^{51} is hydrogen, C_{1-6} alkyl,

R^{52} is hydrogen, C_{1-6} alkyl, phenyl, benzyl, C_{1-6} alkanoyl, or $NR^{51}R^{52}$ may form piperidino,

or

R^4 and R^5 may form,

$-R^{40}-CO-NH-$, $-R^{40}-SO_2-NH-$,
$-R^{40}-C(=S)-NH-$ or
$-R^{40}-CH_2-NH-$,

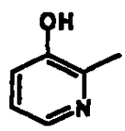
wherein said $-R^{40}-$ represents $-CHR^{401}-O-$, $-CH_2-N\,R^{401}-$, $-CO-NR^{401}-$, (in which R^{401} is hydrogen, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkyl, phenyl, C_{1-6} alkylsulfonyl, C_{3-8} cycloalkylaminocarbonyl, C_{1-6} alkylaminocarbonyl, carbamoyl, di (C_{1-6} alkyl)aminocarbonyl), $-CH_2-CHR^{402}-$, $-CH=CR^{402}-$, (in which R^{402} is hydrogen, halogen, nitro, amino, ciano, benzoylamino, phenylsulfonyl, carbamoyl, hydroxycarbonyl, C_{1-6} alkoxycarbonyl, C_{1-12} alkylaminocarbonyl, halogen substituted C_{1-6} alkylaminocarbonyl, C_{1-6} alkanoylamino, C_{1-6} alkylamino, di(C_{1-6} alkyl)aminocarbonyl, di(C_{1-6} alkyl)aminoC_{1-6} alkylaminocarbonyl, hydroindenylaminocarbonyl, diphenylmethylaminocarbonyl, pyrrolidinocarbonyl, C_{1-6} alkoxy C_{1-6} alkyl amino carbonyl, morpholinocarbonyl, piperazinocarbonyl, phenylC_{1-6}alkylaminocarbonyl, C_{3-8}cycloalkylaminocarbonyl, hydroxycarbonylC_{1-6}alkylaminocarbonyl, C_{3-8} cycloalkylC_{1-6}alkylaminocarbonyl, hydroxyC_{1-6}alkylaminocarbonyl, carboxyethylaminocarbonyl, methylsulfonylaminocarbonyl,)

$-CR^{41}=N-NH-$ (R^{41} is hydroxy, amino, C_{1-6}alkanoylamino) or
$-CR^{42}=N-C=N-$ (R^{42} is amino)

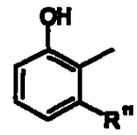
or a salt thereof.

3. The compound or a salt thereof as claimed in claim 1, wherein:

$-R^1$ represents



, or



in which R^{11} is hydrogen, C_{1-12} alkoxy, or $-O-(CH_2)_n-R^{111}$,

wherein n represents an integer selected from 1 to 6, and R^{111} is phenyl, C_{3-8} cycloalkyl;

R^2 represents hydrogen;

R^3 represents 1,2,3,6-tetrahydro-pyridine,

$-CR^{31}R^{32}R^{33}$,

wherein R^{31} is hydrogen,

and

R^{32} and R^{33} form, together with the adjacent carbon atom, a 5 to 8 membered saturated ring interrupted by NH, which ring is optionally substituted by phenyl-C_{1-6} alkyl, C_{1-6} alkoxy substituted phenyl- C_{1-6} alkyl, C_{1-6} alkyl, amino, carboxy, C_{1-6} alkylamino, C_{1-6} alkoxycarbonyl, di(C_{1-6} alkyl)amino, benzylamino, C_{1-6} alkylsulfonyl, piperidino C_{1-6} alkyl carbonyl, or optionally fused by benzene;

or

$-NR^{34}R^{35}$,

wherein R^{34} is hydrogen and

R^{35} is $-(CH_2)_m-NR^{351}R^{352}$(m represents any of integers from 1 to 6)

wherein R^{351} represents hydrogen, C_{1-6} alkyl,

R^{352} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsubstituted phenyl, benzoyl, C_{1-6} alkanoyl, phenylaminocarbonyl, phenylsulfonyl; and

R^4 represents cyano, C_{1-6} alkyl optionally substituted by hydroxy or C_{1-6} alkoxy, or

$-(CH_2)_pNHCOR^{41}$, $-(CH_2)_pNHC(=S)R^{41}$

wherein p represents any of integer from 1 to 6 and R^{41} represents C_{1-6} alkoxy, amino, phenylamino, C_{1-6} alkyl, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-10} cycloalkylamino;

R^5 represents amino,

or

R^4 and R^5 may form,

$-R^{40}-CO-NH-$, $-R^{40}-SO_2-NH-$,
$-R^{40}-C(=S)-NH-$ or
$-R^{40}-CH_2-NH-$,

wherein said -R^{40}- represents –CHR^{401}-O-, -CH_2-N R^{401}-, -CO-NR^{401}-, (in which R^{401} is hydrogen, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkyl, phenyl, C_{1-6} alkylsulfonyl, C_{3-8} cycloalkylaminocarbonyl, C_{1-6} alkylaminocarbonyl, carbamoyl, di (C_{1-6} alkyl)aminocarbonyl), -CH_2-CHR^{402}-, -CH=CR^{402}-, (in which R^{402} is hydrogen, halogen, nitro, amino, ciano, benzoylamino, phenylsulfonyl, carbamoyl, hydroxycarbonyl, C_{1-6} alkoxycarbonyl, C_{1-12} alkylaminocarbonyl, halogen substituted C_{1-6} alkylaminocarbonyl, C_{1-6} alkanoylamino, C_{1-6} alkylamino, di(C_{1-6} alkyl)aminocarbonyl, di(C_{1-6} alkyl)aminoC_{1-6} alkylaminocarbonyl, hydroindenylaminocarbonyl, diphenylmethylaminocarbonyl, pyrrolidinocarbonyl, C_{1-6} alkoxy C_{1-6} alkyl amino carbonyl, morpholinocarbonyl, piperazinocarbonyl, phenylC_{1-6}alkylaminocarbonyl, C_{3-8} cycloalkylaminocarbonyl, hydroxycarbonylC_{1-6}alkylaminocarbonyl, C_{3-8} cycloalkylC_{1-6}alkylaminocarbonyl, hydroxyC_{1-6} alkylaminocarbonyl, carboxyethylaminocarbonyl, methylsulfonylaminocarbonyl,)

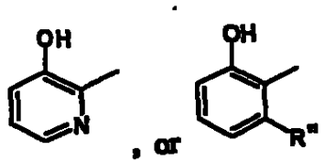
-CR^{41}=N-NH- (R^{41} is hydroxy, amino, C_{1-6}alkanoylamino) or

-CR^{42}=N-C=N- (R^{42} is amino)

or a salt thereof.

4. The compound or a salt thereof as claimed in claim 1, wherein

-R^1 represents



in which R^{11} is hydrogen, C_{1-6} alkoxy, or -O-CH_2-R^{111},

wherein R^{111} is phenyl, C_{3-4} cycloalkyl;

R^2 represents hydrogen;

R^3 represents 1,2,3,6-tetrahydro-pyridine,

$-CR^{31}R^{32}R^{33}$,

wherein R^{31} is hydrogen,

and

R^{32} and R^{33} form, together with the adjacent carbon atom, piperidine or pyrrolidine, which piperidine or pyrrolidine is optionally substituted by C_{1-6} alkyl;

or

$-NR^{34}R^{35}$,

wherein R^{34} is hydrogen and

R^{35} is $-(CH_2)_m-NR^{351}R^{352}$(m represents any of integers from 1 to 6)

wherein R^{351} represents hydrogen, C_{1-6} alkyl,

R^{352} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsubstituted phenyl, benzoyl, C_{1-6} alkanoyl, phenylaminocarbonyl, phenylsulfonyl; and

R^4 represents cyano, hydroxymethyl, or $-CH_2NHCOR^{41}$,

wherein R^{41} represents C_{1-6} alkoxy, amino, phenylamino, C_{1-6} alkyl, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-10} cycloalkylamino;

R^5 represents amino,

or

R^4 and R^5 may form,

$$-R^{40}-CO-NH- \text{ or } -R^{40}-CH_2-NH-,$$

wherein said $-R^{40}-$ represents $-CHR^{401}-O-$, $-CH_2-N\,R^{401}-$, $-CO-NR^{401}-$, (in which R^{401} is hydrogen, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkyl, phenyl, C_{1-6} alkylsulfonyl, C_{3-8} cycloalkylaminocarbonyl, C_{1-6} alkylaminocarbonyl, carbamoyl, di (C_{1-6} alkyl)aminocarbonyl), $-CH_2-CHR^{402}-$, $-CH=CR^{402}-$, (in which R^{402} is hydrogen, halogen, nitro, amino, ciano, benzoylamino, phenylsulfonyl, carbamoyl, hydroxycarbonyl, C_{1-6} alkoxycarbonyl, C_{1-12} alkylaminocarbonyl, halogen substituted C_{1-6} alkylaminocarbonyl, C_{1-6} alkanoylamino, C_{1-6} alkylamino, di(C_{1-6} alkyl)aminocarbonyl, di(C_{1-6} alkyl)aminoC_{1-6} alkylaminocarbonyl, hydroindenylaminocarbonyl, diphenylmethylaminocarbonyl, pyrrolidinocarbonyl, C_{1-6} alkoxy C_{1-6} alkyl amino carbonyl, morpholinocarbonyl, piperazinocarbonyl, phenylC_{1-6}alkylaminocarbonyl, C_{3-8} cycloalkylaminocarbonyl, hydroxycarbonylC_{1-6}alkylaminocarbonyl, C_{3-8} cycloalkylC_{1-6}alkylaminocarbonyl, hydroxyC_{1-6}alkylaminocarbonyl, carboxyethylaminocarbonyl, methylsulfonylaminocarbonyl)

or a salt thereof.

5. The compound as claimed in claim 1 selected from the group consisting of the following compounds:

7-(2-hydroxyphenyl)-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one;

2-amino-6-[2-(benzyloxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinonitrile;

2-amino-6-(2-hydroxy-6-propoxyphenyl)-4-(3-piperidinyl)nicotinonitrile;

2-[6-amino-5-(hydroxymethyl)-4-(3-piperidinyl)-2-pyridinyl]-3-(benzyloxy)phenol;

7-[2-(benzyloxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one;

7-(2-hydroxyphenyl)-5-(3-piperidinyl)-3,4-dihydro-1,8-naphthyridin-2(1H)-one;

2-amino-6-[2-(cyclobutylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)nicotinonitrile;

2-[6-amino-5-(hydroxymethyl)-4-(3-piperidinyl)-2-pyridinyl]-3-propoxyphenol;

7-(2-hydroxy-6-propoxyphenyl)-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one;

ethyl 7-(2-hydroxy-6-propoxyphenyl)-2-oxo-5-(3-piperidinyl)-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate;

7-(2-hydroxy-6-propoxyphenyl)-5-(3-piperidinyl)-3,4-dihydro-1,8-naphthyridin-2(1H)-one;

2-[6-amino-5-(hydroxymethyl)-4-(3-piperidinyl)-2-pyridinyl]-3-(cyclopropylmethoxy)phenol;

2-[6-amino-5-(hydroxymethyl)-4-(4-piperidinyl)-2-pyridinyl]-3-(cyclopropylmethoxy)phenol;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-3,4-dihydro-1,8-naphthyridin-2(1H)-one;

ethyl 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(4-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one;

6'-amino-5'-(hydroxymethyl)-4'-(3-piperidinyl)-2,2'-bipyridin-3-ol;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(4-piperidinyl)-3,4-dihydro-1,8-naphthyridin-2(1H)-one;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-3-fluoro-5-(3-piperidinyl)-1,8-naphthyridin-2(1H)-one;

7-(2-hydroxy-6-propoxyphenyl)-5-(4-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-2-one;

3-(cyclopropylmethoxy)-2-[5-(3-piperidinyl)-1,4-dihydro-2H-pyrido[2,3-d][1,3]oxazin-7-yl]phenol;

2-[6-amino-5-(hydroxymethyl)-4-(3-piperidinyl)-2-pyridinyl]-3-(neopentyloxy)phenol;

2-[6'-amino-5'-(hydroxymethyl)-1,2,5,6-tetrahydro-3,4'-bipyridin-2'-yl]phenol;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-1,8-naphthyridin-2(1H)-one;

N-{[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methyl}acetamide;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,2-dihydro-1,8-naphthyridine-3-carboxamide;

3-acetyl-7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-one;

2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(4-piperidinyl)nicotinonitrile;

2-amino-4-[(2-aminoethyl)amino]-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]nicotinonitrile;

N-{[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methyl}-N'-propylurea;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-(3-piperidinyl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-one;

ethyl [2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methylcarbamate;

2-amino-6-{2-hydroxy-6-[(4-methylpentyl)oxy]phenyl}-4-(4-piperidinyl)nicotinonitrile;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxamide;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-N-isopropyl-2-oxo-5-(3-piperidinyl)-1,2-dihydro-1,8-naphthyridine-3-carboxamide;

ethyl 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxylate;

N-{[2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methyl}urea;

2-amino-6-(2-hydroxy-6-propoxyphenyl)-4-(4-piperidinyl)nicotinonitrile;

N-cyclohexyl-7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxamide;

2-amino-6-[2-(cyclobutylmethoxy)-6-hydroxyphenyl]-4-(4-piperidinyl)nicotinonitrile;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-N,N-dimethyl-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxamide;

2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(1-methyl-3-piperidinyl)nicotinonitrile;

7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxamide;

isopropyl [2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methylcarbamate;

isopropyl 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxylate;

isobutyl 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxylate;

neopentyl 7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxylate;

neopentyl [2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-(3-piperidinyl)-3-pyridinyl]methylcarbamate;
2-amino-6-[2-(hexyloxy)-6-hydroxyphenyl]-4-(4-piperidinyl)nicotinonitrile; and
7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-N-ethyl-2-oxo-5-(3-piperidinyl)-1,4-dihydropyrido[2,3-d]pyrimidine-3(2H)-carboxamide

or a salt thereof.

6. A medicament comprising the compound or a salt thereof as claimed in claim 1 as an active ingredient.

7. A medical composition comprising the compound or a salt thereof as claimed in claim 1 together with one or more pharmaceutically acceptable excipients.

8. A IκB kinase β inhibitor comprising the compound or a salt thereof as claimed in claim 1 as an active ingredient.

9. An anti-inflammatory agent comprising the compound or a salt thereof as claimed in claim 1 as an active ingredient.

10. The anti-inflammatory agent as claimed in claim 9, wherein said agent is used to treat or prevent a disease selected from the group consisting of asthma; allergic rhinitis; atopic dermatitis; hives; conjunctivitis; vernal catarrh; chronic arthrorheumatism; systemic lupus erythematosus; psoriasis; diabrotic colitis; systemic inflammatory response syndrome (SIRS); sepsis; polymyositis; dermatomyositis (DM); Polyaritis nodoa (PN); mixed connective tissue disease (MCTD); Sjoegren's syndrome; and gout.

11. An immunosuppressant comprising the compound or a salt thereof as claimed in claim 1 as an active agent.

12. An agent to treat ischemia comprising the compound or a salt thereof as claimed in claim 1 as an active agent.

13. An anti-tumor agent comprising the compound or a salt thereof as claimed in claim 1 as an active agent.

14. Method for treating diseases by administering to a subject in need thereof an effective amount of a compound according to claim 1.

15. Use of a compound according to claim 1 for the preparation of a medicament for the treatment of asthma.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/EP 01/10405

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7- C07D401/04 C07D213/85 C07D401/14 C07D409/14 C07D401/06
C07D413/14 C07D405/14 C07D471/04 A61P17/00 A61P11/06
A61P29/00 A61K31/4427 A61K31/4353 C07D471/18 C07D498/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MANNA F ET AL: "Anti-inflammatory, analgesic and antipyretic 4,6-disubstituted 3-cyano-2-aminopyridines" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY., vol. 34, no. 3, March 1999 (1999-03), pages 245-254, XP004168450 EDITIONS SCIENTIFIQUE ELSEVIER, PARIS., FR ISSN: 0223-5234 cited in the application tables III,,VII — -/—	1,6-15

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2002	18/02/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/EP 01/10405

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/80 C07D213/73 C07D521/00 C07D513/04

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)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TAKEUCHI, ISAO ET AL: "Syntheses of nitrogen-containing heterocyclic compounds. XXXVII. On the antimicrobial activity and syntheses of 2-phenylquinoline 1-oxides and phenyl-1,8-naphthyridines" retrieved from STN Database accession no. 92:163866 XP002188652 abstract & YAKUGAKU ZASSHI (1979), 99(5), 451-7 , — -/—	1,6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MANNA, F. ET AL: "Anti-inflammatory, analgesic and antipyretic 4,6-disubstituted 3-cyanopyridin-2-ones and 3-cyano-2-aminopyridines" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY., vol. 27, no. 6, 1992, pages 627-632, XP002188651 EDITIONS SCIENTIFIQUE ELSEVIER, PARIS., FR ISSN: 0223-5234 the whole document	1,6-15
A	US 4 003 908 A (DENZEL THEODOR ET AL) 18 January 1977 (1977-01-18) claims	1,6,9
A	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SINGH, GIRWAR ET AL: "Synthesis of some novel 4-imino-3,5,7-trisubstituted pyrido'2,3- d!pyrimidine-2(1H)-thiones and their nucleosides as potential therapeutic agents" retrieved from STN Database accession no. 134:222965 XP002188653 abstract & PHOSPHORUS, SULFUR SILICON RELAT. ELEM. (2000), 165, 107-116 ,	1,6
A	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DESAI, JIGAR ET AL: "Synthesis and biological studies of some 2-amino-3-cyano-4-aryl-6-(2'-hydroxy-3'-bromo/3'-nitro-5-'methylphenyl) pyridines" . retrieved from STN Database accession no. 126:89234 XP002188654 abstract & ORIENT. J. CHEM. (1996), 12(2), 209-210 ,	1,6

INTERNATIONAL SEARCH REPORT

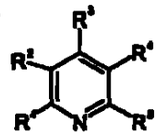
formation on patent family members

Inter nal Application No
PCT/EP 01/10405

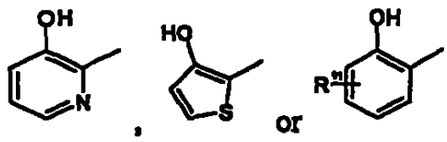
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4003908 A	18-01-1977	US 4048182 A	13-09-1977

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Pyridine compounds of general formula:



wherein -R^1 represents



in which R^{11} is hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-12} alkoxy, nitro, amino, C_{1-6} alkylsulfonylamino, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di (C_{1-6} alkyl)amino, C_{1-6} alkanoylamino, phenyl C_{1-6} alkylamino, phenylsulfonylamino, or -O-$(CH_2)_n$-R^{111} ; R^2 represents hydrogen or halogen; R^3 represents hydrogen, –$CR^{31}R^{32}R^{33}$, or -$NR^{34}R^{35}$; R^4 is hydrogen, carbamoyl, CN, carboxyl, etc.; R^5 is amino, C_{1-6} alkylamino, di C_{1-6} alkylamino, etc. or salt thereof. The compound has an excellent anti-inflammatory activity, and other biological activity.

PATENT COOPERATION TREATY

153

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
RCK4-WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 01/ 10405	10/09/2001	22/09/2000
International Patent Classification (IPC) or national classification and IPC		
C07D401/04		
Applicant		
BAYER AKTIENGESELLSCHAFT		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/04/2002	31/07/2002
Name and mailing address of the IPEA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040 Fax: (+31-70) 340-3016	VERHULST W Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) (July 1998)

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

PCT REQUEST

RCK4-WO

Original (for SUBMISSION) - printed on 16.08.2001 12:57:15 PM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.03.2001)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	RCK4-WO
I	Title of invention	PYRIDINE DERIVATIVES
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II-9	Facsimile No.	0214/30 53482
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III-2	Applicant and/or Inventor	
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III-3-7	State of residence	JP
III-4	Applicant and/or Inventor	
III-4-1	This person is:	applicant and inventor
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III-5	Applicant and/or Inventor	
III-5-1	This person is:	applicant and inventor
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III-8-7	State of residence	~~DE~~
III-9	Applicant and/or Inventor	
III-9-1	This person is:	applicant and inventor
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III-10-7	State of residence	JP
III-11	Applicant and/or inventor	
III-11-1	This person is:	applicant and inventor
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III-12-1	This person is:	applicant and inventor
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III-12-7	State of residence	DE
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III-13-1	This person is:	applicant and inventor
III-13-2	Applicant for	US only
III-13-4	Name (LAST, First)	FUCHIKAMI, Kinji
III-13-5	Address:	7-1-8-A103, Umemidai, Kizu-cho Soraku-gun, Kyoto 619-0215 Japan
III-13-6	State of nationality	JP
III-13-7	State of residence	JP

III-14	Applicant and/or inventor	
III-14-1	This person is:	applicant and inventor
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III-14-7	State of residence	JP
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	common representative
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IV-1-4	Facsimile No.	0214/30 53482
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
V-3	National Patent (States which have become party to the PCT after the issuance of this version of EASY)	And all countries which acceded to the PCT on the date of filing.

V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	22 September 2000 (22.09.2000)	
VI-1-2	Number	2000-289173	
VI-1-3	Country	JP	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	7	-
IX-2	Description	257	-
IX-3	Claims	18	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	283	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		

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IX-20	Language of filing of the international application	English
X-1	Signature of applicant, agent or common representative	i.V. Hollberg
X-1-1	Name	BAYER AKTIENGESELLSCHAFT

ppa. Dr. Linkenheil i.V. Dr. Hollberg

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10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

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DERIVADOS DE PIRIDINA CON ACTIVIDAD INHIBIDORA DE QUINASA IKB (IKK-BETA).

CAMPO TÉCNICO

La presente invención se refiere a nuevos derivados de piridina, a procedimientos para su preparación y a preparaciones farmacéuticas que los contienen. Los derivados de piridina de la presente invención inhiben la actividad de la quinasa IκB β (IKK-β o IKK-beta), así, inhiben la actividad del factor nuclear kappa B (NF-κB) y se pueden usar para la profilaxis y el tratamiento de enfermedades asociadas con la actividad de NF-κB, en particular para el tratamiento de enfermedades inflamatorias.

TÉCNICA ANTERIOR

El factor nuclear kappa B (NF-κB) pertenece a una familia de complejos de factores de transcripción homo y heterodiméricos estrechamente relacionados formados por diversas combinaciones de la familia Rel/NF-κB de polipéptidos. El NF-κB y los miembros de la familia relacionados están implicados en la regulación de más de 50 genes relacionados con la respuesta inmune y antiinflamatoria ((Barnes PJ, Karin M (1997) N Engl J Med 336, 1066-1071) y (Baeuerle PA, Baichwal VR (1997) Adv Immunol 65, 111-137)). En la mayoría de los tipos de células, el NF-κB está presente como un heterodímero que comprende una subunidad de 50 kDa y una de 65 kDa (p50/RelA). El heterodímero se secuestra en el citoplasma junto con un inhibidor de la familia de proteínas NK-kB (IκB) para mantenerse en un estado inactivo. La familia de proteínas IκB enmascara la señal de translocación nuclear de NF-κB. Al estimular las células con diferentes citoquinas (por ejemplo TNF-α, IL-1), ligando CD40, lipopolisacárido (LPS), oxidantes, mitógenos (por ejemplo éster de forbol), virus o

muchos otros. Las proteínas IκB se fosforilan en restos de serina específicos, poliubiquitinados y luego se degradan mediante una ruta dependiente del proteasoma. Libre de IκB, el NF-κB activo es capaz de trasladarse al núcleo donde se une de forma selectiva a secuencias potenciadoras específicas del gen. Entre los genes que son regulados por NF-κB hay muchos que codifican los mediadores proinflamatorios, citoquinas, moléculas de adhesión de células y proteínas de fase aguda. La expresión de algunas de estas citoquinas y mediadores a su vez puede llevar a activación adicional de NF-κB mediante mecanismos autocrinos y paracrinos.

Se dispone de amplias evidencias que sugieren un papel central de NF-κB en muchos trastornos inflamatorios incluyendo inflamación de vías respiratorias y asma ((Yang L *et al*, J Exp Med 188 (1998), 1973-1750), (Hart LA *et al* Am J Respir Crit Care Med 158 (1998), 1585-1592), (Stacy MA *et al*, Biochem Biophys Res Commun 236 (1997), 522-526) (Barnes P y Adcock IM, Trends Pharmacol Sci 18 (1997), 46-50)).

Además, se ha mostrado que los glucocorticoides, que son con mucho los más efectivos para el tratamiento del asma, inhiben la inflamación de las vías respiratorias interactuando directamente con e inhibiendo la actividad de los factores de transcripción NF-κB y activando el péptido-1 (AP-1) ((Barnes P (1997) Pulmon Pharmacol Therapeut 10, 3-19) y (Dumont A *et al* (1998) Trends Biochem Sci 233-235)).

En general la inhibición de la activación de NF-κB da lugar a efectos antiinflamatorios fuertes similares o superiores a los de los esteroides. Por consiguiente, la inhibición de NF-κB debería mejorar los síntomas inflamatorios típicos del asma; rinitis alérgica; dermatitis atópica; urticaria; conjuntivitis; catarro vernal; artritis reumatoide; lupus

eritematoso sistémico; psoriasis; colitis diabrótica; síndrome de respuesta inflamatoria sistémica; sepsis; polimiositis; dermatomiositis; poliartritis nudosa; enfermedad mixta del tejido conjuntivo; síndrome de Sjoegren; gota y similares.

Además, diferentes estudios implican que el NF-κB juega un papel esencial en la transformación neoplásica. Por ejemplo, el NF-κB se asocia con la transformación celular in vitro e in vivo como consecuencia de la sobreexpresión de genes, amplificación, redistribución o translocación (Mercurio, F. y Manning, A. M. (1999) Oncogene, 18:6163-6171). En ciertas células tumorales linfoides humanas, los genes de miembros de la familia NF-κB están redistribuidos o amplificados. Su posible implicación en la patología cancerígena se describe también en Mayo, M. W., Baldwin A. S. (2000) Biochmica et Biophysica Acta 1470 M55-M62. Mayo M. W. *et al* describe que la inhibición de NF-κB da lugar al bloqueo de la iniciación y/o progresión de ciertos cánceres, de forma particular el cáncer colorrectal.

Finalmente el NF-κB puede también estar implicado en la regulación de muerte celular neuronal. Se ha demostrado que el NF-κB comienza a estar activado y promueve la muerte celular en isquemia cerebral focal (Nature medicine vol. 5 nº 5, Mayo 1999).

Estudios intensivos en los últimos años llevaron a la identificación de un complejo de quinasa IκB (IKK) como el responsable de la fosforilación IκB inducida por señal ((Mercurio, F. y Manning, A.M. (1999) Current Opinion in Cell Biology, 11:226-232), (Mercurio, F., y Manning, A.M. (1999) Oncogene 18:6163-6171) (Barnkett, M. y Gilmore T.D. (1999) Oncogene 18, 6910-6924), (Zandi, E., y Karin, M. (1999) 19:4547-4551), (Israel, A. (2000) Trends in Cell Biology 10:129:133), y (Hatada, E. N.,

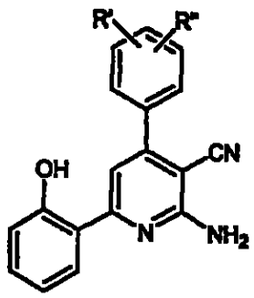
et al (2000) Current Opinion in Immunology, 12:52-58)). Este complejo es el sitio más probable de integración de todos los estímulos diferentes que conducen a la activación de NF-κB. El complejo IKK (peso molecular 700 a 900 kDa) está formado por varias proteínas incluyendo dos quinasas homólogas IκB, denominadas IKK-α e IKK-β, una quinasa cadena arriba, NIK que incluye NF-κB, una proteína estructural llamada IKAP, la cual une las tres quinasas y una subunidad IKK-γ reguladora, la cual interacciona preferentemente con IKK-β.

La IKK-β es una serina-treonina quinasa de 756 aminoácidos que presenta un 52% de identidad y la misma estructura de dominio que IKK-α ((Mercurio F *et al* (1997) Science 278, 860-866), (Woronicz JD y col (1997) Science 278, 866-869), (Zandi E *et al* (1997) Cell 91 243-252). La IKK-β forma homodímeros y heterodímeros con IKK-α in vitro y en células respectivamente. La IKK-β también interactúa con IKK-γ, IKAP, NIK e IκBα. La IκB-β recombinante fosforila IκBα e IκBβ en restos de serina específicos con igual eficacia (Li J *et al* (1998) J Biol. Chem 273, 30736-30741), (Zandi E, Chen Y, Karin M (1998) Science 281, 1360-1363). La IKK-β muestra una actividad quinasa constitutiva mayor en comparación con IKK-α. Esto está de acuerdo con los datos que sugieren que la sobreexpresión de IKK-β activa la transcripción de un gen reportero dependiente de NF-κB con una eficacia mayor en comparación con IKK-α. Se ha mostrado que la IKK-β se activa en varias líneas celulares o células humanas frescas en respuesta a diversos estímulos incluyendo TNF-α, IL-1β, LPS, coestimulación anti-CD3/anti-CD28, proteína quinasa C y calcineurina, estimulación receptor de células B/ligando CD40 y vanadato. La IKK-β se activa en sinoviocitos en forma de fibroblastos (FLS) aislados a partir de líquido sinovial de pacientes que sufren artritis reumatoide o osteoartritis (Zandi E y col (1997) Cell 91, 243-252), (O'Connell MA *et al*

(1998) J Biol. Chem 273, 30410-30414), (Kempiak SJ *et al* (1999) J. Immunol. 162, 3176-3187). Además, la IKK-β se puede activar mediante las quinasas de cadena ariba MEKK-1 y NIK relacionadas estructuralmente, lo más probablemente mediante fosforilación de restos de serina específicos dentro del bucle T (bucle de activación) y mediante ciertas isoformas de la proteína quinasa C ((Nakano H *et al* (1998) Proc Natl Acad Sci USA 95, 3537-3542), (Lee FS *et al* (1998) Proc Natl Acad Sci USA 95, 9319-9324), (Nemoto S *et al* (1998) Mol Cell Biol. 18, 7336-7343), (Lallena MJ *et al* (1999) Mol Cell Biol. 19, 2180-2188)). Se ha mostrado que un mutante catalíticamente inactivo de la IKK-β inhibe la activación de NF-κB por TNF-α, IL-1β, LPS, estimulación anti CD3/anti-CD28 ((Mercurio F *et al* (1997) Science 278, 860-866), (Woronicz JD y col (1997) Science 278, 866-869)). Se observan los mismos efectos cuando se sobreexpresan MEKK1 o NIK. De forma adicional, las mutaciones de IKK-β en el bucle de activación inhibieron la señalización de IL-1 y TNF-α (Delhase M *et al* (1999) Science 284, 309-313). Existe una clara evidencia, en base a los resultados experimentales descritos anteriormente, de una intervención fundamental de la IKK-β en diversos procesos que conducen a la activación de NF-κB.

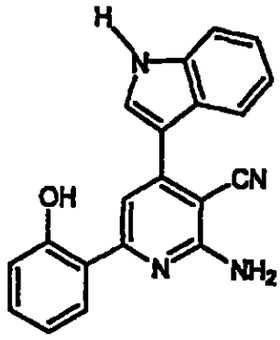
En resumen, la inhibición específica de IKK-β daría lugar a un fuerte efecto antiinflamatorio e inmunomodulador *in vivo* con el potencial de mejorar las causas subyacentes de asma y otras enfermedades. Además se pueden esperar efectos antitumorales y antiisquémicos en un inhibidor IKK-β.

Manna *et al*, describen 3-ciano-2-aminopiridinas 4,6-disustituidas representadas por las fórmulas generales:



en la que (R', R'') representa (OCH_3, OCH_3), (Cl, Cl), (H, Cl), (H, Br), (H, OCH_3), (H, OCH_3), (H, NO_2) o (H, $N(CH_3)_2$),

o



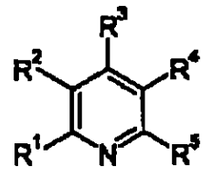
como un agente antiinflamatorio, analgésico y antipirético general (Eur J. Med. Chem. 34, 245-254 (1999)).

Manna *et al* no describe derivados de piridina con grupos alifáticos en la posición 4 del anillo de piridina ni sugiere actividad inhibitoria quinasa IKK-β o NF-κB en los derivados de piridina anteriormente conocidos.

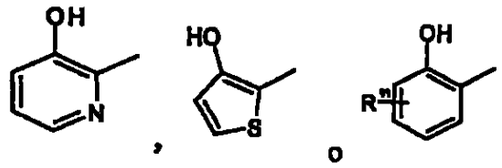
Se ha deseado el desarrollo de un nuevo compuesto que tenga acciones antiinflamatorias eficaces basadas en una actividad inhibitoria y específica selectiva hacia NF-κB.

SUMARIO DE LA INVENCIÓN

Como resultado de extensos estudios sobre la modificación química de los derivados de piridina, los autores de la presente invención han encontrado que el compuesto de nueva estructura química relacionado con la presente invención presenta una actividad inhibitoria de la quinasa IKK-β inesperadamente excelente. La presente invención proporciona la fórmula general siguiente (I) y sales de la misma:



en la que R^1 representa



en la que R^{11} es hidrógeno, alquilo C_{1-6}, halógeno, hidroxi, alcoxi C_{1-12}, nitro, amino, alquil C_{1-6}-sulfonilamino, alcoxi C_{1-6}-carbonilo, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, alcanoil C_{1-6}-amino, fenilalquil C_{1-6}-amino, fenilsulfonilamino o $-O-(CH_2)_n-R^{111}$,

representando n un número entero seleccionado de 0 a 6, y R^{111} es alquenilo C_{2-6}, benzoílo, difenilmetílo, di(alquil C_{1-6})amino, alcanoílo C_{1-6}, alcoxi C_{1-6}-carbonilo, o un anillo saturado o insaturado de 3 a 10 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo formado por S, O y N como heteroátomos y está opcionalmente sustituido con alquilo C_{1-6}, mono o dihalógeno, alquilo C_{1-6} sustituido con halógeno,

nitro, ciano, alcoxi C_{1-6}-carbonilo, fenilo, hidroxi, amino, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, alcanoil C_{1-6}-amino, alcoxi C_{1-6} o carbamoílo;

R^2 representa hidrógeno o halógeno;

R^3 representa hidrógeno o 1,2,3,6-tetrahidropiridina,

$$-CR^{31}R^{32}R^{33},$$

en la que R^{31} es hidrógeno o alquilo C_{1-6},

R^{32} es hidrógeno, α-aminobencilo, alquilo C_{1-6} opcionalmente sustituido con uno o dos sustituyentes seleccionados del grupo formado por hidroxi, amino, fenilo sustituido con amino, fenilo, fenilo sustituido con halógeno y fenilo sustituido con alcoxi C_{1-6}, o un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 átomos seleccionados del grupo formado por S, O y N como heteroátomos y opcionalmente sustituido con alquilo C_{1-6}, y

R^{33} es hidrógeno, amino, alcoxi C_{1-6}-carbonilamino, alquenil C_{2-6}-oxicarbonilamino, piperidin-alquil C_{1-6}-carbonilamino, piperidinil-alquil C_{1-6}-carbonilamino, o

R^{32} y R^{33} pueden formar, junto con el átomo de carbono adyacente, un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo formado por N, O y S como heteroátomos, estando dicho anillo opcionalmente sustituido con fenilalquilo C_{1-6}, fenilalquilo C_{1-6} sustituido con alcoxi C_{1-6}, alquilo C_{1-6}, amino, ciano, hidroxi, carbamoílo, carboxi, alquil C_{1-6}-amino, alcoxi C_{1-6}-carbonilo, di(alquil C_{1-6})

$_{6}$)amino, bencilamino, alquil C_{1-6}-sulfonilo, piperidin-alquil C_{1-6}-carbonilo o opcionalmente condensado con benceno;

o

$-NR^{34}R^{35}$,

en la que R^{34} es hidrógeno o alquilo C_{1-6}, y

R^{35} es hidrógeno, un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo fomado por N, O y S como heteroátomos, o $-(CH_2)_m-NR^{351}R^{352}$ (m representa cualquier número entero de 1 a 6).

representando R^{351} hidrógeno, alquilo C_{1-6},

R^{352} representa hidrógeno, alquilo C_{1-6}, alcanoílo C_{1-6}, fenilo sustituido con alquilo C_{1-6}, benzoílo, alcanoílo C_{1-6}, fenilaminocarbonilo, fenilsulfonilo o

R^{34} y R^{35} pueden formar, junto con el átomo de N adyacente, un anillo heterocíclico saturado de 5 a 8 miembros, y dicho anillo puede contener opcionalmente como átomos distintos del átomo de N adyacente NH, S u O y estar opcionalmente sustituido con carbamoílo, amino o alquilo C_{1-6};

R^4 representa hidroxicarbonilo, alcanoílo C_{1-6}, carbamoílo, nitro, ciano, carboxilo, alcoxi C_{1-6}-carbonilo, alquil C_{1-6}-carbamoílo, alquil C_{1-6}-amino, heteroaril de 5 a 10 miembros-(hidroxi)metilo, heteroarilo de 5 a 10 miembros-alquilo C_{1-6}, o metilo

sustituido con hidroxi y un anillo cíclico saturado de 5 a 7 miembros, alquilo C_{1-6} opcionalmente sustituido con un sustituyente seleccionado del grupo formado por hidroxi, alcoxi C_{1-6}, alquil C_{1-6}-sulfonilamino, alquil C_{1-6}-carbonilamino, arilo C_{5-10}, aril C_{5-10}-sulfonilo, aril C_{5-10}-sulfanilo, ariloxi C_{5-10}, imidazolilo o pirrolidinoxi sustituido con dioxo,

$-(CH_2)_pNHCOR^{41}$, $-(CH_2)_pNHC(=S)R^{41}$

en las que p representa cualquier número entero de 1 a 6 y R^{41} representa alcoxi C_{1-6}, amino, fenilamino, alquilo C_{1-6}, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, cicloalquil C_{3-10}-amino,

R^3 y R^4 pueden formar junto con los átomos de carbono en el anillo de piridina, monocicloalquilo o bicicloalquilo de 4 a 10 miembros opcionalmente interrumpidos por NH y opcionalmente sustituidos con bencilo, =NH o =O;

R^5 representa $NR^{51}R^{52}$,

en la que R^{51} es hidrógeno, alquilo C_{1-6},

R^{52} es hidrógeno, alquilo C_{1-6}, fenilo, bencilo, alcanoílo C_{1-6}, o $NR^{51}R^{52}$ puede formar un anillo saturado de 5 a 6 miembros que contiene opcionalmente NH u O como otros heteroátomos distintos del átomo de N adyacente,

o

R^4 y R^5 pueden formar,

$-R^{40}$-CO-NH-

$-R^{40}$-SO_2-NH-

$-R^{40}$-C(=S)-NH-

$-R^{40}$-CH_2-NH-

en las que dicho $-R^{40}-$ representa $-CHR^{401}$-O-, $-CH_2$-N R^{401}-, $-CO-NR^{401}-$, $-CH_2-CHR^{401}-$, $-CH=CR^{401}-$, (siendo R^{401} alcanoílo C_{1-6}, alquilo C_{1-6}, fenilo, alquil C_{1-6}-sulfonilo, cicloalquil C_{3-8}-aminocarbonilo, hidrógeno, halógeno, nitro, amino, ciano, benzoilamino, fenilsulfonilo, carbamoílo, hidroxicarbonilo, alcoxi C_{1-6}-carbonilo, alquil C_{1-12}-aminocarbonilo, alquil C_{1-6}-aminocarbonilo sustituido con halógeno, alcanoil C_{1-6}-amino, alquil C_{1-6}-amino, di(alquil C_{1-6})aminocarbonilo, di(alquil C_{1-6})aminoalquil C_{1-6}-aminocarbonilo, hidroindenilaminocarbonilo, difenilmetilaminocarbonilo, pirrolidinocarbonilo, alcoxi C_{1-6}-alquil C_{1-6}-aminocarbonilo, morfolinocarbonilo, piperazinocarbonilo, fenilalquil C_{1-6}-aminocarbonilo, hidroxicarbonilalquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-aminocarbonilo, cicloalquil C_{3-8}-alquil C_{1-6}-aminocarbonilo, hidroxialquil C_{1-6}-aminocarbonilo, carboxietilaminocarbonilo, alquil C_{1-6}-sulfonilaminocarbonilo),

$-CR^{41}$=N-NH- (R^{41} es hidrógeno, amino o alcanoil C_{1-6}-amino),

$-CR^{42}$=N-C=N- (R^{42} es hidrógeno o amino).

Los compuestos de la presente invención presentan sorprendentemente una excelente

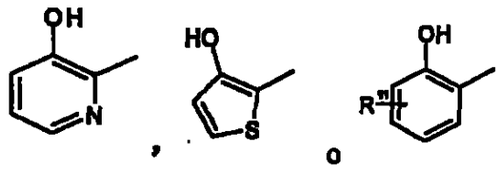
actividad de inhibición de la quinasa IKK-β y actividad de inhibición de citoquinas. Por tanto, son adecuados especialmente como inhibidores de NF-κB y de forma particular para la producción de medicamentos o composiciones médicas, que pueden ser útiles para tratar las enfermedades dependientes de NF-κB.

De forma más específica, debido a que los derivados de piridina de la presente invención inhiben la actividad de la quinasa IKK-β, estos son útiles para el tratamiento y profilaxis de enfermedades que implican actividad de NF-κB como las siguientes: síntomas inflamatorios incluyendo asma; rinitis alérgica; dermatitis atópica; urticaria; conjuntivitis; catarro vernal; artrorreumatismo crónico; lupus eritematoso sistémico; psoriasis; colitis diabrótica; síndrome de respuesta inflamatoria sitémica (SIRS); sepsis; poliomiositis; dermatomiositis (DM); poliartritis nudosa (PN); enfermedad mixta del tejido conjuntivo (MCTD); síndrome de Sjoegren; gota y similares.

Los compuestos de la presente invención son también útiles para el tratamiento y profilaxis de enfermedades como isquemia y tumores, ya que las enfermedades también están relacionadas con la actividad de quinasa IKK-β y de NF-κB.

Los compuestos preferidos de fórmula (I) son aquellos en los que:

R^1 representa



en la que R^{11} es hidrógeno, alquilo C_{1-6}, halógeno, hidroxi, alcoxi C_{1-12}, amino, alcanoil C_{1-6}-amino, fenilalquil C_{1-6}-amino, fenilsulfonilamino o $-O-(CH_2)_n-R^{111}$,

representando n un número entero seleccionado de 1 a 6, y R^{111} es alquenilo C_{2-6}, benzoílo, difenilmetilo, di(alquil C_{1-6})amino, alcanoílo C_{1-6}, alcoxi C_{1-6}-carbonilo, o un anillo saturado o insaturado de 3 a 10 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo formado por S, O y N como heteroátomos y está opcionalmente sustituido con alquilo C_{1-6}, mono o dihalógeno, alquilo C_{1-6} sustituido con halógeno, nitro, ciano, alcoxi C_{1-6}-carbonilo, fenilo;

R^2 representa hidrógeno;

R^3 representa hidrógeno o 1,2,3,6-tetrahidropiridina,

$-CR^{31}R^{32}R^{33}$,

en la que R^{31} es hidrógeno o alquilo C_{1-6},

R^{32} es hidrógeno, α-aminobencilo, alquilo C_{1-6} opcionalmente sustituido con uno o dos sustituyentes seleccionados del grupo formado por hidroxi, amino, fenilo sustituido con amino, fenilo, fenilo sustituido con halógeno y fenilo sustituido con alcoxi C_{1-6}, o un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 átomos seleccionados del grupo formado por S, O y N como heteroátomos y opcionalmente sustituido con alquilo C_{1-6}, y

R^{33} es hidrógeno, amino, alcoxi C_{1-6}-carbonilamino, alquenil C_{2-6}-oxicarbonilamino,

piperidino-alquil C_{1-6}-carbonilamino, o

R^{32} y R^{33} pueden formar, junto con el átomo de carbono adyacente, un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo formado por N, O y S como heteroátomos, estando dicho anillo opcionalmente sustituido con fenilalquilo C_{1-6}, fenilalquilo C_{1-6} sustituido con alcoxi C_{1-6}, alquilo C_{1-6}, amino, carboxi, alquil C_{1-6}-amino, alcoxi C_{1-6}-carbonilo, di(alquil C_{1-6})amino, bencilamino, alquil C_{1-6}-sulfonilo, piperidino-alquil C_{1-6}-carbonilo o opcionalmente condensado con benceno;

o

$-NR^{34}R^{35}$,

en la que R^{34} es hidrógeno y

R^{35} es hidrógeno, un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo formado por N, O y S como heteroátomos, o $-(CH_2)_m-NR^{351}R^{352}$ (m representa cualquier número entero de 1 a 6).

en la que R^{351} representa hidrógeno, alquilo C_{1-6},

R^{352} representa hidrógeno, alquilo C_{1-6}, alcanoílo C_{1-6}, fenilo sustituido con alquilo C_{1-6}, benzoílo, alcanoílo C_{1-6}, fenilaminocarbonilo, fenilsulfonilo o

R^{34} y R^{35} pueden formar, junto con el átomo de N adyacente, un anillo heterocíclico saturado de 5 a 8 miembros, y dicho anillo puede contener opcionalmente como átomos distintos del átomo de N adyacente NH, S u O y estar opcionalmente sustituido con carbamoílo, amino o alquilo C_{1-6};

R^4 representa hidroxicarbonilo, alcanoílo C_{1-6}, carbamoílo, ciano, carboxilo, alcoxi C_{1-6}-carbonilo, alquil C_{1-6}-carbamoílo, alquil C_{1-6}-amino, heteroarilo de 5 a 10 miembros-(hidroxi)metilo, heteroarilo de 5 a 10 miembros-alquilo C_{1-6}, o metilo sustituido con hidroxi y un anillo cíclico saturado de 5 a 7 miembros, alquilo C_{1-6} opcionalmente sustituido con un sustituyente seleccionado del grupo formado por hidroxi, alcoxi C_{1-6}, alquil C_{1-6}-sulfonilamino, alquil C_{1-6}-carbonilamino, arilo C_{5-10}, aril C_{5-10}-sulfanilo, aril C_{5-10}-sulfenilo, ariloxi C_{5-10}, imidazolilo o pirrolidinoxi sustituido con dioxo,

$$-(CH_2)_pNHCOR^{41}, \quad -(CH_2)_pNHC(=S)R^{41}$$

en las que p representa cualquier número entero de 1 a 6 y R^{41} representa alcoxi C_{1-6}, amino, fenilamino, alquilo C_{1-6}, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, cicloalquil C_{3-10}-amino,

R^3 y R^4 pueden formar junto con los átomos de carbono en el anillo de piridina, monocicloalquilo o bicicloalquilo de 4 a 10 miembros opcionalmente interrumpidos por NH y opcionalmente sustituidos con bencilo, =NH o =O;

R^5 representa $NR^{51}R^{52}$,

en la que R^{51} es hidrógeno, alquilo C_{1-6},

R^{52} es hidrógeno, alquilo C_{1-6}, fenilo, bencilo, alcanoílo C_{1-6} o $NR^{51}R^{52}$ puede formar piperidino,

o

R^4 y R^5 pueden formar

$-R^{40}-CO-NH-$, $-R^{40}-SO_2-NH-$
$-R^{40}-C(=S)-NH-$ o
$-R^{40}-CH_2-NH-$,

representando dicho $-R^{40}-$ $-CHR^{401}-O-$, $-CH_2-N\ R^{401}-$, $-CO-NR^{401}-$, (siendo R^{401} hidrógeno, alcanoílo C_{1-6}, alcoxi C_{1-6}-carbonilo, alquilo C_{1-6}, fenilo, alquil C_{1-6}-sulfonilo, cicloalquil C_{3-8}-aminocarbonilo, alquil C_{1-6}-aminocarbonilo, carbamoílo, di(alquil C_{1-6})aminocarbonilo, $-CH_2-CHR^{402}-$, $-CH=CR^{402}-$, (siendo R^{402} hidrógeno, halógeno, nitro, amino, ciano, benzoilamino, fenilsulfonilo, carbamoílo, hidroxicarbonilo, alcoxi C_{1-6}-carbonilo, alquil C_{1-12}-aminocarbonilo, alquil C_{1-6},-aminocarbonilo sustituido con halógeno, alcanoil C_{1-6}-amino, alquil C_{1-6}-amino, di(alquil C_{1-6})aminocarbonilo, di(alquil C_{1-6})amino-alquil C_{1-6}-aminocarbonilo, hidroindenilaminocarbonilo, difenilmetilaminocarbonilo, pirrolidinocarbonilo, alcoxi C_{1-6}-alquil C_{1-6}-aminocarbonilo, morfolinocarbonilo, piperazinocarbonilo, fenil-alquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-aminocarbonilo, hidroxicarbonil-alquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-alquil C_{1-6}-aminocarbonilo, hidroxialquil C_{1-6}-

aminocarbonilo, carboxietilaminocarbonilo, metilsulfonilaminocarbonilo).

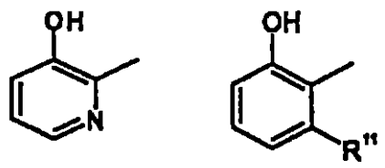
$-CR^{41}=N-NH-$ (R^{41} es hidroxi, amino, alcanoil C_{1-6}-amino) o

$-CR^{42}=N-C=N-$ (R^{42} es amino).

o una de sus sales.

Los compuestos más preferidos de fórmula (I) son aquellos en los que:

$-R^1$ representa



o

en la que R^{11} es hidrógeno, alcoxi C_{1-12}, u $-O-(CH_2)_n-R^{111}$,

representando n un número entero seleccionado de 1 a 6, y R^{111} es fenilo, cicloalquilo C_{3-8};

R^2 representa hidrógeno;

R^3 representa 1,2,3,6-tetrahidropiridina,

$-CR^{31}R^{32}R^{33}$,

en la que R^{31} es hidrógeno,

y

R^{32} y R^{33} forman, junto con el átomo de carbono adyacente un anillo saturado de 5 a 8 miembros interrumpido por NH, estando dicho anillo opcionalmente sustituido con fenilalquilo C_{1-6}, fenilalquilo C_{1-6} sustituido con alcoxi C_{1-6}, alquilo C_{1-6}, amino, carboxi, alquil C_{1-6}-amino, alcoxi C_{1-6}-carbonilo, di(alquil C_{1-6})amino, bencilamino, alquil C_{1-6}-sulfonilo, piperidino-alquil C_{1-6}-carbonilo o opcionalmente condensado con benceno;

o

$-NR^{34}R^{35}$,

en la que R^{34} es hidrógeno y

R^{35} es $-(CH_2)_m-NR^{351}R^{352}$ (m representa cualquier número entero de 1 a 6).

en la que R^{351} representa hidrógeno, alquilo C_{1-6},

R^{352} representa hidrógeno, alquilo C_{1-6}, alcanoílo C_{1-6}, fenilo sustituido con alquilo C_{1-6}, benzoílo, alcanoílo C_{1-6}, fenilaminocarbonilo, fenilsulfonilo; y

R^4 representa ciano, alquilo C_{1-6} opcionalmente sustituido con hidroxi o alcoxi C_{1-6}, o

$-(CH_2)_pNHCOR^{41}$, $-(CH_2)_pNHC(=S)R^{41}$

en las que p representa cualquier número entero de 1 a 6 y R^{41} representa alcoxi C_{1-6}, amino, fenilamino, alquilo C_{1-6}, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, cicloalquil C_{3-10}-amino,

R^5 representa amino,

o

R^4 y R^5 pueden formar,

$-R^{40}$-CO-NH-, $-R^{40}$-SO_2-NH-
$-R^{40}$-C(=S)-NH- o
$-R^{40}$-CH_2-NH-

representando dicho $-R^{40}$- $-CHR^{401}$-O-, $-CH_2-NR^{401}$-, -CO-NR^{401}-, (en las cuales R^{401} es hidrógeno, alcanoílo C_{1-6}, alcoxi C_{1-6}-carbonilo, alquilo C_{1-6}, fenilo, alquil C_{1-6}-sulfonilo, cicloalquil C_{3-8}-aminocarbonilo, alquil C_{1-6}-aminocarbonilo, carbamoílo, di(alquil C_{1-6})aminocarbonilo, $-CH_2-CHR^{402}$-, $-CH=CR^{402}$-, (en las cuales R^{402} es hidrógeno, halógeno, nitro, amino, ciano, benzoilamino, fenilsulfonilo, carbamoílo, hidroxicarbonilo, alcoxi C_{1-6}-carbonilo, alquil C_{1-12}-aminocarbonilo, alquil C_{1-6},-

aminocarbonilo sustituido con halógeno, alcanoil C_{1-6}-amino, alquil C_{1-6}-amino, di(alquil C_{1-6})aminocarbonilo, di(alquil C_{1-6})amino-alquil C_{1-6}-aminocarbonilo, hidroindenilaminocarbonilo, difenilmetilaminocarbonilo, pirrolidinocarbonilo, alcoxi C_{1-6}-alquil C_{1-6}-aminocarbonilo, morfolinocarbonilo, piperazinocarbonilo, fenilalquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-aminocarbonilo, hidroxicarbonilalquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-alquil C_{1-6}-aminocarbonilo, hidroxialquil C_{1-6}-aminocarbonilo, carboxietilaminocarbonilo, metilsulfonilaminocarbonilo).

$-CR^{41}=N-NH-$ (R^{41} es hidroxi, amino o alcanoil C_{1-6}-amino) o

$-CR^{42}=N-C=N-$ (R^{42} es amino).

o una de sus sales.

Los compuestos preferidos de la presente invención son los siguientes o sus sales:

7-(2-hidroxifenil)-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-2-ona;

2-amino-6-[2-(benciloxi)-6-hidroxifenil]-4-(3-piperidinil)nicotinonitrilo;

2-amino-6-(2-hidroxi-6-propoxifenil)-4-(3-piperidinil)nicotinonitrilo;

2-[6-amino-5-(hidroximetil)-4-(3-piperidinil)-2-piridinil]-3-(benciloxi)fenol;

7-[2-(benciloxi)-6-hidroxifenil]-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3d][1,3]oxazin-2-ona;

trifluoroacetato de 2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)nicotinonitrilo;

7-[2-(hidroxifenil)-5-(3-piperidinil)-3,4-dihidro-1,8-naftiridin-2(1H)-ona;

2-amino-6-[2-(ciclobutilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)nicotinonitrilo;

2-[6-amino-5-(hidroximetil)-4-(3-piperidinil)-2-piridinil]-3-propoxifenol;

7-(2-hidroxi-6-propoxifenil)-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3d][1,3]oxazin-2-ona;

7-(2-hidroxi-6-propoxifenil)-2-oxo-5-(3-piperidinil)-1,2,3,4-tetrahidro-1,8-naftiridin-3-carboxilato de etilo;

7-(2-hidroxi-6-propoxifenil)-5-(3-piperidinil)-3,4-dihidro-1,8-naftiridin-2(1H)-ona;

2-[6-amino-5-(hidroximetil)-4-(3-piperidinil)-2-piridinil]-3-(ciclopropilmetoxi)fenol;

2-[6-amino-5-(hidroximetil)-4-(4-piperidinil)-2-piridinil]-3-(ciclopropilmetoxi)fenol;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-3,4-dihidro-1,8-naftiridin-2(1H)-ona;

7-(2-ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,2,3,4-tetrahidro-1,8-naftiridin-3-carboxilato de etilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(4-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-2-ona;

6'-amino-5'-(hidroximetil)-4'-(3-piperidinil)-2,2'-bipiridin-3-ol;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3fluoro-5-(4-piperidinil)-3,4-dihidro-1,8-naftiridin-2(1H)-ona;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-1,8-naftiridin-2(1H)-ona;

7-(2-hidroxi-6-propoxifenil)-5-(4-piperidinil)-1,4-dihidro-2H-pirido[2,3d][1,3]oxazin-2-ona;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-2-ona;

3-(ciclopropilmetoxi)-2-[5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-7-il]fenol;

2-[6-amino-5-(hidroximetil)-4-(3-piperidinil)-2-piridinil]-3-(neopentiloxi)fenol;

2-[6'-amino-5'-(hidroximetil)-1,2,5,6-tetrahidro-3,4'-bipiridin-2'-il]fenol;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-1,8-naftiridin-2(1H)-ona;

N-{[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]metil}acetamida;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,2-dihidro-1,8-naftiridin-3-carboxamida;

3-acetil-7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-3,4-dihidropirido[2,3-d]pirimidin-2(1H)-ona;

2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(4-piperidinil)nicotinonitrilo;

2-amino-4-[(2-aminoetil)amino]-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]nicotinonitrilo;

N-{[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]metil}-N'-propilurea;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-3,4-dihidropirido[2,3-d]pirimidin-2(1H)-ona;

[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]-metilcarbamato de etilo;

2-amino-6-{2-hidroxi-6-[(4-metilpentil)oxi]fenil}-4-(4-piperidinil)nicotinonitrilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,2,3,4-tetrahidro-1,8-naftiridin-3-carboxamida;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-N-isopropil-2-oxo-5-(3-piperidinil)-1,2-dihidro-1,8-naftiridin-3-carboxamida;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido[2,3-d]pirimidin-3(2H)-carboxilato de etilo;

N-{[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]metil}urea;

2-amino-6-(2-hidroxi-6-propoxifenil)-4-(4-piperidinil)nicotinonitrilo;

N-ciclohexil-7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido[2,3-d]pirimidin-3(2H)-carboxamida;

2-amino-6-[2-(ciclobutilmetoxi)-6-hidroxifenil]-4-(4-piperidinil)nicotinonitrilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-N,N-dimetil-2-oxo-5-(3-piperidinil)-1,4-dihidropirido[2,3-d]pirimidin-3(2H)-carboxamida;

2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(1-metil-3-piperidinil)nicotinonitrilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido[2,3-d]pirimidin-3(2H)-carboxamida;

[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]metilcarbamato de isopropilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido-[2,3-d]pirimidin-3(2H)-carboxilato de isopropilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido-[2,3-d]pirimidin-3(2H)-carboxilato de isobutilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido-[2,3-d]pirimidin-3(2H)-carboxilato de neopentilo;

[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]metilcarbamato de neopentilo;

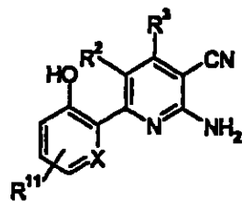
2-amino-6-[2-(hexiloxi)-6-hidroxifenil]-4-(4-piperidinil)nicotinonitrilo; y

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-N-etil-2-oxo-5-(3-piperidinil)-1,4-dihidropirido[2,3-d]pirimidin-3(2H)-carboxamida;

El compuesto de fórmula (I) de la presente invención puede prepararse, aunque sin

quedar limitado a los mismos, combinando diversos procedimientos conocidos. En algunas realizaciones, uno o más de los sustituyentes, como grupo amino, grupo carboxilo y grupo hidroxilo de los compuestos empleados como materiales de partida o intermedios se protegen de forma ventajosa con un grupo protector conocido por los expertos en la técnica. Ejemplos de grupos protectores están descritos en "Protective Groups in Organic Síntesis (2° edición)" de Greene y Wuts.

El compuesto (I-a).

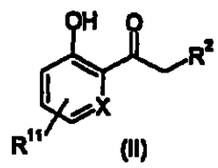


(I-a)

en el que X es CH o N, R^{11}, R^2 y R^3 son como se ha definido,

o una de sus sales, se puede preparar por ejemplo mediante la reacción A siguiente.

El compuesto de fórmula (II).

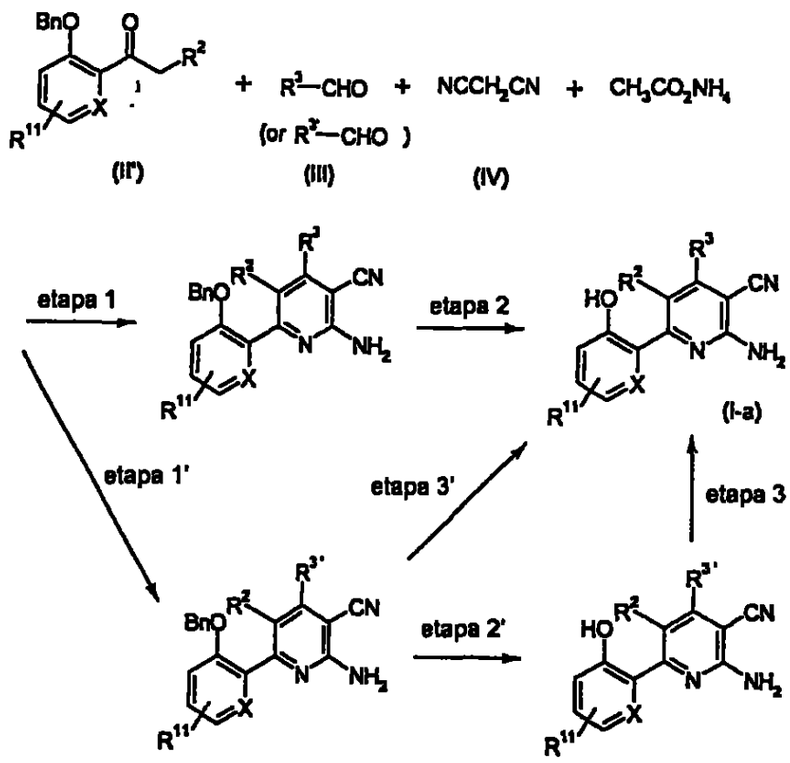


(II)

en la que R^{11} y R^2 son como se han definido anteriormente,

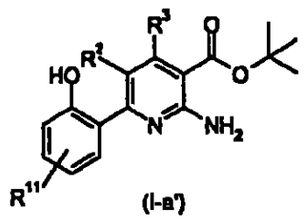
se hacen reaccionar con un aldehído de fórmula R^3-CHO(III), un nitrilo de fórmula $NCCH_2CN$ (IV) y una sal de amonio como acetato de amonio. R^3 es como se definió anteriormente. De forma ventajosa se puede emplear R^3-CHO(III') en lugar de R^3-

CHO(III) en algunos casos. $R^{3'}$ puede representar R^3 esterificado por etilo, butilo terciario o similar: u otros ésteres o sustituyentes que puedan convertirse fácilmente en R^3 por procedimientos convencionales. El grupo hidroxilo del compuesto de fórmula (II) se protege con un grupo protector adecuado (por ejemplo bencilo, metoxibencilo y sililo) durante la reacción y se desprotege después. $R^{3'}$ también puede tratarse con ácidos para obtener R^3.



REACCIÓN A

En el esquema anterior, se puede reemplazar CN en la posición C-3 por carboxilatos derivados de alcoholes terciarios, como COOtBu usando $NCCH_2$-COOtBu (IV') en lugar de $NCCH_2CN$ (IV). En este caso se puede obtener el siguiente compuesto (I-a').



(I-a')

La etapa 1 y la 1' de la reacción A se puede llevar a cabo sin un disolvente o en un disolvente incluyendo, por ejemplo, éteres, como dioxano y tetrahidrofurano; hidrocarburos aromáticos como benceno, tolueno y xileno; nitrilos como acetonitrilo; amidas como dimetilformamida (DMF) y dimetilacetamida; sulfóxidos como dimetil sulfóxido y otros.

La temperatura de reacción puede fijarse opcionalmente dependiendo de los compuestos que vayan a reaccionar. La temperatura de reacción es normalmente, pero sin quedar limitada a la misma, de aproximadamente 50°C a 200°C. La reacción puede tener lugar durante, normalmente, 30 minutos a 48 horas y preferiblemente de 1 a 24 horas.

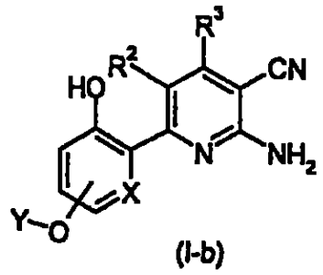
Los compuestos de fórmula general (II), (III), (III') están disponibles comercialmente o se pueden preparar con técnicas conocidas.

La etapa 2 y 2' de la reacción A se puede llevar a cabo por ejemplo en atmósfera de hidrógeno con catálisis de hidrógeno, como Pd-C en un disolvente incluyendo, por ejemplo, ésteres, como acetato de etilo, éteres, como dioxano y tetrahidrofurano; hidrocarburos aromáticos como benceno, tolueno y xileno; nitrilos como acetonitrilo; amidas como dimetilformamida (DMF) y dimetilacetamida; sulfóxidos como dimetil sulfóxido y otros.

La temperatura de reacción puede ser, pero sin estar limitada a la misma, de aproximadamente 50°C a 200°C. La reacción puede llevarse a cabo durante, normalmente, 30 minutos a 48 horas y preferiblemente de 1 a 24 horas.

La etapa 3 y 3' de la reacción A puede ser de un tipo cualquiera de reacción convencional que parta de un éster para dar R^3, por ejemplo, tratamiento ácido, tratamiento alcalino, amidación e hidrogenación: o otra reacción como alquilación o similar para obtener R^3.

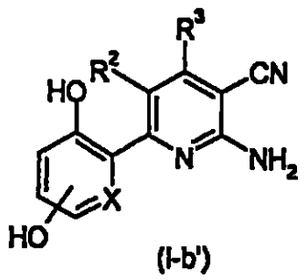
De forma alternativa, el compuesto (I-b).



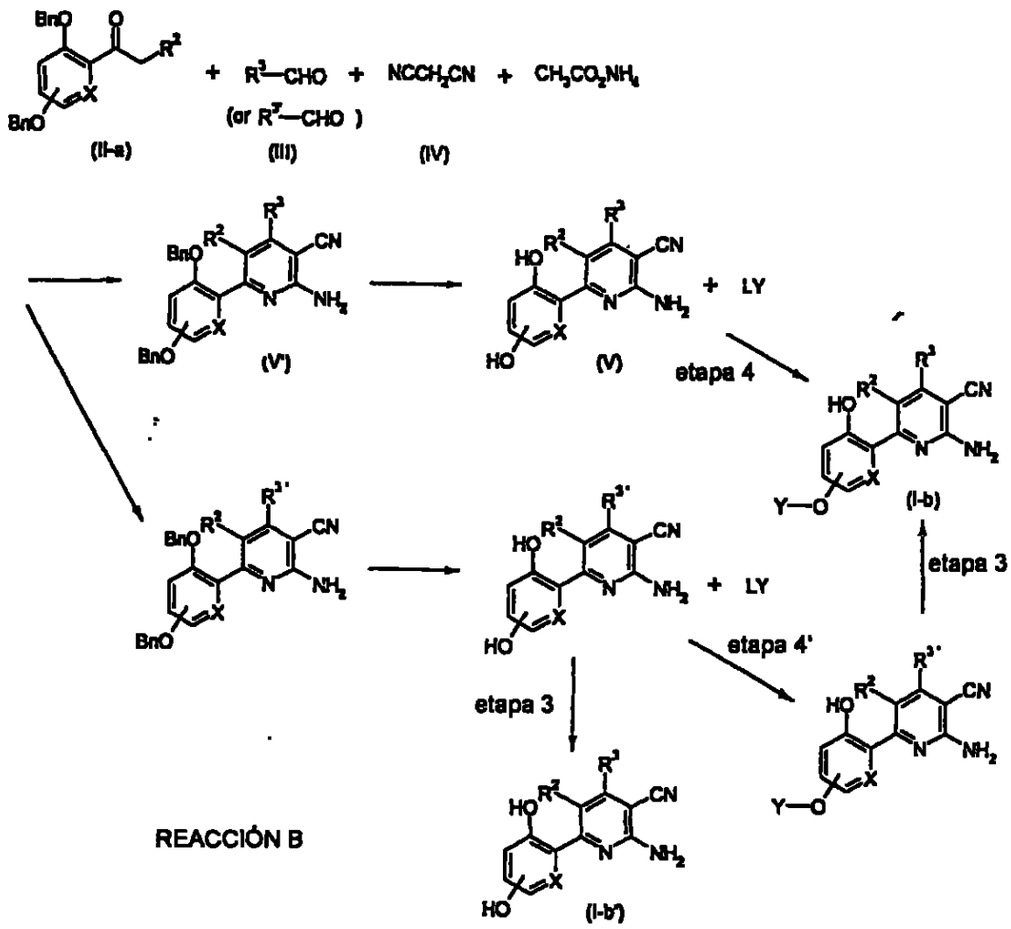
(I-b)

en el que X, R^2 y R^3 son como se definieron anteriormente e Y es alquilo C_{1-12} o R^{111}-$(CH_2)_n$-, en la que R^{111} y *n* son como se definieron anteriormente, o una de sus sales se puede obtener mediante la reacción B siguiente.

El compuesto (I-b') también se puede obtener en la reacción B.



(I-b')



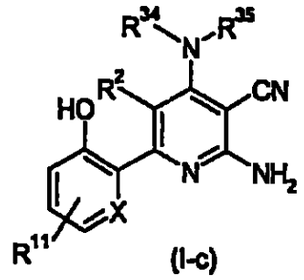
En la reacción B, el compuesto de fórmula (II-a) se hace reaccionar con un aldehído (III), un nitrilo (IV) y acetato de amonio en las mismas condiciones que la reacción A para obtener el compuesto de fórmula (V'). Los grupos protectores bencilo en el compuesto de fórmula general (II-a) se pueden reemplazar por algún grupo protector adecuado. El grupo protector se retira luego tras la reacción. En la etapa 4 de la reacción B, el compuesto (V) se hace reaccionar con L-Y, donde L representa un grupo saliente, como un átomo de halógeno por ejemplo, cloro, bromo o yodo; grupo aril C_6-C_{10}-sulfoniloxi, por ejemplo bencenosulfoniloxi, polisulfoniloxi o p-toluenosulfoniloxi; y

grupo alquil C_1-C_4-sulfoniloxi, por ejemplo metanosulfoniloxi y similares. Y representa alquilo C_1-C_6 o $-(CH_2)_n-R^{111}$ (donde R^{111} es como se definió anteriormente). La reacción con el compuesto (V) y L-Y se puede llevar a cabo en un disolvente incluyendo, por ejemplo, alcoholes como metanol y etanol; éteres, como dioxano y tetrahidrofurano (THF); nitrilos como acetonitrilo; amidas como dimetilformamida (DMF) y dimetilacetamida; sulfóxidos como dimetil sulfóxido y otros. Opcionalmente, se pueden mezclar y usar dos o más disolventes seleccionados de los enumerados anteriormente.

La temperatura de reacción de la reacción entre el compuesto (V) y L-Y se fija opcionalmente dependiendo de los compuestos que vayan a reaccionar. La temperatura de reacción es normalmente, pero sin quedar limitada a la misma, de aproximadamente −10°C a 200°C y preferiblemente de aproximadamente 10°C a 80°C. La reacción se puede llevar a cabo durante, normalmente, 30 minutos a 48 horas y preferiblemente de 1 a 24 horas. De forma ventajosa la reacción se puede llevar a cabo en presencia de una base. Los ejemplos de base incluyen un hidruro de metal alcalino como hidruro de sodio o hidruro de potasio; alcóxido de metal alcalino como metóxido de sodio o etóxido de sodio; hidróxido de metal alcalino como hidróxido de sodio o hidróxido de potasio; carbonatos como carbonato de sodio o carbonato de potasio e hidrogenocarbonatos como hidrogenocarbonato de sodio e hidrogenocarbonato de potasio; aminas orgánicas como trietilamina.

La etapa 3 de la reacción B es la misma que para la reacción A.

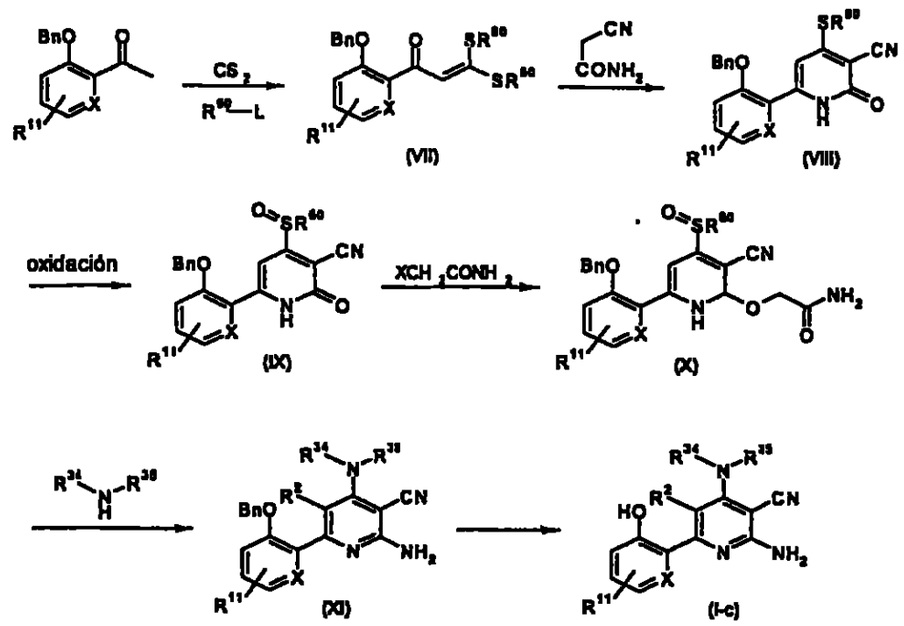
De forma alternativa, el compuesto de fórmula (I-c) siguiente:



(I-c)

en el que X, R^{11}, R^2, R^{34} y R^{35} son como se definieron anteriormente, se puede preparar de forma ventajosa mediante la reacción C siguiente.

REACCIÓN C



En primer lugar, el compuesto de fórmula (VI) puede hacerse reaccionar con disulfuro de carbono y R^{60}-L (en el que R^{60} representa alquilo C_{1-6} y L representa un grupo saliente como se definió anteriormente) para obtener el compuesto de fórmula (VII). El grupo protector bencilo en el compuesto de fórmula (VI) se puede reemplazar por cualquier grupo protector adecuado. La presente reacción se puede llevar a cabo en

presencia de una base, como la combinación de hidruro de sodio y dimetilacetamida.

El compuesto resultante (VII) puede hacerse reaccionar con cianoacetamida en presencia de un disolvente y una base. Luego el compuesto (VIII) se puede oxidar para dar el compuesto (IX). El compuesto (IX) se hace reaccionar luego con halogenoacetamida como cloroacetamida en presencia de una base en un disolvente. El compuesto resultante (X) se hace reaccionar con $NHR^{34}R^{35}$ (R^{34} y R^{35} son como se definieron anteriormente). Finalmente el producto generado se hace reaccionar con una base y se desprotege para obtener el compuesto (I-c).

Los disolventes empleados en cada proceso de la reacción incluyen, por ejemplo, éteres, como dioxano y tetrahidrofurano; hidrocarburos aromáticos como benceno, tolueno y xileno, nitrilos como acetonitrilo; amidas como dimetilformamida (DMF) y dimetilacetamida, sulfóxidos como dimetil sulfóxido y otros. El disolvente anterior se puede emplear solo o en combinación.

Los ejemplos de base usada en la reacción incluyen hidruro de metal alcalino como hidruro de sodio o hidruro de potasio; alcóxido de metal alcalino como metóxido de sodio o etóxido de sodio; hidróxido de metal alcalino como hidróxido de sodio o hidróxido de potasio; carbonatos como carbonato de sodio o carbonato de potasio e hidrogenocarbonatos como hidrogenocarbonato de sodio e hidrogenocarbonato de potasio; aminas orgánicas como trietilamina.

La temperatura de reacción puede fijarse opcionalmente dependiendo del compuesto a hacer reaccionar. La temperatura de reacción, a menos que se especifique otra cosa, es

de aproximadamente 10°C a 200°C. Cada proceso de la reacción se puede llevar a cabo durante, normalmente, 30 minutos a 48 horas y preferiblemente de 1 a 24 horas.

El grupo amino en la posición 2 del anillo de piridina se modifica, en caso necesario, de acuerdo con el procedimiento convencional para preparar otros grupos como alquilamino, alcanoilamino, etc.

Cuando R^{11} es alquil C_{1-6}-sulfonilamino, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, alcanoil C_{1-6}-amino, fenilalquil C_{1-6}-amino o fenilsulfonilamino, se deriva de $-NH_2$ mediante procedimientos convencionales durante el curso de la reacción A.

Los compuestos de fórmulas (I-a), (I-b) y (I-c) se pueden hacer reaccionar además para modificar los sustituyentes en la posición 2 y 3 del anillo de piridina para la síntesis de los compuestos deseados dentro del alcance de la presente invención. También se pueden modificar en el curso de las reacciones A, B y C anteriores, los sustituyentes en la posición 2 y en la posición 3 del anillo de piridina.

El resto amino en la posición 2 puede modificarse por procedimientos convencionales como sigue:



en los que L es el grupo saliente y es como se definió anteriormente, Z es bencilo, alquilo C_{1-6} o fenilo, o NHZ puede formar un anillo saturado de 5 a 6 miembros que contiene opcionalmente NH u O como el otro heteroátomo a parte del átomo de N

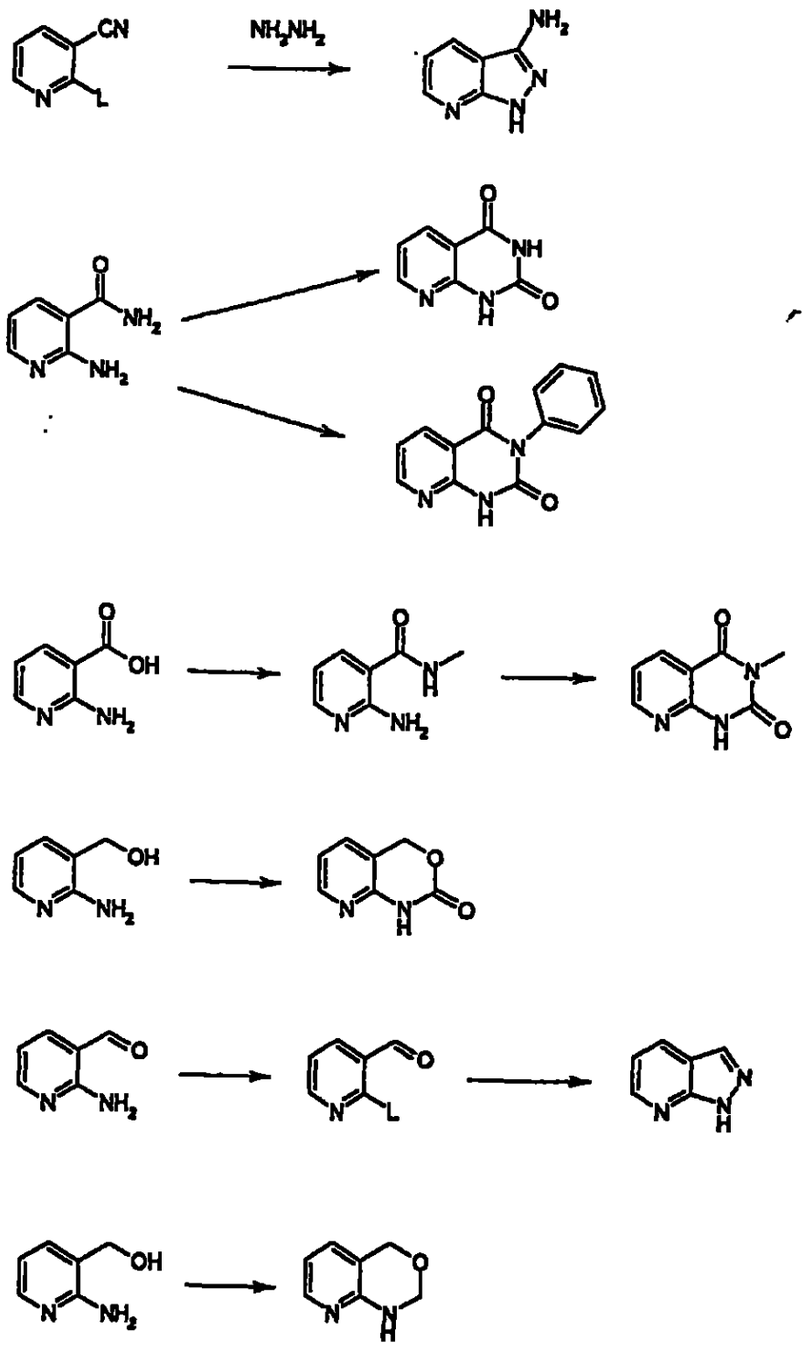
adyacente.

En otra realización el resto amino en la posición 2 se puede convertir en amida usando ácido clorhídrico.

El resto ciano en la posición 3 se puede convertir en carbamoilo por hidrólisis convencional alcalina.

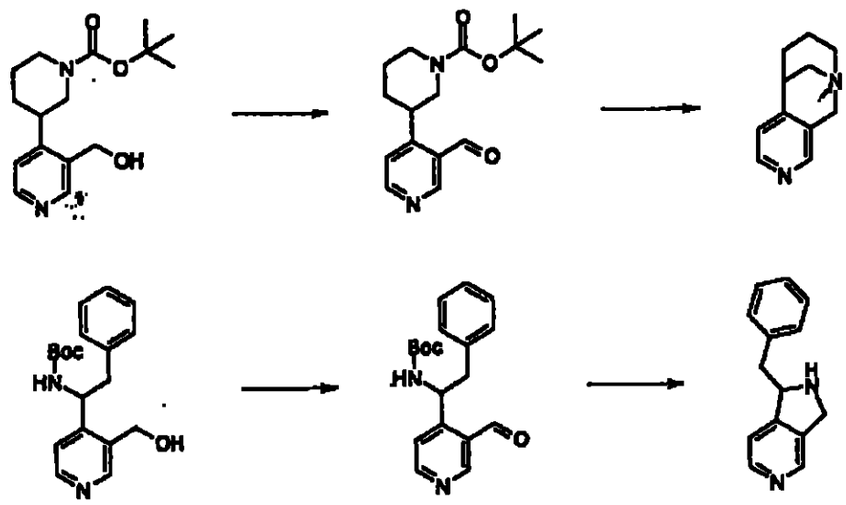
El butoxicarbonilo terciario en la posición 3 se puede modificar fácilmente por reacciones convencionales de éster a alcohol, carboxilo y similares. El alcohol o carboxi se puede convertir además en otros sustituyentes por procedimientos convencionales.

En alguna realización, los sustituyentes de las posiciones 2 y 3 juntos forman un anillo que opcionalmente presenta sustituyentes. Se puede emplear cualquier procedimiento convencional o combinación de cualquier procedimiento convencional para formar los anillos. Los ejemplos de formación de los anillos se muestran a continuación.



Aún en otra realización, los sustituyentes en las posiciones 3 y 4 juntos forman un anillo

que presenta opcionalmente sustituyentes. Se puede emplear cualquier procedimiento convencional o combinación de cualquier procedimiento convencional para formar los anillos. Los ejemplos de formación de anillos se muestran a continuación.



Cuando el compuesto representado por la fórmula (I) o una de sus sales tiene isómeros tautoméricos y/o estereoisómeros (por ejemplo isómeros geométricos e isómeros conformacionales), se incluyen también dentro del alcance de la presente invención cada uno de ellos por separado y la mezclas.

Cuando el compuesto representado por la fórmula (I) o una de sus sales presenta un carbono asimétrico en la estructura, sus compuestos ópticamente activos y mezclas racémicas se incluyen también en el alcance de la presente invención.

Las sales típicas del compuesto representado por la fórmula (I) incluye sales preparadas por reacción de los compuestos de la presente invención con un ácido mineral u orgánico, o una base orgánica o inorgánica. Las mencionadas sales se conocen como

sales de adición de ácidos y sales de adición de bases, respectivamente.

Los ácidos para formar sales de adición de ácidos incluyen ácidos inorgánicos como, sin limitarse a, ácido sulfúrico, ácido fosfórico, ácido clorhídrico, ácido bromhídrico, ácido yodhídrico y similares y ácidos orgánicos, como, sin limitarse a, ácido p-toluenosulfónico, ácido metanosulfónico, ácido oxálico, ácido p-bromofenilsulfónico, ácido carbónico, ácido succínico, ácido cítrico, ácido benzoico, ácido acético y similares.

Las sales de adición de bases incluyen las derivadas de bases inorgánicas, como, sin limitarse a, hidróxido de amonio, hidróxido de metal alcalino, hidróxidos, carbonatos, bicarbonatos de metales alcalinotérreos y similares, y bases orgánicas como, sin limitarse a, etanolamina, trietilamina, tri(hidroximetil)aminometano y similares. Los ejemplos de bases inorgánicas incluyen hidróxido de sodio, hidróxido de potasio, carbonato de potasio, carbonato de sodio, bicarbonato de sodio, bicarbonato de potasio, hidróxido de calcio, carbonato de calcio y similares.

Se puede modificar el compuesto de la presente invención o una de sus sales, dependiendo de sus sustituyentes, para formar ésteres de alquilo inferior o otros ésteres conocidos; y/o hidratos u otros solvatos. Estos ésteres, hidratos y solvatos están incluidos dentro del alcance de la presente invención.

El compuesto de la presente invención se puede administrar en formas orales, como, sin limitarse a, comprimidos normales y con recubrimiento entérico, cápsulas, píldoras, polvos, gránulos, elixires, tinturas, solución, suspensiones, jarabes, aerosoles sólidos y

líquidos y emulsiones. También se pueden administrar en formas parenterales, como, sin limitarse a, intravenosa, intraperitoneal, subcutánea, intramuscular y formas similares, bien conocidas por aquellos expertos en las técnicas farmacéuticas. Los compuestos de la presente invención se pueden administrar de forma intranasal vía tópica usando vehículos intranasales adecuados, o por vías transdérmicas empleando sistemas de liberación transdérmicos bien conocidos por los expertos en la técnica.

La pauta de dosificación usando compuestos de la presente invención se selecciona por un experto en la técnica farmacéutica, teniendo en cuenta una serie de factores, incluyendo, sin limitarse a, edad, peso, sexo y estado médico del receptor, la gravedad de la afección a tratar, la vía de administración, el estado de la función metabólica y de excreción del receptor, la forma de dosificación empleada, el compuesto y su sal en cuestión que se emplee.

Los compuestos de la presente invención se formulan preferiblemente antes de la administración junto con uno o más excipientes farmacéuticamente aceptables. Los excipientes son sustancias inertes como, sin limitarse a, vehículos, diluyentes, agentes aromatizantes, edulcorantes, lubrificantes, solubilizantes, agentes de suspensión, aglutinantes, agentes disgregantes de comprimido y material de encapsulado.

Otra realización de la presente invención es una formulación farmacéutica que comprende un compuesto de la invención y uno o más excipientes farmacéuticamente aceptables que sean compatibles con el resto de ingredientes de la formulación y no sea perjudicial para el receptor. Las formulaciones farmacéuticas de la invención se preparan por la combinación de una cantidad terapéuticamente eficaz de los compuestos

de la invención junto con uno o más excipientes farmacéuticamente aceptables para el mismo. En la preparación de las composiciones de la presente invención, el ingrediente activo se puede mezclar con un diluyente, o incluirse en un vehículo, el cual puede estar en forma de una cápsula, sobrecitos, papelillos u otros recipientes. El excipiente puede actuar como diluyente, el cual puede ser un material sólido, semisólido o líquido que actúa como un vehículo o puede estar en forma de comprimidos, píldoras, polvos, pastillas, elixires, suspensiones, emulsiones, soluciones, jarabes, aerosoles, ungüentos que contienen, por ejemplo, hasta un 10% en peso del compuesto activo, cápsulas de gelatina blanda y dura, supositorios, soluciones inyectables estériles y polvos empaquetados estériles.

Para la administración oral, el ingrediente activo puede combinarse con un vehículo farmacéuticamente aceptable no tóxico y oral, como, sin limitarse a, lactosa, almidón, sacarosa, glucosa, carbonato de sodio, manitol, sorbitol, carbonato de calcio, fosfato de calcio, sulfato de calcio, metilcelulosa y similares; opcionalmente junto con agentes disgregantes, como, sin limitarse a, maíz, almidón, metilcelulosa, agar, bentonita, goma xantana, ácido algínico y similares; y opcionalmente, agentes aglutinantes, por ejemplo, sin limitarse a, gelatina, goma arábiga, azúcares naturales, betalactosa, edulcorantes de maíz, gomas naturales y sintéticas, goma arábiga, tragacanto, alginato de sodio, carboximetilcelulosa, polietilenglicol, ceras y similares; y, de forma opcional, agentes lubricantes, por ejemplo, sin limitación estearato de magnesio, estearato de sodio, ácido esteárico, oleato de sodio, benzoato de sodio, acetato de sodio, cloruro de sodio, talco y similares.

En formas de polvo, el vehículo puede estar como un sólido finamente dividido, el cual

es una mezcla de ingrediente activo finamente dividido. El ingrediente activo puede mezclarse con un vehículo que presenta propiedades ligantes en proporciones adecuadas y compactarse en la forma y tamaño deseada para producir comprimidos. Los polvos y comprimidos contienen preferiblemente de aproximadamente 1 a aproximadamente 99 por ciento en peso del ingrediente activo que es la nueva composición de la presente invención. Los vehículos sólidos adecuados son carboximetilcelulosa de magnesio, ceras de bajo punto de fusión y manteca de cacao.

Las formulaciones líquidas estériles incluyen suspensiones, emulsiones, jarabes y elixires. El ingrediente activo se puede disolver o suspender en un vehículo farmacéuticamente aceptable, como agua estéril, disolvente orgánico estéril o una mezcla de disolvente orgánico estéril y agua estéril.

El ingrediente activo se puede también disolver en un disolvente orgánico adecuado, por ejemplo polipropilenglicol acuoso. Se pueden preparar otras composiciones por dispersión del ingrediente activo finamente dividido en almidón acuoso o solución de carboximetilcelulosa de sodio o en aceite adecuado.

La formulación puede estar en una forma de dosis unitaria, la cual es una unidad fisicamente discreta, adecuada para la administración en seres humanos u otros mamíferos. Una forma de dosis unitaria puede ser una cápsula o comprimido, o un número de cápsulas o comprimidos. Una "dosis unitaria" es una cantidad previamente determinada del compuesto activo de la presente invención, calculada para producir el efecto terapéutico deseado, junto con uno o más excipientes. La cantidad de ingrediente activo en una dosis unitaria puede variar o ajustarse de aproximadamente 0,1 a

aproximadamente 1000 mg o más de acuerdo con el tratamiento particular.

Las dosificaciones orales típicas de la presente invención, cuando se empleen para los efectos indicados variarán de aproximadamente 0,01 mg/kg/dia a aproximadamente 100 mg/kg/día, preferiblemente de 0,1 mg/kg/dia a 30 mg/kg/dia, y lo más preferiblemente de aproximadamente 0,5 mg/kg/día a aproximadamente 10 mg/kg/dia. En caso de administración parenteral, se ha probado que en general es ventajoso administrar cantidades de aproximadamente 0,001 a 100 mg/kg/día, preferiblemente de 0,01 mg/kg/día a 1 mg/kg/día. Los compuestos de la presente invención se pueden administrar en una única dosis diaria o se puede administrar la dosis total diaria en dosis divididas dos, tres o más veces al día. Por supuesto, cuando el suministro es de forma transdérmica la administración es continua.

El efecto de los presentes compuestos se evaluó con los siguientes ensayos y pruebas farmacológicas.

[Ensayo inhibidor de la quinasa IKK-β]

(1) Preparación de proteína quinasa IKK-β

se genera por PCR un fragmento de ADNc que codifica el marco de lectura abierto de la IKK-β humana usando de un par de cebadores diseñados a partir de la secuencia publicada (Woronicz JD *et al* (1997) Science 278, 866-869). Se obtuvo una matriz a partir de ADNc Quickclone (Clontech) empleando un kit Elongase™ Amplification (Life Technologies). Los fragmentos de ADN

generados por PCR se purificaron en gel y se subclonaron en pBluescript. Los fragmentos de ADNc clonados en pBluescript se insertaron en ADNpc3.1/His C KpnI/NotI, y se transfirieron a pVL1393 SmaI/XbaI (Pharmingen) para construir un vector de transferencia de baculovirus. Luego el vector, junto con los baculovirus linearizados (BaculoGold™, Pharmingen) se usó para transfectar las células Sf21 (Invitrogen, San Diego, CA). Los baculovirus recombinantes generados se clonaron y amplificaron en células Sf21, se desarrollaron en medio celular de insecto TNM-FH (Life Technologies, Inc) se suplementaron con FCS al 10%, 50 g/ml de gentamicina, Pluronic F-68 (Life Technologies, Inc.) al 0,1% como cultivo de suspensión (200 ml en un matraz Erlenmeyer de 1 l; 27°C; 130 rpm). Las células Sf21 se infectaron con este virus amplificado con una multiplicidad de infección de 5 siguiendo los protocolos convencionales (Crossen R, Gruenwald S (1997) Baculovirus Expresión Vector System Instruction Manual, Pharmingen Corporation) y se recogieron 48 horas después. Se lisaron las células para obtener la proteína quimérica producida de quinasa IKK-β condensada con histidina (IKK-beta marcada con His).

(2) Preparación de proteínas de fusión GST-IκBα purificadas.

Se construyó un vector de expresión que contiene la secuencia de nucleótidos que codifica la proteína de expresión de GST con los restos aminoácidos 1 a 54 de IκBα bajo el control de un promotor inducible de IPTG. El vector de expresión se introdujo en E. Coli y se cultivó y lisó el transformante para obtener una proteína de fusión GST-IκBα. Luego la proteína de fusión resultante se purificó y biotiniló para el ensayo de la quinasa.

(3) Medida de la actividad de la quinasa IKK-β.

Se llevó a cabo el ensayo de la quinasa en formato de 96 pocillos de IKK-β para comprobar la actividad inhibitoria de los compuestos de la presente invención. En primer lugar se colocaron 5 µl de un compuesto de ensayo en presencia de dimetil sulfóxido al 2,5% (DMSO) en cada pocillo en una placa de 96 pocillos con fondo en forma de U. (Falcon). Se colocaron 5 µl de DMSO al 2,5% para los pocillos de control de fondo (BG) y fosforilación total (TP). Se diluyeron IKK-β recombinante (final 0,6 µg/ml) y bio-GST-IκBα (1-54) (final 0,2 µM) en 25 µl de tampón β de quinasa 2x (Tris-HCl 40 mM, pH 7,6, 40 mM $MgCl_2$, β-glicerofosfato 40 mM, p-nitrofenilfosfato 40 mM, EDTA 2 nM, fosfato de creatina 40 mM, DTT 2 mM, Na_3VO_4 2 mM, BSA 0,2 mg/ml y fluoruro de fenilmetilsulfonilo 0,8 mM) y se transfirieron a la placa de 96 pocillos. Se transfirió Bio-GST-IκBα (1-54) en 25 µl de tampón β de quinasa 2x sin IKK-β a los pocillos BG. Luego se añadieron 20 µl de ATP 12,5 µM, 62,5 µCi/ml de [γ-^{33}P]ATP (Amersham Pharmacia Biotech) y la mezcla resultante se incubó durante 2 horas a temperatura ambiente. Las reacciones de la quinasa se terminaron con la adición de 150 µl de tampón de terminación (EDTA 100 mM, 1 mg/ml de BSA, 0,2 mg de NaN_3). Se transfirieron 150 µl de la muestra a muramil tripéptido (MTP) blanco recubierto de estreptavidina (Streffens Biotechniche Analysen GmbH #08114E14.FWD) para la captura de los sustratos biotinilados. Después de 1 hora de incubación, se eliminó la radiactividad no ligada por lavado de los pocillos cinco veces con 300 µl de tampón de lavado que incluye NaCl al 0,9% y Tween-20 al 0,1% (en peso/volumen) usando un lavador de placa MW-96 (BioTec). Se determinó la radiactividad ligada tras la adición de 170 µl de un cóctel de centelleo MicroScint-PS (Packard) empleando

un contador de centelleo TopCount.

[Ensayo inhibidor de tirosina quinasa Syk para selectividad]

(1) Preparación de proteína Syk

Se clonó un fragmento de ADNc que codifica el marco abierto de lectura de la Syk humana a partir de ARN completo de línea celular de linfoma de Burkitt B humano, Raji (American Type Culture Collection) empleando el procedimiento RT-PCR, El fragmento de ADNc se insertó en pAcG2T (Pharmingen, San Diego, CA) para construir un vector de transferencia de baculovirus, Luego el vector, junto con los baculovirus linealizados (BaculoGoldTM, Pharmingen) se empleó para transfectar células Sf21 (Invitrogen, San Diego, CA).

Los bacilovirus recombinantes generados se clonaron y amplificaron en células Sf21. Las células Sf21 se infectaron con este virus con título elevado amplificado para producir una proteína quimérica de la quinasa Syk condensada con glutatión-S-transferasa (GST).

Se purificó la GST-Syk resultante usando columna de glutatión (Amersham Pharmacia Biotech AB, Uppsala, Sweeden) de acuerdo con las instrucciones del fabricante. Se comprobó por SDS-PAGE que la pureza de la proteína era de más de un 90%.

(2) Síntesis de un péptido

A continuación, se sintetizó un fragmento de péptido de 30 restos incluyendo

dos restos de tirosinasa, KISDFGLSKALRADENYYKAQTHGKWPVKW, con un sintetizador de péptidos. El extremo N terminal del fragmento se biotiniló luego para obtener péptido de bucle de activación (AL) biotinilado.

(3) Medida de la actividad de tirosina quinasa Syk

Se diluyeron todos los reactivos con el tampón de ensayo de la quinasa Syk (Tris-HCl 50 mM (pH 8,0), $MgCl_2$ 10 mM, Na_3VO_4 0,1 mM, BSA 0,1%, DTT 1 mM). Primeramente se pone una mezcla (35 µl) que incluye 3,2 µg de GST-Syk y 0,5 µg de AL en cada pocillo de una placa de 96 pocillos. Luego se añaden a cada pocillo 5 µl de un compuesto de ensayo en presencia de dimetil sulfóxido al 2,5% (DMSO). A esta mezcla se añaden 300 µM de ATP (10 µl) para iniciar la reacción de la quinasa. La mezcla de reacción final (50 µl) comprende GST-Syk 0,65 nM, AL 3 µM, ATP 30 µM, un compuesto de ensayo, DMSO al 0,25% y un tampón de ensayo de quinasa Syk.

La mezcla se incubó durante 1 hora a temperatura ambiente (TA) y se terminó la reacción con la adición de 120 µl de tampón de terminación (Tris-HCl 50 mM (pH 8,0), EDTA 10 mM, NaCl 500 mM, BSA 0,1%). La mezcla se transfirió a placas recubiertas de estreptavidina y se incubó durante 30 minutos a temperatura ambiente para combinar biotina-AL en las placas. Después de lavar tres veces las placas con solución salina tamponada con Tris (TBS) (Tris-HCl 50 mM (pH 8,0), NaCl 138 mM, 2,7 KCl 2,7 mM) que contiene Tween-20 al 0,05%, se añadieron y se incubaron a temperatura ambiente durante 60 minutos 100 µl de solución de anticuerpos constituida por Tris-HCl 50 mM (pH 8,0), NaCl 138 mM, KCl 27 mM, BSA 1%, anticuerpo monoclonal antifosfotirosina 60 ng/ml, 4G10 (Upstate Biotechnology), marcado previamente con

europio, kit Amersham Pharmacia. Después del lavado, se añadieron 100 µl de solución de intensificación (Amersham Pharmacia Biotech) y luego se midió la fluorescencia según tiempo con un contador ARVO múltiple (Wallac Oy, Finlandia) a 340 nm para excitación y 615 nm para emisión con 400 ms de retraso y 400 ms de ventana.

[Medida de la producción RANTES en respuesta a TNF-α en células A549]

(1) Preparación de células A549

Se mantuvo la línea de células del epitelio del pulmón A549 (ATCC #CCL-885) en medio de Eagle modificado por Dulbecco (D-MEM, Nikken Biomedical Institute) suplementado con FCS al 10% (Gibco), penicilina 100 U/ml, estreptomicina 100 µg/ml de estreptomicina y glutamina 2 nM (medio de cultivo). Se sembraron cuarenta mil (4×10^4) células (80 µl/pocillo) en cada pocillo de una placa de cultivo de tejido de 96 pocillos de fondo plano (Falcon #3072). La placa se dejó en reposo durante 2 horas, así las células se adhirieron al fondo de cada pocillo. Se añadió a cada pocillo un vehículo de 10 µl (DMSO al 1%), diluciones en serie de los compuestos de ensayo en DMSO al 1% o dexametasona 5 nM en DMSO al 1% como referencia. La mezcla (90 µl/pocillo) se incubó durante 1 hora a 37°C. Después de 1 hora, se añadió TNF-α (10 µl) en medio de cultivo a la mezcla para obtener 100 µl de mezcla de reacción. La mezcla de reacción se cultivó durante 24 horas para estimular las células con TNF-α 100 ng/ml. También se prepararon células con vehículo sin estimulación de TNF-α.

(2) Medida de producción de RANTES

La concentración de RANTES liberada de las células en los sobrenadantes de cada pocillo se determinó luego empleando una técnica de inmunoanálisis de enzima en sándwich cuantitativo. En primer lugar se puso mAb anti-huRANTES de ratón 2 µg/ml (R&D Systems, #mAb678) en tampón PBS (pH 7,4, 100 µl) en cada pocillo de una placa fluoro NUNC de 96 pocillos (Nalge Nunc, Nueva York USA) (final 200 ng/pocillo) y la placa se dejó en reposo durante la noche a 4°C para que se recubra por el anticuerpo. Cada pocillo de la placa se lavó luego tres veces con 350 µl de tampón de lavado (Tween-20 0,05%, NaCl 0,85% y Tris/HCl pH 7,4 25mM). Se añadieron (200 µl) a cada pocillo tampón de bloqueo que contenía BSA al 1% (Sigma pureza 99%, 100 g), sacarosa al 5% (Nacalai tesque, pureza 99%, 500 g) y azida al 0,02% (Nakalai tesque, 100%, 500 g) y luego se dejó la placa en reposo durante 4 horas para que se estabilizase el anticuerpo recubierto. A continuación se pusieron 50 µl de sobrenadante del cultivo celular preparado en el apartado (1) anterior en cada pocillo de la placa NUNC fluoro de 96 pocillos con anticuerpo recubierto. Se usó RANTES recombinante humano (Pepro Tech, Inc. #300-06) como patrón para la determinación de producción RANTES (intervalo lineal entre 1 y 10 ng/ml). Se añadió (50 µl) a cada pocillo mAb anti-huRANTES de ratón marcado con Eu (60 ng/ml: R&D Systems, #mAb278) en PBS suplementado con BSA al 1% y Tween 20 al 0,05%. Las mezclas de reacción se incubaron a temperatura ambiente durante 4 horas. Después del lavado con tampón de lavado (Tween-20 al 0,05%, NaCl al 0,85% y Tris/HCl 25 mM pH 7,4, 350 µl/pocillo) durante 5 minutos usando un lavador Sera (Bio-Tech, #MW-96R), se añadió a cada pocillo solución de intensificación (DELFIA, #1244-405, 100 µl/pocillo). Se incubó la placa durante 10 minutos a temperatura ambiente con agitación moderada. Se

midió la intensidad de fluorescencia con un fluorímetro DELFIA (Wallac). La excitación tuvo lugar a 340 nm y se midió la emisión a 615 nm.

[Medida de la producción de TNF-α en respuesta a LPS a partir de células mononucleares de sangre periférica (PBMC)]

(1) Preparación de PBMC

Se prepararon PBMC humanas obteniendo en primer lugar sangre de donantes sanos y aislando las células de la misma. El aislamiento se ejecutó por procedimiento de centrifugación en gradiente Ficoll empleando Ficoll Pacque (Pharmacia #17-1440-02). En las tres horas de donación se usaron PBMC aisladas. Una vez lavadas tres veces con PBS, se resuspendieron las PBMC con RPMI 1640 (Nikken BioMedical Institute) suplementado con FCS al 10% (Gibco), penicilina 100 U/ml, estreptomicina 100 μg/ml y glutamina 2 mM (medio de cultivo). Las células (1×10^5 en 150 μl/pocillo) se sembraron en cada pocillo de la placa de cultivo de tejidos de fondo plano de 96 pocillos (Falcon #3072). Se añadieron 20 μl de vehículo a cada pocillo (DMSO al 1%), diluciones en serie del compuesto de prueba en DMSO al 1% o dexametasoma 250 nm en DMSO 1% como referencia. Se incubó la mezcla (170 μl/pocillo) durante 1 hora a 37°C. Después de una hora, se añadieron 20 ng/ml de LPS (30 μl) en medio de cultivo a la mezcla para obtener 200 μl de mezcla de reacción. La mezcla de reacción se cultivó durante 7 horas para estimular las células con LPD 3 ng/ml. También se prepararon células con vehículo sin la estimulación con LPS. Se recogieron luego los sobrenadantes de la mezcla de reacción.

(2) Medida de la producción de TNF-α

La concentración de TNF-α en los sobrenadantes se determinó empleando un kit ELISA DuoSet™ (GenzymeTechne, Minneapolis, USA) siguiendo las recomendaciones del fabricante. En primer lugar se puso TNF-α Ab antihumano de ratón 4 μg/ml en tampón de PBS (100 μl) en cada pocillo de la placa de 96 pocillos (NUNC, MaxisorpTM) y se dejó que la placa reposase durante la noche a 4°C para que se recubriese con el anticuerpo. Cada pocillo de la placa se lavó luego 5 veces con 350 μl de tampón de lavado que contiene PBS, Tween 20 (Nakalai Tesque) empleando Lavador Sera (BioTech, #MW-96R). Se añadieron a cada pocillo 300 μl de BSA al 1% (Sigma), sacarosa al 5% en PBS. Tras 2 horas de incubación a temperatura ambiente, se descargó el tampón y se añadieron 50 μl de medio de cultivo. A continuación se pusieron 50 μl de sobrenadante de cultivo celular estimulado preparado en el apartado (1) anterior en cada pocillo de la placa de 96 pocillos. Se empleó TNF-α recombinante humano (Genzyme Techne) como patrón para la determinación de la producción de TNF-α (intervalo lineal entre 30 y 2.000 pg/ml). Las mezclas de reacción se incubaron durante una hora a temperatura ambiente. Tras lavar cinco veces, se añadió a cada pocillo 100 μl de anticuerpo TNF-α antihumano biotilinado (Genzyme Techne, 300 ng/ml) en BSA 0,1%, Tween al 0,05% en PBS (diluyente reactivo) y se incubó a temperatura ambiente durante 1 hora. Después de lavar cinco veces, se añadió a cada pocillo 100 μl de peroxidasa de rábano picante conjugada con estreptavidina (Genzyme Techne, 1/100 en diluyente reactivo). Después de 20 minutos cada pocillo de la placa se lavó cinco veces con tampón de lavado (350 μl/pocillo). El sustrato de peroxidasa de rábano picante y H_2O_2 (kit de detección de peroxidasa TMBZ, SUMILON #ML-1120T)

se añadieron a la mezcla y esta se dejó en reposo a temperatura ambiente. La reacción se finalizó después de 10 minutos con la adición de H_2SO_4 2N. Se midió la densidad óptica a 450 nm usando un lector de microplaca (Labosystems, Multiscan Multisoft). Se llevó a cabo la cuantificación de la producción de TNF-α en cada muestra por comparación de las densidades ópticas de cada muestra y la curva del patrón.

[Medida de la producción de IL-2 en células T Junkat en respuesta a estimulación de anticuerpos]

La producción de IL-2 se mide en células T junkat (clon E6-1; ATCC # TIB-152) en respuesta a la estimulación con anticuerpos anti-CD3/anti-CD28.

(1) Preparación de anticuerpos inmovilizados

En primer lugar se pusieron en cada pocillo de la placa de 96 pocillos los anticuerpos anti-CD3 (400 ng/pocillo Nichirei, UN-T3 4 µg/ml en 100 µl de PBS Dulbecco) y se dejó la placa en reposo durante 2 horas a temperatura ambiente para que se recubriese con el anticuerpo. Cada pocillo de la placa se lavó luego con 250 µl de PBS 3 veces.

(2) Preparación de cultivo celular Jurkat.

Se cultivaron células T Jurkat en medio RPMI 1640 suplementado con suero de bovino fetal inactivado con calor, L-glutamina 2 mM, penicilina G 100 U/ml y estreptomicina 100 µg/ml (medio de cultivo). Se sembraron doscientas mil (2 x 10^5) células (190 µl/pocillo) en cada pocillo de placas de cultivo de tejido con

fondo en forma de U de 96 pocillos (Falcon #3077). Se añadieron 10 µl de vehículo (DMSO al 2%) a cada pocillo, y diluciones en serie de compuestos en DMSO al 0,2% o ciclosporina A como referencia en DMSO al 0,2%. La mezcla (200 µl) se incubó durante una hora a 37°C en un ambiente humidificado de CO_2 al 5%.

(3) Estimulación de la célula

La mezcla de reacción obtenida en (2) (100 µl) se puso en cada pocillo de la placa de anticuerpos inmovilizados preparada en (1). Se añaden a este pocillo anticuerpos antiCD28 (Nichirei, KOLT-21, 6 µg/ml en medio de cultivo celular, 50 µl/pocillo) y anticuerpos de cadena kappa antirratón de cabra (Bethyl Laboratories), (Cat#A90-119A) 10 µl/ml en medio de cultivo, 50 µl/ml). Se incubó la mezcla de reacción en cada pocillo durante 24 horas a 37°C para estimular la células con anticuerpos anti-CD3 inmobilizados (400 ng/pocillo) y anticuerpos anti-CD28 (1,5 µg/ml) y luego receptores de entrecruzamiento en las células con anticuerpos de cadena kappa antirratón (2,5 µg/ml).

(4) Medida de la producción de IL-2

Se recogieron entonces los sobrenadantes de la mezcla de reacción. Se determinó la concentración de IL-2 en los sobrenadantes empleando un kit de desarrollo ELISA (GenzymeTechne, Minneapolis, USA) siguiendo las recomendaciones del fabricante. En primer lugar se pusieron en cada pocillo de la placa de 96 pocillos (NUNC, Maxisorp™) 2 µg/ml de Ab anti-huIL de ratón en tampón de PBS (100 µl) de ratón 2 µg/ml dejándose la placa en reposo durante la noche a 4°C para que se recubriera con el anticuerpo. Cada pocillo de

la placa se lavó luego cinco veces con 350 µl de tampón de lavado que contenía PBS, Tween 20 al 0,05% (Nakalai tesque) empleando Sera Washer (Bio-Tech, #MW-96R). Se añadieron a cada pocillo 250 µl de BSA al 1% (Sigma) en PBS, Tween 20 al 0,05% (tampón de dilución). Después de dos horas de incubación a temperatura ambiente se descargó el tampón y se añadieron 50 µl de medio de cultivo. A continuación se pusieron 50 µl de sobrenadante de cultivo celular estimulado preparado en (3) en cada pocillo de la placa de 96 pocillos con anticuerpo anti-huIL-2 de ratón recubierto. Se empleó IL-2 humano recombinante (Genzyme Techne) como el patrón para la determinación de la producción de IL-2 (intervalo lineal entre 200 y 5.400 pg/ml). La mezcla de reacción se incubó durante 1 hora a temperatura ambiente. Tras lavar 5 veces, se añadieron 100 µl de anticuerpo anti-huIL-2 de conejo biotinilado (Genzyme Techne, 1,25 µg/ml) en tampón de dilución a cada pocillo y se incubó a temperatura ambiente durante una hora. Después de cinco lavados se añadieron a cada pocillo 100 µl de peroxidasa de rábano picante conjugada con estreptavidina (Genzime Techne, 1/1000 en tampón de dilución). Después de 20 minutos se lavó cada pocillo de la placa cinco veces con tampón de lavado (350 µl/pocillo). Se añadieron a la mezcla sustrato y H_2O_2 (kit de detección de peroxidasa TMBZ, SUMILON #ML-1120T) y se dejó en reposo a temperatura ambiente. Se finalizó la reacción después de 10 minutos añadiendo H_2SO_4 2N. Se midió la densidad óptica a 450 nm usando un lector de microplaca (Labosystems, Multiscan Multisoft). La cuantificación de la producción de IL-2 en cada muestra se llevó a cabo por comparación de las densidades ópticas de cada muestra y la curva patrón.

[Producción de TNF-α inducido por LPS de ratón]

Se agruparon en dos grupos ratones hembra BALB/c de ocho semanas de edad, un grupo de control y un grupo de tratamiento. Se administró una solución que contenía LPS 200 μg/ratón en solución salina fisiológica al 0,9% por inyección intraperitoneal (ip) en los ratones de control. Los ratones del grupo de control se inyectaron primero ip con compuestos de la presente invención 30 minutos antes de la inyección de LPS. Se recogió sangre de cavidad venosa posterior de los ratones tratados y control, antestesiando con pentobarbital (80 mg/kg, i.p.) después de 90 minutos de la inyección de LPS y se añadió a una placa de 96 pocillos que contenía solución de EDTA al 2%. Se separó el plasma por centrifugación a 1800 rpm durante 10 minutos a 4°C y luego se diluyó cuatro veces con solución salina tamponada con fosfato (pH 7,4) que contenía albúmina de suero bovino al 1%. La concentración de TNF-α en la muestra se determinó empleando un kit ELISA (Pharmingen, San Diego, CA).

Se determinó el nivel medio de TNF-α en cinco ratones de cada grupo y se calculó el porcentaje de reducción en los niveles de TNF-α. Los ratones tratados mostraron una disminución significativa en el nivel de TNF-α en comparación con los ratones de control. Los resultados indicaron que los compuestos de la presente invención pueden limitar la actividad de la citoquina inducida por LPS.

Los resultados del ensayo celular (A549) y de la prueba *in vitro* se muestran a continuación en los ejemplos y en las tablas de los ejemplos. Los datos corresponden a los compuestos como se obtuvieron por síntesis en fase sólida y por tanto a niveles de pureza de aproximadamente 40 a 90%. Por razones prácticas, los compuestos se

agrupan en cuatro clases de actividad como se muestra a continuación:

CI_{50} in vitro = A (=o<) 0,5 μM < B (=o<) 2 μM < C (=o<) 10 μM < D

CI_{50} celular = A (=o<) 1 μM < B (=o<) 10 μM < C

Los compuestos de la presente invención también muestran una excelente selectividad y fuerte actividad en otros ensayos de actividad celular e *in vivo*.

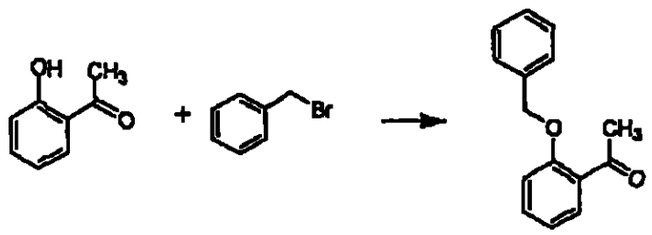
EJEMPLOS

La presente invención se describirá detalladamente a continuación mediante los ejemplos, si bien en ningún modo se considerará que definen las metas y alcance de la presente invención.

En los ejemplos siguientes, todos los datos cuantitativos, si no se define de otra forma, se refieren a porcentajes en peso. Los espectros de resonancia magnética nuclear de protón (RMN de ^1H) están registrados a 300 o 500 MHz con un equipo Brucker DRX-300.

Los desplazamientos del 500 Brucker UltraShield TM y químicos se dan en partes por millón con relación al tetrametilsilano (TMS). Los espectros de masas se obtienen usando técnicas de ionización por electronebulización (ES) (micromass Platform LC).

[Compuesto de partida 1A]

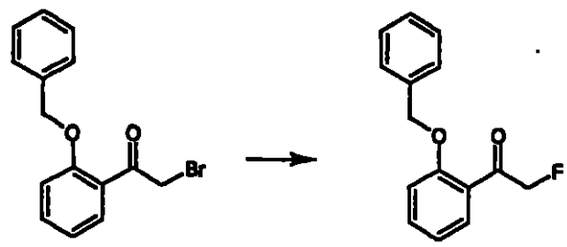


(Compuesto de partida 1A).

Se calentó a reflujo una mezcla de 2'-hidroxiacetofenona (68,1 g, 0,500 mol), bromuro de bencilo (94,1 g, 0,550 mol) y K_2CO_3 (103 g, 0,750 mol) en acetona (1 l), se continuó agitando durante la noche. Después de enfriar hasta temperatura ambiente se concentró la mezcla a presión reducida. El residuo se diluyó con agua, y se extrajo con acetato de etilo. La fase orgánica separada se lavo con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida proporcionando 1-[2-(benciloxi)fenil]etanona en forma de un aceite incoloro. (100 g, rendimiento; 88%).

[Compuesto de partida 1B]

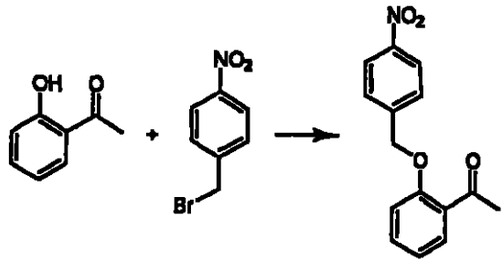
Se añadió a una solución de 2'-hidroxiacetofenona (6,79 g, 30 mmol) en éter (200 ml) una solución de bromo (5,00 g, 31 mmol) en éter (20 ml). Una vez agitado a temperatura ambiente durante 30 minutos, la mezcla se diluyó con éter (100 ml) y se lavó con $NaHCO_3$ acuoso saturado (100 ml) y con salmuera (100 ml) sucesivamente. La fase orgánica combinada se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo se lavó con éter y hexano sucesivamente y se secó a presión reducida proporcionando 1-[2-(benciloxi)fenil]-2-bromoetanona. (8,42 g, rendimiento; 92%).



(Compuesto de partida 1B).

Se añadió a una solución de 1-[2-(benciloxi)fenil]-2-bromoetanona (2,59 g, 8,5 mmol) y piridina (1,37 ml, 17 mmol) en THF hidrogenodifluoruro de tetrabutilamonio (4,78 g, 17 mmol). La mezcla de reacción se agitó a reflujo durante 22 horas. La mezcla se diluyó con éter (250 ml), luego se lavó con ácido clorhídrico acuoso 1 N (100 ml) y salmuera (100 ml) sucesivamente. La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna en gel de sílice (hexano/acetato de etilo, 4:1) proporcionando 1-[2-benciloxi)fenil]-2-fluoroetanona (688 mg; rendimiento 33%).

[Compuesto de partida 1C]



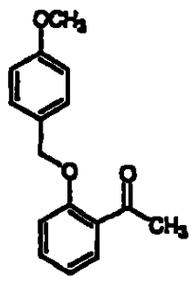
(Compuesto de partida 1C).

Se añadió a una solución agitada de 2'-hidroxiacetofenona (5,000 g, 36,724 mmol) en acetonitrilo (200 ml) carbonato de potasio (7,613 g, 55,086 mmol). Se agitó la mezcla a

50°C durante 30 minutos. Se añadió a la mezcla bromuro de 4-nitrobencilo (8,727 g, 40,396 mmol), y se continuó agitando a 50°C durante 12 horas. Se añadieron a la mezcla carbonato de potasio (0,508 g, 3,672 mmol) y bromuro de 4-nitrobencilo (0,793 g, 3,672 mmol) y se agitó la mezcla resultante a 50°C durante 12 horas. Una vez enfriada a temperatura ambiente, la mezcla de reacción se concentró a presión reducida y se diluyó con acetato de etilo. La fase orgánica se lavó en agua, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo resultante se lavó con hexano proporcionando 1-{2-[(4-nitrobencil)oxi]fenil} etanona en forma de un sólido blanco. (8,900 g, rendimiento; 89%).

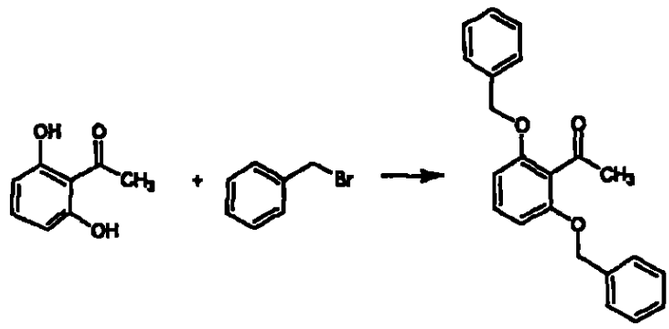
[Compuesto de partida 1D]

Se preparó metoxibencil-acetofenona de la misma forma que en el método para preparar el compuesto de partida 1A, salvo que se sustituyó el bromuro de bencilo por cloruro de metoxibencilo.



(Compuesto de partida 1D).

[Compuesto de partida 1E]



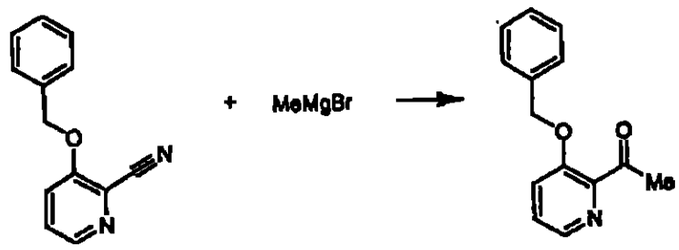
(Compuesto de partida 1E).

Se agitó a reflujo durante la noche una suspensión de (2', 6' –dihidroxi)acetofenona (25,0 g, 164 mmol), bromuro de bencilo (40 ml, 337 mmol), carbonato de potasio (136 g, 986 mmol) y yoduro de sodio (2,5 g, 16 mmol) en acetona (500 ml). Se concentró la mezcla a presión reducida, y se diluyó con acetato de etilo (500 ml) y agua (250 ml). Se extrajo la fase acuosa separada con acetato de etilo (200 ml x 2). La fase orgánica combinada se lavó con salmuera (100 ml), se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo se trituró con hexano, se recogió mediante filtración, se lavó con hexano y se secó a presión reducida proporcionando 1-[2,6-bis (benciloxi)fenil]etanona (2,49 g, rendimiento; 46%).

[Compuesto de partida 1F]

Se agitó a temperatura ambiente una suspensión de 3-hidroxipicolinonitrilo (3,00 g, 25,0 mmol), preparada de acuerdo con "Synthesis" 316 (1983) y "J. Org. Chem." 48 1375 (1983), carbonato de potasio (5,40 g, 39,1 mmol) y bromuro de bencilo (5,10 g, 29,8 mmol) en acetona (150 ml) durante 20 horas. Se filtró la mezcla de reacción y se evaporó el filtrado. Se purificó el residuo mediante cromatografía en columna en gel de sílice (acetato de etilo / n-hexano = 1/3 a 1/2) seguida de recristalización en acetato de

etilo / n-hexano = 1/4 proporcionando 3-benciloxipicolinonitrilo en forma de un sólido incoloro (4,354 g, rendimiento; 83%).



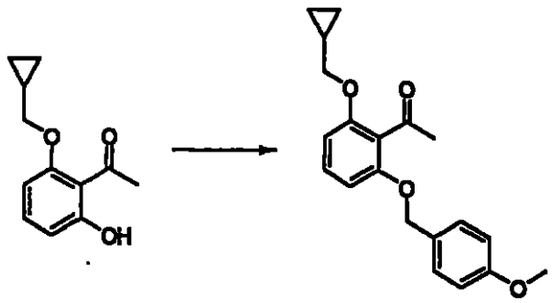
(Compuesto de partida 1F).

Se añadió gota a gota a una solución fría (0°C) de 3-benciloxipicolinonitrilo (2,50 g, 11,9 mmmol) en tetrahidrofurano (100 ml) bromuro de metilmagnesio 0,92 M en tetrahidrofurano (150 ml, 138 mmol). Se agitó la mezcla a 0°C durante 30 minutos y luego a temperatura ambiente durante 4 horas. Se vertió la mezcla de reacción en agua (2000 ml) y se acidificó con ácido sulfúrico al 10% (500 ml). Tras haber agitado durante 30 minutos, se vertió la mezcla de reacción lentamente en una solución acuosa saturada de $NaHCO_3$ y se extrajo con acetato de etilo. Se lavó la fase orgánica con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. Se purificó el residuo mediante cromatografía en columna en gel de sílice (acetato de etilo / n-hexano = 1/3) proporcionando 1-(2-benciloxifenil)-etanona en forma de un aceite incoloro (2,49 g, rendimiento; 92%).

[Compuesto de partida 1G]

Se añadió a una solución agitada de 1-(2,6-dihidroxifenil)etanona (50,0 g, 328 mmol) en acetona (1000 ml) carbonato de potasio (227 g, 1643 mmol) y (bromometilo) ciclopropano (35,1 ml, 361 mmol). La mezcla se agitó a 50°C durante 2 días. Se filtró

la mezcla de reacción a través de celite® y luego se concentró el filtrado a presión reducida. Se diluyó el residuo con agua y se extrajo con acetato de etilo. Se lavó la fase orgánica separada con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El residuo se suspendió en hexano. Luego la suspensión se agitó a 80°C durante 30 minutos. Se filtró la solución y se dejó que el filtrado se enfriase a temperatura ambiente. El sólido blanco resultante se recogió mediante filtración, se lavó con hexano, y se secó a presión reducida proporcionando 1-{2-[(ciclopropilmetil)oxi]-6-hidroxifenil}etanona en forma de un sólido amarillo pálido (56,3 g, rendimiento; 83%).

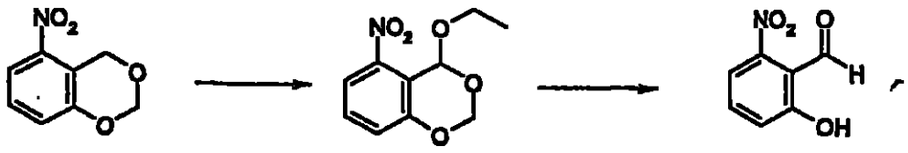


(Compuesto de partida 1G).

Se añadió a una solución agitada de 1-{2-[(ciclopropilmetil)oxi]-6-hidroxifenil}etanona (56,3 g, 272 mmol) en acetona (1000 ml) carbonato de potasio (188 g, 1364 mmol), cloruro de 4-metoxibencilo (40,9 ml, 330 mmol) y yoduro de tetrabutilamonio (20,2 ml, 54,6 mmol). La mezcla se agitó a reflujo durante la noche. Se dejó que la mezcla de reacción se enfriase a temperatura ambiente, se filtró a través de celite®, y luego se concentró el filtrado a presión reducida. Se diluyó el residuo con agua y se extrajo con acetato de etilo. Se lavó la fase orgánica separada con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. Luego el sólido blanco resultante se recristalizó con etanol, se recogió mediante filtración, se lavó con etanol y se secó a presión reducida proporcionando 1-{2-(ciclopropilmetoxi)-6-[(4-

metoxibencil)oxi]fenil}etanona en forma de un sólido blanco (79,2 g, rendimiento; 89%).

[Compuesto de partida 1H]



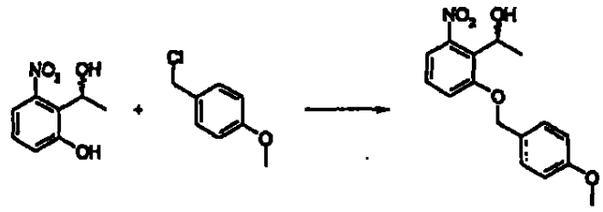
Se añadieron a una solución agitada de 5-nitro-4H-1,3-benzodioxina (10,0g, 55,203 mmol) en tetracloruro de carbono (70 ml) N-bromosucinimida (10,808 g, 60,723 mmol) y 2, 2'-azobisisobutironitrilo (0,906 g, 5,520 mmol). Se agitó la mezcla a 100°C durante 2 horas. Una vez enfriada a temperatura ambiente, se añadió a la mezcla una solución de etoxido de sodio (4,884 g, 71,764 mmol) en etanol (70 ml), y se continuó agitando a temperatura ambiente durante 3 horas. La reacción se desactivó con agua y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía en columna en gel de sílice (hexano/acetato de etilo = 9/1) proporcionando 4-etoxi-5-nitro-4H-1,3-benzodioxina en forma de aceite amarillo pálido (10,8 g, rendimiento; 87%).

Se añadió a una solución agitada de 4-etoxi-5-nitro-4H-1,3-benzodioxina (5,80 g, 25,755 mmol) en etanol (15 ml) y THF (10 ml) 4N HCl en 1,4-dioxano (20 ml). Se agitó la mezcla a 60°C durante 6 horas y a 90°C durante 6 horas. Una vez enfriada a temperatura ambiente, se diluyó la mezcla de reacción con agua y se extrajo con acetato de etilo. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía en columna en gel de sílice

(hexano / acetato de etilo = 9/1) proporcionando 2-hidroxi-6-nitrobenzaldehido en forma de aceite amarillo pálido (4,450 g, rendimiento; cuantitativo).

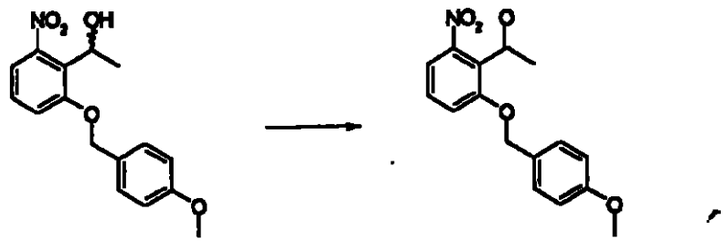


Se añadió gota a gota a una solución agitada de 2-hidroxi-6-nitrobenzaldehido (4,5 g, 26,926 mmol) trimetilaluminio (2M en tolueno, 27 ml) en atmósfera de argon. Se agitó la mezcla a temperatura ambiente durante 1 hora. Se vertió la mezcla de reacción en ácido clorhídrico 1N acuoso frío (0°C) y se extrajo con acetato de etilo. Se lavó la fase orgánica con salmuera y se secó sobre Na_2SO_4, se filtró y se evaporó. Se purificó el residuo mediante cromatografía en columna en gel de sílice (hexano / acetato de etilo = 9/1) proporcionando 2-(1-hidroxietil)-3-nitrofenol en forma de un aceite naranja (4,660 g, rendimiento; 95%).

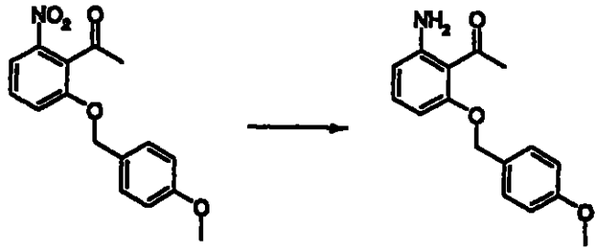


Se añadió a una solución agitada de 2-(1-hidroxietil)-3-nitrofenol (0,300 g, 1,638 mmol) en acetona (5 ml) carbonato de potasio (0,25 g, 1,802 mmol). Se agitó la mezcla a temperatura ambiente durante 15 minutos, y se añadió a la mezcla cloruro de 4-metoxibencilo (0,22 ml, 1,638 mmol). Se agitó la mezcla a temperatura ambiente durante 2 horas y a 60°C durante 3 horas. La reacción se desactivó con una solución acuosa saturada de cloruro de amonio y se extrajo con acetato de etilo. La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó por cromatografía en columna en gel de sílice (hexano / acetato de etilo = 4/1) Se lavó el compuesto

purificado con éter diisopropílico proporcionando 1-{2-[(4-metoxibencil)oxi]-6-nitrofenil}etanol en forma de un sólido blanco (0,201 g, rendimiento; 41%).



Se añadieron a una solución enfriada (0°C), agitada de 1-{2-[(4-metoxibencil)oxi]-6-nitrofenil}etanol (0,20 g, 0,659 mmol) en diclorometano (20 ml) tamices moleculares de 4A (1 g), N-óxido de N-metilmorfolina (0,15 g, 1,319 mmol) y perrutenato de tetra-n-propilamonio (0,01 g). La mezcla se agitó a temperatura ambiente durante 12 horas. Se filtró la mezcla de reacción a través de celite® y se diluyó el filtrado con acetato de etilo. Se lavó la fase orgánica con una solución acuosa saturada de cloruro de amonio y se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida proporcionando 1-{2-[(4-metoxibencil)oxi]-6-nitrofenil}etanona en forma de un sólido blanco (0,159 g, rendimiento; 80%). Se utilizó el residuo para la siguiente etapa sin más purificación.

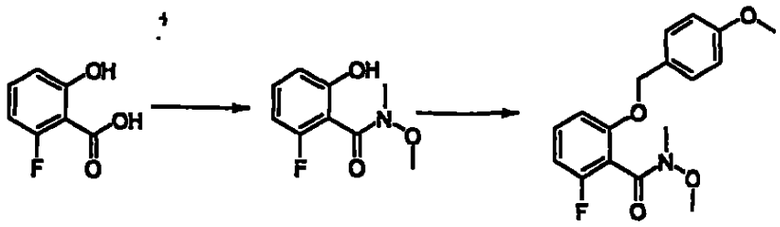


(Compuesto de partida 1H).

Se añadió a una suspensión agitada de 1-{2-[(4-metoxibencil)oxi]-6-nitrofenil}etanona (0,50 g, 1,659 mmol) en etanol una solución de cloruro de amonio (0,10 g, 1,825 mmol) en agua (5 ml) seguida de polvo de hierro (0,75 g). Se agitó la mezcla a 100°C durante 1

hora. Se filtró la mezcla de reacción a través de celite®. Se diluyó el filtrado con acetato de etilo y se lavó con agua. La fase orgánica separada se lavó con salmuera y se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida proporcionando 1-{2-amino-6-[(4-metoxibencil)oxi]fenil}etanona en forma de un sólido amarillo (0,790 g, rendimiento; 108%). Se utilizó el residuo para la siguiente etapa sin más purificación.

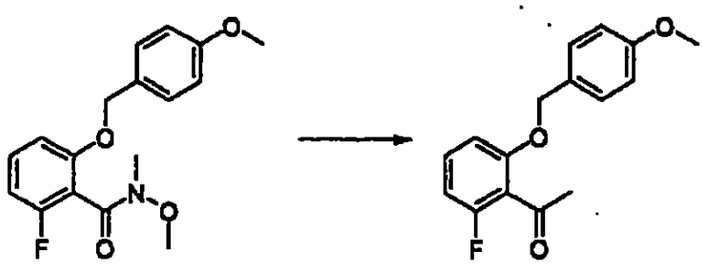
[Compuesto de partida 11]



Se añadieron a una solución fría (0°C) de ácido 2-fluoro-6-hidroxibenzoico (5,00 g, 32,029 mmol) en dimetilformamida (200 ml) clorhidrato de N,O-dimetilhidroxilamina (6,25 g, 64,057 mmol), clorhidrato de 1-etil-3-(3-dimetilaminoprpil)carbodiimida (9,82, 48,043 mmol), 1-hidroxibenzotriazol (5,19 g, 38,435 mmol) y trietilamina (8,93 ml, 64,057 mmol). Se agitó la mezcla a temperatura ambiente durante 15 horas. La mezcla de reacción se extrajo con acetato de etilo y agua. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo resultante se purificó por cromatografía en columna en gel de silice (acetato de etilo / hexano = 2/1) proporcionando 2-fluoro-6-hidroxi-N-metoxi-N-metilbenzamida en forma de un sólido naranja (4,320 g, rendimiento; 68%).

Se añadieron a una solución agitada de 2-fluoro-6-hidroxi-N-metoxi-N-metilbenzamida (4,320 g, 21,689 mmol) en acetona (50 ml) cloruro de 4-metoxi bencilo (3,74 g, 23,858 mmol), carbonato de potasio (4,50 g, 32,534 mmol) y yoduro de potasio (360 mg, 2,169

mmol). Se agitó la mezcla a reflujo durante 15 horas. Una vez enfriada a temperatura ambiente, se filtró la mezcla de reacción y se concentró el filtrado a presión reducida. Se extrajo el residuo con acetato de etilo y agua. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo resultante se purificó por cromatografía en columna en gel de sílice (hexano / acetato de etilo = 2/1) proporcionando 2-fluoro-N-metoxi-6-[(4-metoxibencil)oxi]-N-metilbenzamida en forma de un aceite amarillo pálido (6,926 g, rendimiento; cuantitativo).

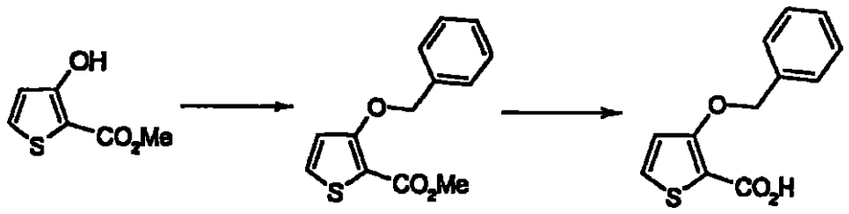


(Compuesto de partida 1I).

Se añadió a una solución fría (0°C) de 2-fluoro-N-metoxi-6-[(4-metoxibencil)oxi]-N-metilbenzamida (6,926 g, 21,70 mmol) en tetrahidrofurano (10 ml) bromuro de metilmagnesio 1 N en tetrahidrofurano (43,40 ml, 43,40 mmol). Se agitó la mezcla de reacción a reflujo durante 4 horas. Una vez enfriada a temperatura ambiente, la mezcla de reacción se desactivó con una solución acuosa saturada de $NaHCO_3$, y se extrajo con acetato de etilo. La fase orgánica separada se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo resultante se purificó por cromatografía en columna en gel de sílice (hexano : acetato de etilo, 3/1) proporcionando 1-{2-fluoro-6-[(4-metoxibencil)oxi]fenil}etanona en forma de un sólido amarillo pálido (1,21 g, rendimiento; 20%).

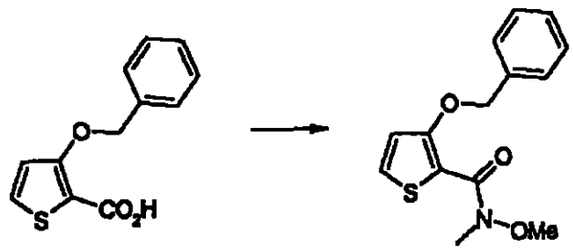
227.
226

[Compuesto de partida 1J]

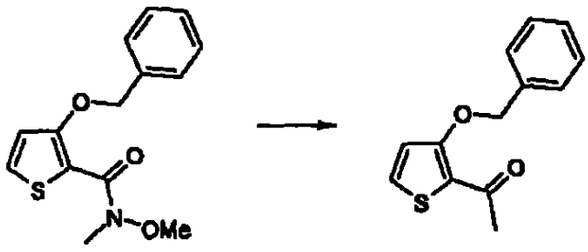


Se agitó a reflujo durante 1 hora y media una mezcla de 3-hidroxi-2-tiofenocarboxilato de metilo (5,00 g, 31,61 mmol), bromuro de bencilo (3,76 ml, 31,61 mmol), y K_2CO_3 (4,81 g, 34,77 g) en acetona (50 ml). Una vez enfriada a temperatura ambiente, la mezcla se filtró, y el filtrado se concentró a presión reducida. El residuo se purificó por cromatografía en columna en gel de sílice (hexano : acetato de etilo=15/1 a 9/1) proporcionando 3-(benciloxi)-2-tiofenocarboxilato de metilo en forma de un aceite amarillo pálido (7,91 g, rendimiento: cuantitativo).

Se añadió a una solución de 3-(benciloxi)-2-tiofenocarboxilato de metilo (7,85 g, 31,61 mmol) en MeOH (32 ml) y THF (16 ml) NaOH 2 N (21 ml), y la mezcla se agitó a reflujo durante 10 horas, y luego se concentró a presión reducida. El residuo se diluyó con agua, se lavó con éter. La fase acuosa separada se acidificó con HCl 5N. El sólido precipitado se recogió mediante filtración, se lavó con hexano, y se secó a presión reducida a 60°C proporcionando ácido 3-(benciloxi)-2-tiofenocarboxílico en forma de un sólido amarillo (6,76 g, rendimiento: 91%).



Se añadieron a una solución de ácido 3-(benciloxi)-2-tiofenocarboxílico (3,00 g, 12,81 mmol) en CH_2Cl_2 (30 ml) cloruro oxálico (1,34 ml, 15,4 mmol) y DMF (0,05 ml). La mezcla se agitó a temperatura ambiente durante 1 hora, y se concentró a presión reducida. El residuo se disolvió con acetato de etilo (10 ml). Luego se añadió la solución a una mezcla de clorhidrato de N,O-dimetilhidroxiamina (1,50 g, 15,37 mmol) y K_2CO_3 (3,54 g, 25,62 mmol) en acetato de etilo (30 ml) y agua (30 ml) a 0°C. Se agitó vigorosamente la mezcla a 0°C durante media hora, y a temperatura ambiente durante 1 hora y media. Se separó la fase orgánica, se lavó con 1 N HCl, $NaHCO_3$ saturado, y salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. El residuo se purificó por cromatografía en columna en gel de sílice (n-hexano/acetato de etilo = 2/1) proporcionando 3-(benciloxi)-N-metoxi-N-metil-2-tiofenocarboxamida en forma de un sólido amarillo pálido (3,473 g, rendimiento; 98%).

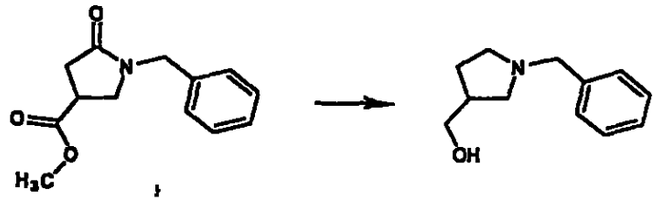


(Compuesto de partida 1J).

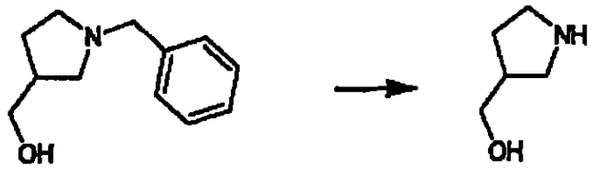
Se añadió a una solución fría (0°C) de 3-(benciloxi)-N-metoxi-N-metil-2-tiofenocarboxamida (3,47 g, 12,50 mmol) en THF (50 ml) una solución de bromuro de metilmagnesio en THF (1 M, 35 ml). Una vez agitado a 0° durante 1 hora, la mezcla de reacción se desactivó con una solución acuosa saturada de NH_4Cl, se diluyó con agua, y se extrajo con acetato de etilo. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. El residuo se purificó por cromatografía en columna en gel de sílice (hexano/acetato de etilo/CH_2Cl_2 = 3/1/1) seguida por

recristalización con n-hexano/acetato de etilo proporcionando 1-[3-(benciloxi)-2-tienil]etanona en forma de un sólido blanco (2,592 g, rendimiento; 89%).

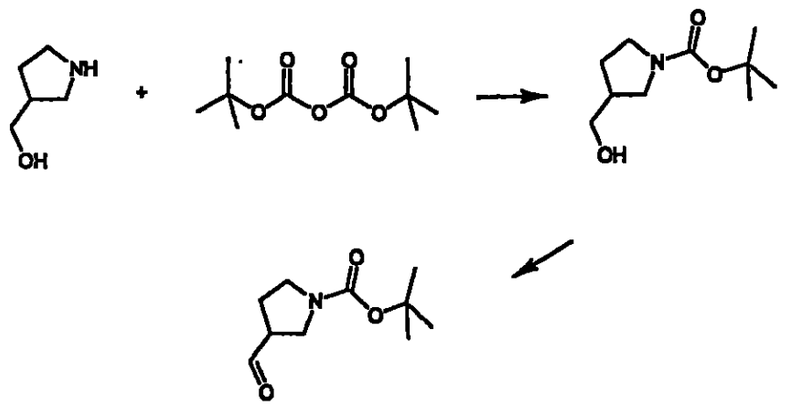
[Compuesto de partida 2A]



Se añadió a una suspensión fría (0°C) de hidruro de litio y aluminio (2,44 g, 64 mmol) en THF (40 ml) 1-bencil-5-oxo-3-pirrolidincarboxilato de metilo (5,00 g, 21 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 horas. Se añadieron a la mezcla de reacción agua (2,5 ml), 15% de solución acuosa de hidróxido de sodio (2,5 ml), y agua (7,5 ml), sucesivamente. La mezcla se filtró a través de celite®. El filtrado se concentró a presión reducida proporcionando (1-bencil-3-pirrolidinil)metanol. (4,16 g, rendimiento; cuantitativo).



Se añadió a una suspensión de $Pd(OH)_2$ (0,4 g) en metanol (30 ml) (1-bencil-3-pirrolidinil)metanol. (4,16 g, 21 mmol). La mezcla de reacción se agitó en atmósfera de hidrógeno durante 24 horas. Se diluyó la mezcla de reacción con acetato de etilo (200 ml), luego se filtró a través de celite®. Se concentró el filtrado a presión reducida proporcionando 3-pirrolidinilmetanol (2,33 g, rendimiento; cuantitativo).



(Compuesto de partida 2A).

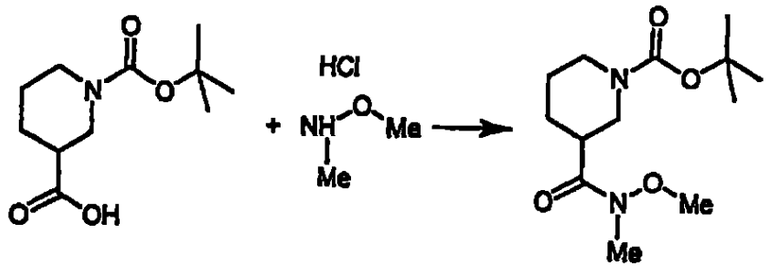
Se añadió a una solución de 3-pirrolidinilmetanol (2,33 g, 21 mmol) y trietilamina (4,8 ml, 35 mmol) en diclorometano (60 ml) dicarbonato de di(*terc*-butilo) (5,3 g, 24 mmol) a 0°C. Se agitó la mezcla de reacción a temperatura ambiente durante 26 horas. Se diluyó la mezcla con acetato de etilo (200 ml), y se lavó con HCl 1N (100 ml), con una solución acuosa saturada de $NaHCO_3$ (100 ml) y con salmuera (100 ml), sucesivamente. La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida proporcionando 3-(hidroximetil)-1-pirrolidincarboxilato de *terc*-butilo (4,06 g, rendimiento; 96%).

Se añadió a una mezcla fría (0°C) de 3-(hidroximetil)-1-pirrolidincarboxilato de *terc*-butilo (4,0 g, 20 mmol), diclorometano (100 ml), dimetil sulfóxido (20 ml) y trietilamina (16,9 ml, 121 mmol) en atmósfera de argon complejo trióxido de azufre-piridina (9,63 g, 60 mmol). Se dejó que la mezcla de reacción se calentase a temperatura ambiente, y se continuó agitando durante 1 hora. Se extrajo la mezcla con éter (200 ml) y una solución acuosa saturada de $NaHCO_3$ (100 ml). Se extrajo de nuevo la fase acuosa separada con éter (100 ml x 2). La fase orgánica combinada se lavó con

una solución acuosa HCl 1N (100 ml), una solución acuosa saturada de $NaHCO_3$ (100 ml), y salmuera (100 ml), sucesivamente. La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida (5,32 g, rendimiento; cuantitativo).

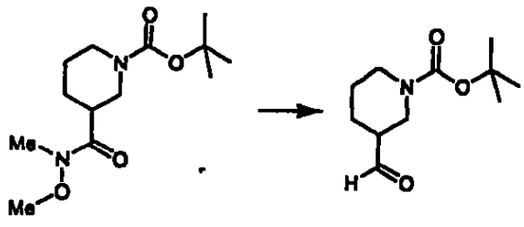
[Compuesto de partida 2B]

Se añadieron a una solución enfriada (0°C), agitada de ácido 3-piperidinecarboxílico (100,000 g, 774,233 mmol) en dioxano (400 ml) 2N NaOH (400 ml, 800 mmol) y dicarbonato de di-*terc*-butilo (168,978 g, 774,233 mmol). Se dejó que la mezcla se calentase a temperatura ambiente, y se continuó agitando durante 12 horas. Se concentró la mezcla a presión reducida. Se diluyó el residuo con agua y se acidificó (pH 3-4) con una solución acuosa HCl 1N. El sólido resultante se recogió mediante filtración. El sólido blanco se disolvió en acetato de etilo y se lavó con agua. La fase orgánica separada se secó sobre Na_2SO_4, se filtró y se concentró. El sólido resultante se suspendió en hexano y se recogió mediante filtración, y se secó a presión reducida proporcionando ácido 1-(*terc*-butoxicarbonil)-3-piperidín carboxílico en forma de un sólido blanco (156 g, rendimiento; 88%).



Se añadió a una solución fría (0°C) de ácido 1-(*terc*-butoxicarbonil)-3-piperidín carboxílico (7,000 g, 30,531 mmol) en diclorometano (200 ml), incluyendo trietilamina (4,681 ml, 33,584 mmol) hexafluorofosfato de benzotriazol-1-il-oxo-tris-pirrolidino-

fosfonio (15,885g, 30,531 mmol), N,O-dimetilhidroxiamina (3,276 g, 33,584 mmol) y trietilamina (4,255 ml, 30,531 mmol) sucesivamente. Se dejó que la mezcla se calentase a temperatura ambiente, y se continuó agitando durante 12 horas. Se diluyó la mezcla de reacción con diclorometano y se lavó con una solución acuosa HCl 1N, una solución acuosa saturada de $NaHCO_3$, y salmuera, sucesivamente. La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo resultante se purificó por cromatografía en columna en gel de silice (cloroformo/acetato de etilo = 10/1-9/1) proporcionando éster *terc*-butílico del ácido 3-{[metoxi(metil)amino]carbonil}-1-piperidín-carboxílico en forma de un sólido blanco (8,050 g, rendimiento; 96%).

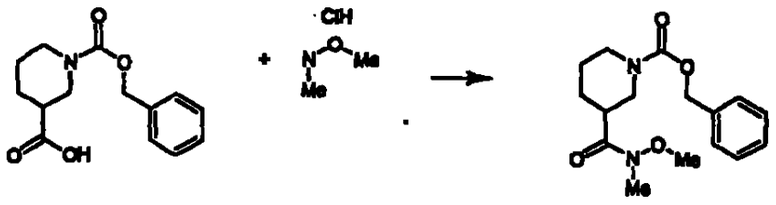


(Compuesto de partida 2B).

Se añadió gota a gota a una suspensión enfriada (-15°C), agitada de hidruro de litio y aluminio (4,355 g, 114,743 mmol) en éter dietílico (500 ml), una solución de éster *terc*-butílico del ácido 3-{[metoxi(metil)amino]carbonil}-1-piperidín-carboxílico (25,00 g, 91,795 mmol) en THF (150 ml) durante 30 minutos. La mezcla de reacción se desactivó con hidrógenosulfato de potasio acuoso 1N (300 ml), y extrajo con una mezcla 1:1 de éter dietílico y acetato de etilo. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida proporcionando éster *terc*-butílico del ácido 3-formil-piperidín-1-carboxílico, que se utilizó para las siguientes etapas sin más purificación. (22,56 g, rendimiento; cuantitativo).

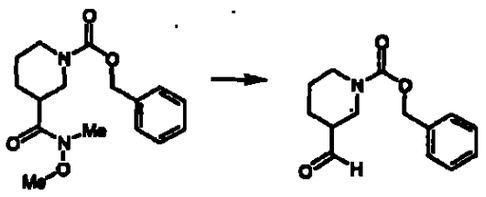
[Compuesto de partida 2C]

Se añadió a una solución enfriada (0°C) y agitada de ácido nipecotínico (3,0 g, 23,3 mmol) en 1,4-dioxano (12 ml) una solución 2N NaOH (24,0 ml, 48,0 mmol) seguida por una solución de cloroformiato de bencilo (3,96 g, 23,2 mmol) en 1,4-dioxano (12 ml). Se dejó que la mezcla de reacción se calentase a temperatura ambiente, y se continuó agitando durante 3 horas. Se concentró la mezcla a presión reducida. El residuo se diluyó con agua y se acidificó con 1H HCl (pH 3-4). Se extrajo la mezcla con acetato de etilo, y la fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. El sólido blanco resultante se suspendió en hexano, se recogió por filtración, se lavó con hexano, y se secó a presión reducida proporcionando ácido 1-[(benciloxi)carbonil]-3-piperidincarboxílico en forma de un sólido blanco (4,4 g, rendimiento; 71%).



Se añadió gota a gota a una solución enfriada (-15°C a –20°C) y agitada de ácido 1-[(benciloxi)carbonil]-3-piperidincarboxílico (4,0 g, 15,2 mmol) en THF seco (50 ml) incluyendo metilmorfolina (2 ml) una solución de cloroformiato de isobutilo, (2,28 g, 16,7 mmol) en THF (10 ml). Después de agitar la mezcla a la misma temperatura durante 20 minutos, se añadió una solución de clorhidrato de N,O-dimetilhidroxilamina (1,63 g, 16,7 mmol) en THF (20 ml) incluyendo metilmorfolina (2 ml). Se dejó que la mezcla de reacción se calentase a temperatura ambiente, y luego se continuó agitando durante 16 horas. La mezcla de reacción se concentró a presión reducida y se repartió entre acetato de etilo y agua. La fase orgánica separada se lavó con HCl 1N, $NaHCO_3$,

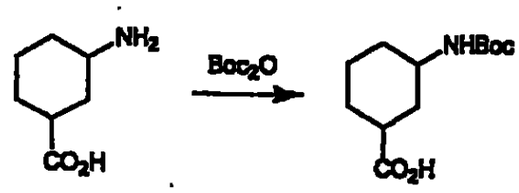
y salmuera, sucesivamente. La fase orgánica se secó sobre $NaSO_4$, se filtró y se concentró a presión reducida proporcionando 3-{[metoxi(metil)amino]carbonil}-1-piperidincarboxilato de bencilo en forma de un aceite incoloro (4,7 g, rendimiento; cuantitativo).



(Compuesto de partida 2C).

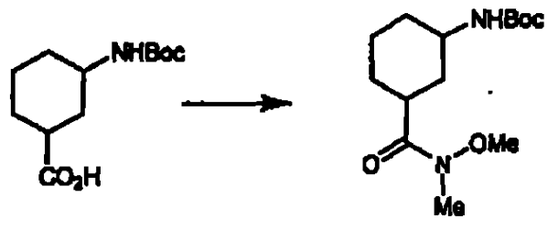
Se añadió gota a gota a una suspensión enfriada (-78°C) de hidruro de litio y aluminio (0,70 g, 18,4 mmol) en THF seco (100 ml) en atmósfera de argon una solución 3-{[metoxi(metil)amino]carbonil}-1-piperidincarboxilato de bencilo (4,5 g, 14,7 mmol) en THF (30 ml), y se continuó agitando a –78°C durante 45 minutos. La mezcla de reacción se disolvió con $KHSO_4$ 0,5 N (130 ml), y luego se extrajo con éter. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida proporcionando 3-formil-1-piperidincarboxilato de bencilo en forma de un aceite incoloro (0,54 g, rendimiento; 82%).

[Compuesto de partida 2D]

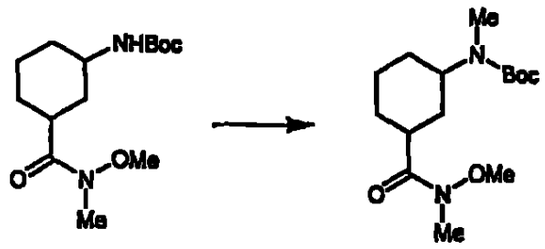


Se añadió a una mezcla enfriada (0°C) de ácido 3-aminociclohexano-carboxílico (10,0

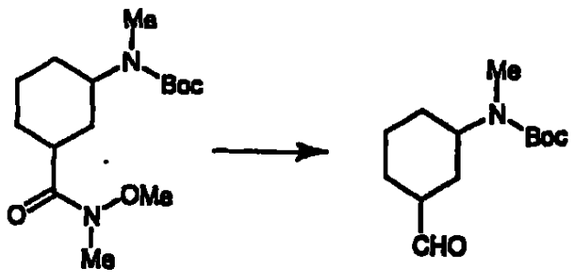
g, 69,8 mmol) en 1,4 dioxano (100 ml) y NaOH 2N (100 ml) dicarbonato de di(*terc*-butil) (15,2 g, 69,8 mmol). Se agitó la mezcla a temperatura ambiente durante 1 hora y media, y luego se neutralizó con HCl 2N. La mezcla resultante se concentró a presión reducida. El residuo se acidificó con HCl 2N y se extrajo con acetato de etilo. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. El sólido residual se trituró con hexano, se recogió por filtración, y se secó a presión reducida proporcionando ácido 3-[(*terc*-butoxicarbonil)amino]ciclohexanocarboxílico en forma de un sólido blanco (8,00 g, rendimiento; 47%).



Se añadieron a una solución fría (0°C) de ácido 3-[(*terc*-butoxicarbonil)amino]-ciclohexanocarboxílico (5,00 g, 20,6 mmol) en CH_2Cl_2 (50 ml) incluyendo trietilamina (3,1 ml, 22,2 mmol) hexa-fluorofosfato de benzotriazol-1-iloxitris(pirrolidino)fosfonio (10,7 g, 20,6 mmol), clorhidrato de N,O-dimetilhidroxiamina (2,21 g, 20,6 mmol) y Et_3N (3,2 ml, 23,0 mmol) sucesivamente. Se dejó que la mezcla resultante se calentase a temperatura ambiente, y se continuó agitando durante 18 horas. La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó con HCl 1N, una solución acuosa saturada de $NaHCO_3$, y salmuera, sucesivamente. La fase orgánica se secó sobre Na_2SO_4, se filtró y se evaporó. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo=1:1) proporcionando 3-{[metoxi(metil)amino]carbonil}ciclohexilcarbamato de *terc*-butilo en forma de un aceite incoloro (5,39 g, rendimiento; 92%).



Se añadió gota a gota a una suspensión de NaH (60%, 340 mg, 8,38 mmol) en THF (10 ml) una solución de 3-{[metoxi(metil)amino]carbonil}ciclohexilcarbamato de *terc*-butilo (2,00 g, 6,98 mmol) en THF (10 ml) seguido por yoduro de metilo (1,09 g, 7,68 mmol). Se agitó la mezcla a 60°C durante media hora. Después de enfriarse a temperatura ambiente, la mezcla se vertió en agua y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo = 1/1) proporcionando N-[3-(N-metoxi-N-metil-carbamoil)ciclohexil]-N-metilcarbamato de *terc*-butilo en forma de un aceite incoloro (1,94 g, rendimiento; 93%).



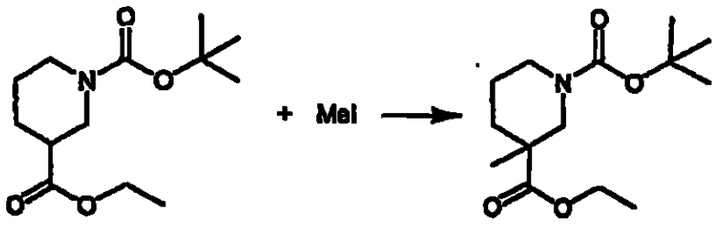
(Compuesto de partida 2D).

Se añadió gota a gota a una suspensión fría (0°C) de $LiAlH_4$ (380 mg, 9,9 mmol) en Et_2O (40 ml) una solución N-[3-(N-metoxi-N-metil-carbamoil)ciclohexil]-N-metilcarbamato de *terc*-butilo (2,38 g, 7,92 mmol) en Et_2O (40 ml) durante 10 minutos.

Se agitó la mezcla de reacción a 0°C durante media hora, y se disolvió con $KHSO_4$ 1N (100 ml). La fase orgánica se separó, se secó sobre $MgSO_4$ y se evaporó proporcionando 3-formilciclohexil(metil)carbamato de *terc*-butilo en forma de un aceite incoloro, que se utilizó para la siguiente etapa sin purificación (1,66 g, rendimiento; 87%).

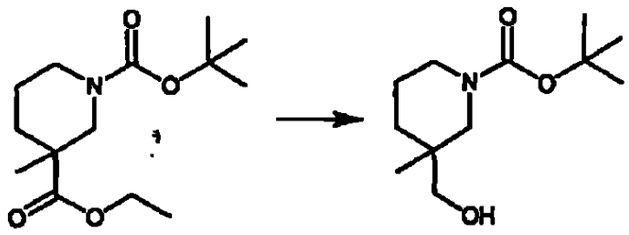
[Compuesto de partida 2E]

Se añadió a una solución fría (0°C) de nipecotato de etilo (7,86 g, 50 mmol) en CH_2Cl_2 (120 ml) dicarbonato de di-*terc*-butilo (11,46 g, 52,5 mmol). La mezcla resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se diluyó con un 5% de solución acuosa de $NaHCO_3$. La fase orgánica se separó, se secó sobre $MgSO_4$, se filtró y se evaporó a presión reducida proporcionando 1,3-piperidindicarboxilato de 1-*terc*-butilo y 3-etilo (12,8 g, rendimiento; cuantitativo).

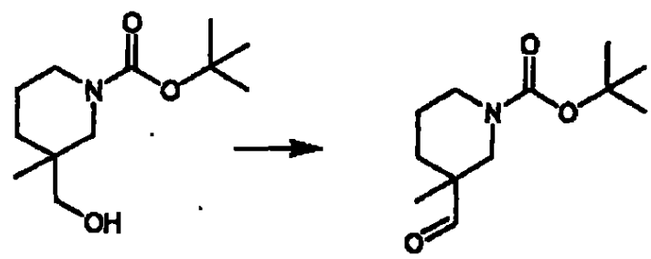


Se añadió gota a gota a una solución fría (-78°C) de diisopropilamida de litio (LDA) (23,3 mmol) en THF (10 ml) en atmósfera de argon una solución de 1,3-piperidindicarboxilato de 1-*terc*-butilo y 3-etilo (3,0 g, 11,6 mmol) en THF (5 ml), luego agitado a –50°C durante 2 horas. Se añadió a la mezcla resultante una solución de MeI (1,98 g, 14 mmol) en THF a –50°C. Se dejó que la mezcla de reacción se calentase a temperatura ambiente y se desactivó con una solución acuosa saturada de NH_4Cl. La mezcla se concentró a presión reducida, y el residuo se repartió entre acetato de etilo y

agua. La fase orgánica se separó, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El producto bruto se purificó mediante cromatografía en columna en gel de sílice (hexano:acetato de etilo, 9:1) proporcionando 3-metil-1,3-piperidindicarboxilato de 1-*terc*-butilo y 3-etilo en forma de un aceite amarillo pálido (2,27 g, rendimiento; 72%).



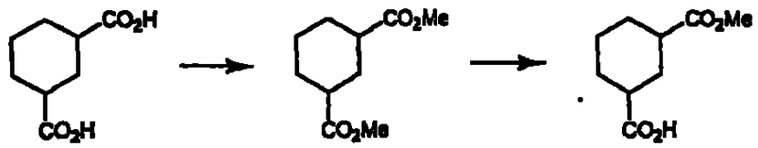
Se añadió a una solución fría (-20°C) de 3-metil-1,3-piperidindicarboxilato de 1-*terc*-butilo y 3-etilo (2,3 g, 8,48 mmol) en THF seco $LiBH_4$ (2M en THF, 10,6 mmol), y se continuó agitando durante la noche. Se dejó que la mezcla de reacción se calentase a temperatura ambiente. La mezcla de reacción se enfrió con agua helada y se acidificó (pH 5-6) con HCl 1N acuoso. La mezcla se concentró a presión reducida, y luego se extrajo con acetato de etilo. La fase orgánica se separó, se secó sobre $MgSO_4$, se filtró y se evaporó. El producto bruto se purificó mediante cromatografía en columna en gel de sílice (hexano: acetato de etilo, 4:1-3:1) proporcionando 3-(hidroximetil)-3-metil-1-piperidincarboxilato de *terc*-butilo en forma de un aceite incoloro (1,5 g, rendimiento; 78%).



(Compuesto de partida 2E).

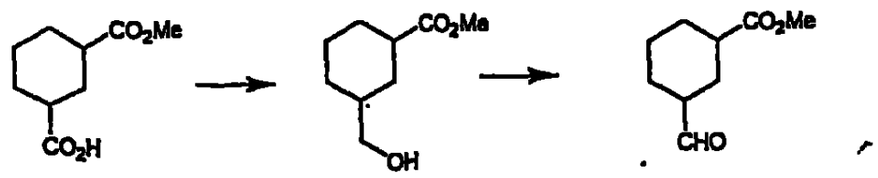
Se añadieron a una solución enfriada con agua helada de 3-(hidroximetil)-3-metil-1-piperidincarboxilato de *terc*-butilo (1,5 g, 6,6 mmol) en CH_2Cl_2 DMSO (7,1 g, 91,6 mmol), Et_3N (5,5 ml, 39,8 mmol), y complejo de trióxido de azufre-Piridina (3,1 g, 19,9 mmol) sucesivamente. Se agitó la mezcla a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó con éter, se purificó mediante cromatografía en columna en gel de sílice (hexano: acetato de etilo, 5:1 - 4:1) proporcionando 3-formil-3-metil-1-piperidincarboxilato de *terc*-butilo en forma de un aceite incoloro (1,3 g, rendimiento; 86%).

[Compuesto de partida 2F]



Se añadió a una solución de ácido 1,3-ciclohexanodicarboxílico (10g, 58 mmol) en MeOH (50 ml) H_2SO_4 concentrado (2 ml). Luego se agitó la mezcla a temperatura ambiente durante 4 horas. La mezcla se concentró a presión reducida, y luego se repartió entre acetato de etilo y una solución acuosa saturada de $NaHCO_3$. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó proporcionando dimetilo 1,3-ciclohexanodicarboxilato en forma de un aceite incoloro (11,6 g, rendimiento; cuantitativo). Se añadió gota a gota a una solución de dimetilo 1,3-ciclohexanodicarboxilato (11,6 g, 57,9 mmol) en MeOH (58 ml) una solución de NaOH 1N (58 ml) durante 1 hora a 0°C. Se agitó a la mezcla resultante a 0°C durante media hora, y a temperatura ambiente durante 2 horas. La mezcla se concentró a presión reducida, y la solución residual se repartió entre acetato de etilo y agua. La fase acuosa se separó, se acidificó con HCl concentrado (15 ml), se saturó con NaCl, y luego se

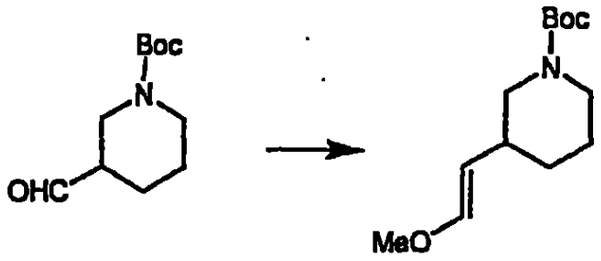
extrajo con acetato de etilo. El extracto se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida proporcionando ácido 3-(metoxicarbonil)ciclohexanocarboxílico en forma de un aceite incoloro (6,16 g, rendimiento; 57%).



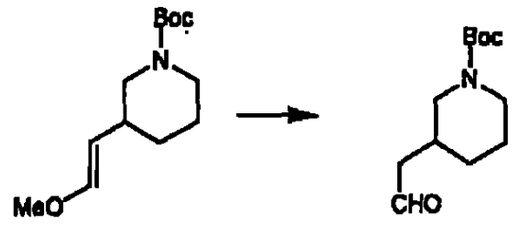
(Compuesto de partida 2F).

Se añadió a una solución fría (-78°C) de ácido 3-(metoxicarbonil)ciclohexanocarboxílico (1,25 g, 6,71 mmol) en THF (20 ml) $BH_3 \cdot Me_2S$ (0,7 ml, 7,38 mmol). La mezcla resultante se agitó a –78°C hasta temperatura ambiente durante la noche. La mezcla de reacción se desactivó con una solución acuosa saturada de NH_4Cl y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, y se evaporó. El residuo se purificó mediante cromatografía en columna en gel de sílice (n-hexano/acetato de etilo = 2/1) proporcionando 3-(hidroximetil)ciclo-hexanocarboxilato de metilo en forma de un aceite incoloro (845 mg, rendimiento; 73%). Se añadió a una solución de 3-(hidroximetil)ciclohexanocarboxilato de metilo (840 mg, 4,88 mmol) en Et_3N (4,4 ml, 32 mmol) y DMSO (10 ml) complejo de trióxido de azufre-piridina (2,56 g, 16,1 mmol). La mezcla se agitó a temperatura ambiente durante una hora. La mezcla de reacción se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. El residuo se purificó mediante cromatografía en columna en gel de sílice (n-hexano/acetato de etilo = 2/1) proporcionando 3-formilciclohexanocarboxilato de metilo en forma de un aceite amarillo pálido (795 mg, rendimiento; 96%).

[Compuesto de partida 2G]



Se añadió a una suspensión de cloruro de metoximetilfosfonio (5,14g, 15 mmol) en THF (18 ml) *terc*-butóxido de potasio (1,98 g, 15 mmol) a 0°, y se agitó la mezcla a 0°C durante media hora. Se añadió gota a gota a – 20°C una solución de 3-formil-1-piperidincarboxilato de *terc*-butilo (2,13 g, 10 mmol)) en THF (8 ml), y la mezcla resultante se agitó a 0°C hasta temperatura ambiente durante la noche. La mezcla se repartió entre tolueno y agua. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. La purificación mediante cromatografía en columna en gel de sílice (hexano/acetato de etilo = 5/1) produjo 3-(2-metoxietenil)-1-piperidincarboxilato de *terc*-butilo en forma de un aceite incoloro (1,16 g, rendimiento; 48%).

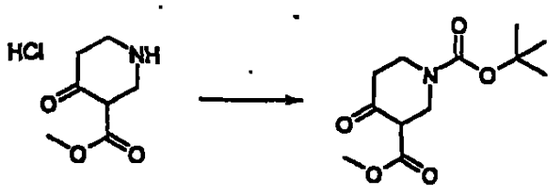


(Compuesto de partida 2 G).

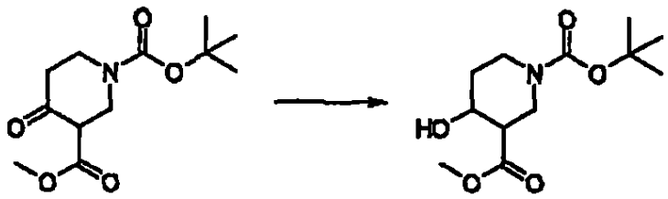
Se disolvió 3-(2-metoxietenil)-1-piperidincarboxilato de *terc*-butilo (1,16 g, 4,81 mmol)

en ácido fórmico al 90% (2 ml). Se agitó la mezcla a temperatura ambiente durante 40 minutos. Luego se repartió la mezcla entre acetato de etilo y se saturó en una solución acuosa de $NaHCO_3$. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. La purificación mediante cromatografía en columna en gel de sílice (hexano/acetato de etilo = 4/1) produjo 3-(2-oxoetil)-1-piperidincarboxilato de *terc*-butilo en forma de un aceite incoloro (652 g, rendimiento; 60%).

[Compuesto de partida 2H]

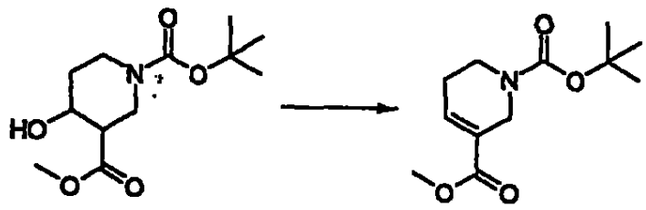


Se añadió a una mezcla fría (0°C) de 3-metoxicarboni-4-piperidona HCl (10 g, 51,6 mmol) y trietilamina (10,8 ml, 77,5 mmol) en diclorometano (100 ml) una solución de dicarbonato de di-terc.butilo (11,8 g, 54,2 mmol) en diclorometano (100 ml). La mezcla se agitó a temperatura ambiente durante 2 horas y se concentró a presión reducida. El residuo se desactivó con agua, se extrajo con éter, se secó sobre MgSO4, se filtró y se evaporó proporcionando 4-oxo-1,3-piperidindicarboxilato de 1-*terc*-butilo y 3-metilo, que se utilizó para la siguiente reacción sin más purificación. (14,9 g, rendimiento; cuantitativo).

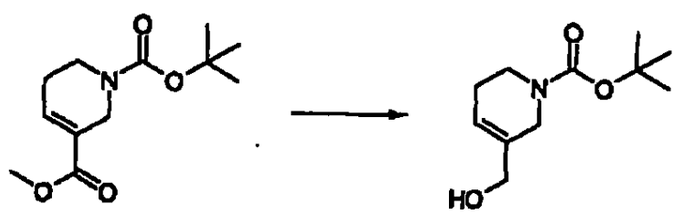


Se añadió a una solución fría (0°C) de 4-oxo-1,3-piperidindicarboxilato de 1-*terc*-butilo y 3-metilo (134,0 g, 520,8 mmol) en metanol (800 ml) $NaBH_4$ (9,85 g, 260,4 mmol) de

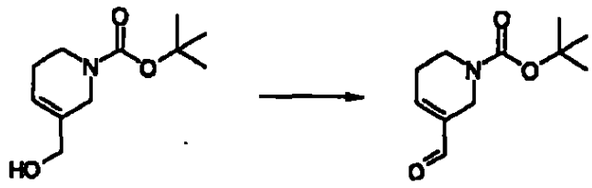
una vez. Se agitó la mezcla resultante durante la noche y se dejó que se calentase a temperatura ambiente. El disolvente se eliminó a presión reducida, el residuo se disolvió en acetato de etilo, se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida proporcionando 4-hidroxi-1,3-piperidindicarboxilato de 1-*terc*-butilo y 3-metilo, que se utilizó para la siguiente reacción sin más purificación. (120,8 g, rendimiento 90%).



Se añadió gota a gota a una solución fría (0°C) de 4-hidroxi-1,3-piperidincarboxilato de 1-*terc*-butilo y 3-metilo (1,64 g, 6,32 mmol), 4-dimetilaminopiridín (16,0 mg, 0,13 mmol)y trietilamina (2,64 ml, 19,0 mmol) en diclorometano (25 ml) anhídrido trifluoroacético (1,12 ml, 7,91 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 40 horas. La reacción se desactivó con una solución de K_2CO_3 al 10%, se extrajo con $CHCl_3$. La fase orgánica separada se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó a presión reducida. El producto bruto se purificó mediante cromatografía en columna en gel de sílice (hexano: acetato de etilo = 5:1) proporcionando 5,6-dihidro-1,3(2H)-piridindicarboxilato de 1-*terc*-butilo y 3-metilo en forma de un aceite amarillo pálido (707,4 g, rendimiento; 46%).



Se añadió gota a gota a una solución fría (-20°C) de 5,6-dihidro-1,3(2H)-piridindicarboxilato de 1-*terc*-butilo y 3-metilo (700,0 g, 2,90 mmol) en tolueno seco (40 ml) una solución de hidruro de diisobutilaluminio en tolueno (1,5M, 4,83 ml, 7,25 mmol) en atmósfera de argon. La mezcla de reacción se agitó a 0°C durante 30 minutos y luego se agitó a temperatura ambiente. La reacción se desactivó añadiendo agua y se continuó agitando durante 1 hora más. Las sales de alumino precipitadas se filtraron. Se diluyó el filtrado con una solución saturada de NH_4CL, se extrajo con acetato de etilo. La fase orgánica separada se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó proporcionando 5-(hidroximetil)-3,6-dihidro-1(2H)-piridincarboxilato de *terc*-butilo, que se utilizó para la siguiente reacción sin más purificación. (580,0 mg, rendimiento 94%).

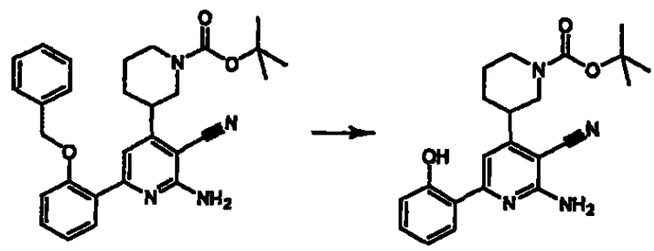


(Compuesto de partida 2H).

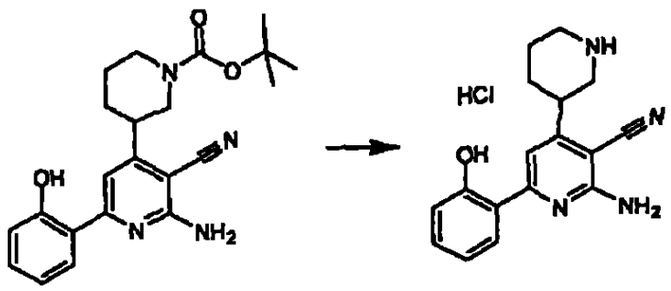
Se añadió a una solución de 5-(hidroximetil)-3,6-dihidro-1(2H)-piridincarboxilato de *terc*-butilo (14,65 g, 68,69 mmol) en diclorometano MnO_2 (89,58 g, 1030,36 mmol), luego se agitó durante la noche a temperatura ambiente. La mezcla de reacción se filtró a través de Celite®, el filtrado se concentró a presión reducida proporcionando 5-formil-3,6-dihidro-1(2H)-piridincarboxilato de *terc*-butilo, que era lo suficientemente puro como para utilizarse en la siguiente reacción. (13,55 g, rendimiento 94%).

Ejemplo 1-1

(1) Se agitó a 150°C durante 2 horas una mezcla de 2'-benciloxiacetofenona (compuesto de partida 1A) (10,00 g, 44,19 mmol), 3-formil-1-piperidín carboxilato de *terc*-butilo (compuesto de partida 2B) (10,37 g, 44,61 mmol), malononitrilo (3,21 g, 48,61 mmol), y acetato de amonio (17,03 g, 220,97 mmol) en tolueno (50 ml). Después de enfriarse a temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo. La fase orgánica se lavó con agua y salmuera saturada, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante cromatografía en columna en gel de sílice (hexano/acetato de etilo = 2/1). El compuesto purificado (aceite amarillo) se recristalizó en etanol proporcionando 3-{2-amino-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo en forma de un sólido blanco (5,83 g, rendimiento; 27%).



(2) Se agitó a temperatura ambiente una mezcla de 3-{2-amino-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (2,160 g, 4,457 mmol) y Pd-C al 10% (0,720 g) en acetato de etilo (30 ml) durante 2 días en atmósfera de hidrógeno (3 atm). Se filtró la mezcla a través de celite® y se concentró el filtrado a presión reducida. Se recristalizó el residuo en éter dietílico, proporcionando 3-[2-amino-3-ciano-6-(2-hidroxifenil)-4-piridinil]-1-piperidin-carboxilato de *terc*-butilo en forma de un sólido blanco (0,180 g, 10%).



(3) A una solución agitada de 3-[2-amino-3-ciano-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,170 g, 0,431 mmol) en dioxano (30 ml), se añadió HCl 4 N en dioxano (3 ml). Se agitó la mezcla a temperatura ambiente durante 12 horas. Se recogieron los precipitados resultantes por filtración y se lavó el filtrado con dioxano, proporcionando clorhidrato de 2-amino-6-(2-hidroxifenil)-4-(3-piperidinil)nicotinonitrilo (0,075 g, rendimiento: 53%).

Peso molecular: 330,82

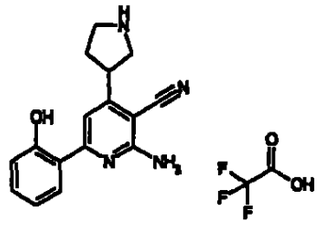
Espectrometría de masas: 295 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A/(Jurkat)-A

RMN de ^1H (300 MHz, DMSO-d_6): 1,81 - 1,89 (4H, m), 2,88 - 2,92 (1H, m), 3,31 - 3,40 (4H, m), 6,89 - 6,94 (2H, m), 7,32 - 7,38 (1H, m), 7,43 (1H, s), 8,05 (1H, d, J = 7,4 Hz), 8,83 - 8,85 (1H, s a), 9,45 - 9,47 (1H, s a).

Ejemplo 1-2



Utilizando el compuesto de partida 2A en lugar de 2B, se preparó trifluoroacetato de 2-amino-6-(2-hidroxifenil)-4-(3-pirrolidinil)nicotinonitrilo de manera similar a la descrita en el Ejemplo 1-1.

Peso molecular: 394,36

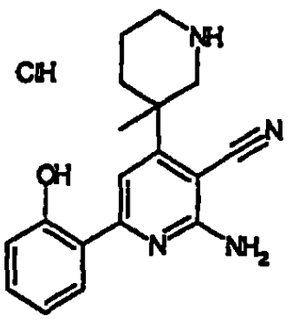
Espectrometría de masas: 281 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A594)-A/(Jurkat)-B

RMN de ^1H (500 MHz, DMSO-d_6): 2,10 (1H, m), 3,60 - 3,70 (2H, m), 6,91 (2H, m), 7,36 - 7,44 (4H, m), 8,05 (1H, d, J = 8,2 Hz), 9,00 (2H, a), 13,35 (1H, s).

Ejemplo 1-3



Utilizando el compuesto de partida 2E en lugar de 2B, se preparó clorhidrato de 2-amino-6-(2-hidroxifenil)-4-(3-metilpiperidin-3-il)nicotinonitrilo de manera similar a la

descrita en el ejemplo 1-1.

Peso molecular: 344,85

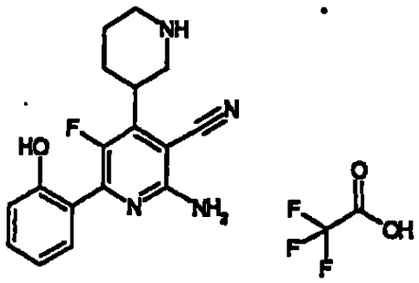
Espectrometría de masas: 309 $(M + H)^+$

Grado de actividad in vitro: B

Grado de actividad celular: (A594)-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,52(3H, s), 1,78 (2H, d a, J = 38,1 Hz), 1,97 - 2,04 (1H, m), 2,37 - 2,44 (1H, m), 2,99 (2H, d a, J = 31,7 Hz), 3,34 (1H, dd, J = 5,5, 12,5 Hz), 3,75 (1H, dd, J = 5,5, 12,5 Hz), 6,92 - 6,96 (2H, m), 7,22 (1H, s), 7,33 - 7,39 (2H, m), 8,05 - 8,08 (1H, m), 9,02 (1H, s a), 9,42 (1H, s a).

Ejemplo 1-4



Utilizando el compuesto de partida 1B en lugar de 1A, se preparó trifluoroacetato de 2-amino-5-fluoro-6-(2-hidroxifenil)-4-(3-piperidinil)nicotinonitrilo de manera similar a la descrita en el ejemplo 1-1.

Peso molecular: 426,37

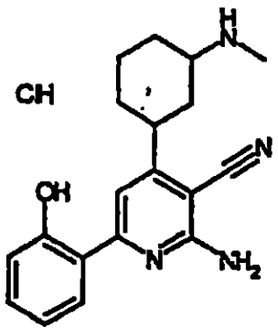
Espectrometría de masas: 313 $(M + H)^-$

Grado de actividad in vitro: A

Grado de actividad celular: (A594)-B/(Jurkat)-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,77(2H, m), 1,95 (3H, m), 1,94 (1H, t, J = 10,7 Hz), 3,25 - 3,37 (2H, m), 3,50 (1H, d, J = 12,0 Hz), 6,90 (1H, dt, J = 1,0,8,2 Hz), 6,93 (1H, d, J = 8,2 Hz), 7,03 (2H, s), 7,32 (1H, dt, J = 1,6,8,5 Hz), 7,47 (1H, dd, J = 1,6,7,9 Hz), 8,73 (2H, a), 10,72 (1H, s).

Ejemplo 1-5



Utilizando el compuesto de partida 2D en lugar de 2B, se preparó clorhidrato de 2-amino-6-(2-hidroxifenil)-4-[3-metilamino]ciclohexil]nicotinonitrilo de la misma manera que se describió en el ejemplo 1-1.

Peso molecular: 358,87

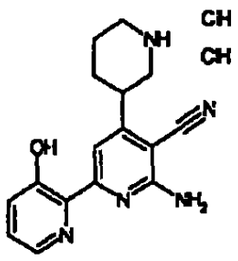
Espectrometria de masas: 323 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A594)-B

RMN de ^1H (300 MHz, DMSO-d_6): 1,34 - 1,86(5H, m), 1,86 - 2,04 (1H, m), 2,04 - 2,30 (2H, m), 2,50 - 2,60 (3H, m), 2,76 - 2,95 (1H, m), 3,17 (1H, s a), 6,85 - 6,96 (2H, m), 7,20 - 7,40 (3H, m), 7,99 (1H, d, J = 8,1 Hz), 9,11 (2H, s a).

Ejemplo 1-6



Utilizando el compuesto de partida 1F en lugar de 1A, se preparó clorhidrato de 6-amino-3'-hidroxi-4-(3-piperidinil)-2,2'-bipiridin-5-carbonitrilo de la misma manera que se describió en el ejemplo 1-1.

Peso molecular: 368,27

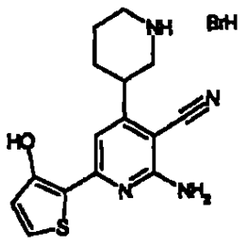
Espectrometría de masas: 337 $(M + H)^-$

Grado de actividad in vitro: A

Grado de actividad celular: (A594)-A

RMN de ^1H (500 MHz, DMSO-d_6): 1,78 - 1,82(2H, m), 1,93 - 1,95 (2H, m), 3,03 - 3,07 (1H, m), 3,27 - 3,37 (3H, m), 3,56 (1H, m), 7,39 (1H, dd, J = 1,6,8,5 Hz), 7,43 (1H, dd, J = 4,1,8,5 Hz), 7,56(1H, a), 7,76 (1H, a), 8,23 (1H, dd, J = 1,6,4,1 Hz), 8,78 (1H, a), 9,18 (1H, a).

Ejemplo 1-7



Utilizando el compuesto de partida 1J en lugar de 1A, se preparó bromhidrato de 2-

amino-6-(3-hidroxi-2-tienil)-4-(3-piperidinil)nicotinonitrilo de la misma manera que se describió en el ejemplo 1-1.

Peso molecular: 381,30

Espectrometría de masas: 301(M + H)$^+$

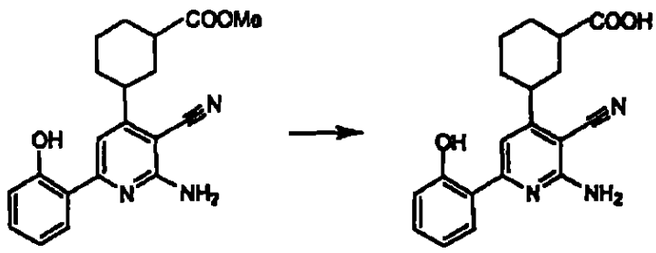
Grado de actividad in vitro: A

Grado de actividad celular: (A594)-A

RMN de ^{1}H (500 MHz, DMSO-d_6): 1,69 - 1,84(2H, m), 1,84 - 2,00 (2H, m), 2,94 - 3,06 (1H, m), 3,12 - 3,28 (2H, m), 3,28 - 3,40 (2H, m), 6,82 (2H, d, J = 5,4 Hz), 6,83 (1H, s), 7,63 (2H, d, J = 5,4 Hz), 8,55 - 8,70 (1H, m), 8,85 - 9,00 (1H, m).

Ejemplo 1-8

Utilizando el compuesto del partida 2F en lugar de 2B, se preparó 3-[2-amino-3-ciano-6-(2-hidroxifenil)-4-piridinil]ciclohexanocarboxilato de metilo de manera similar a la descrita en el ejemplo 1-1.



Se agitó a 60°C durante 4 horas una suspensión de 3-[2-amino-3-ciano-6-(2-hidroxifenil)-4-piridinil]ciclohexanocarboxilato de metilo (151 mg, 0,43 mmol) en NaOH 2N (1 ml) y THF (2 ml). Se neutralizó la mezcla resultante con HCl 1 N (2 ml) y

después se diluyó con agua. Se recogieron los precipitados resultantes por filtración, se lavaron con EtOH y se secaron (a 60°C, 2 horas, presión reducida), proporcionando ácido 3-[2-amino-3-ciano-6-(2-hidroxifenil)-4-piridinil]ciclohexanocarboxílico en forma de un sólido amarillo (105 mg, rendimiento: 72%).

Peso molecular: 337,38

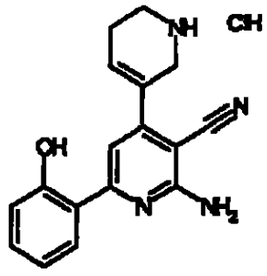
Espectrometría de masas: 338 $(M + H)^+$

Grado de actividad in vitro: B

Grado de actividad celular: (A594)-C

RMN de ^1H (300 MHz, DMSO-d_6): 1,30 - 2,14 (8H, m), 2,30 - 2,59 (1H, m), 2,70 - 2,89 (1H, m), 6,83-6,93 (2H, m), 7,24 - 7,38 (4H, m), 8,00 - 8,10 (1H, m), 12,41 (1H, s), 13,47 (1H, s).

Ejemplo 1-9



Utilizando el compuesto del partida 1D en lugar de 1A, y el compuesto del partida 2H en lugar de 2B, se preparó clorhidrato de 2'-amino-6'-(2-hidroxifenil)-1,2,5,6-tetrahidro-3,4'-bipiridin-3'-carbonitrilo de la misma manera que se describió en el ejemplo 1-1.

Peso molecular: 328,80

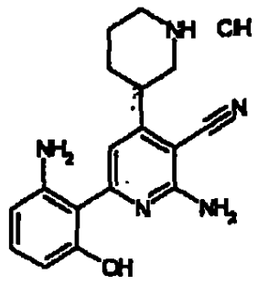
Espectrometría de masas: 293 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A594)-A

RMN de ^1H (500 MHz, DMSO-d_6): 2,52 (2H, s a), 3,24 (2H, s a), 4,05 (2H, s a), 6,45 (1H, s), 6,90 - 6,93 (2H, m), 7,35 - 7,46 (4H, m), 8,01 - 8,02 (1H, m), 9,37 (1H, s a).

Ejemplos 1-10



Utilizando el compuesto del partida 1H en lugar de 1A, se preparó clorhidrato de 2-amino-6-(2-amino-6-hidroxifenil)-4-(3-piperidinil)nicotinonitrilo de la misma manera que se describió en el ejemplo 1-1.

Peso molecular: 345,83

Espectrometría de masas: 310 $(M + H)^+$

Grado de actividad in vitro: C

Grado de actividad celular: (A594)-C

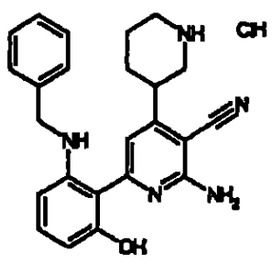
RMN de ^1H (500 MHz, DMSO-d_6): 1,81 - 1,92 (3H, m), 2,89 - 2,93 (1H, m), 3,28 - 3,32 (3H, m), 6,97 (2H, dd, j = 11,7,8,2 Hz), 7,30 (2H, t, J = 8,2 Hz), 9,01 (1H, m), 9,59 (1H, m).

Ejemplos 1-11

(1) Utilizando el compuesto del partida 1H en lugar de 1A, se preparó 3-(2-amino-6-{2-amino-6-[(4-metoxibencil)oxi]fenil}-3-ciano-4-piridinil)-1-piperidincarboxilato de *terc*-butilo de la misma manera que se describió en la etapa (1) del ejemplo 1-1.

(2) A una solución agitada enfriada (0°C) de 3-(2-amino-6-{2-amino-6-[(4-metoxibencil)oxi]fenil}-3-ciano-4-piridinil)-1-piperidincarboxilato de *terc*-butilo (0,30 g, 0,566 mmol) en metanol (10 ml), que incluía ácido acético (0,03 g, 0,566 mmol), se añadió benzaldehído (0,08 ml, 1,133 mmol) seguido de cianoborohidruro de sodio (0,04 g, 0,566 mmol) y se continuó la agitación a 0°C durante 3 horas. Se inactivó la reacción con agua y se extrajo con acetato de etilo. Se secó la fase orgánica sobre sulfato de sodio, se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo= 4/1), proporcionando 3-(2-amino-6-{2-(bencilamino)-6-[(4-metoxibencil)oxi]fenil}-3-ciano-4-piridinil)-1-piperidin-carboxilato de *terc*-butilo en forma de un sólido amorfo amarillo (0,299 g, 85%).

(3) A continuación se trató el sólido amorfo amarillo en condiciones ácidas de manera similar a la de la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de 2-amino-6-[2-(bencilamino)-6-hidroxifenil]-4-(3-piperidinil)nicotinonitrilo.



Peso molecular: 435,96

Espectrometría de masas: 400 $(M + H)^+$

Grado de actividad in vitro: B

Grado de actividad celular: (A594) C

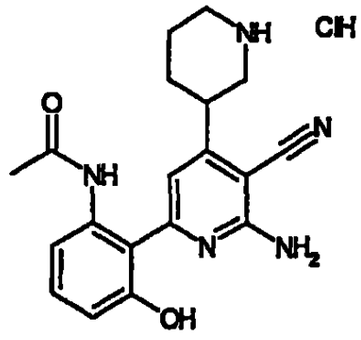
RMN de ^1H (500 MHz, DMSO-d_6): 1,69 - 1,83 (2H, m), 1,90 - 1,92 (2H, m), 2,89 - 2,92 (1H, m), 3,18 (1H, m), 3,28 - 3,33 (3H, m), 4,28 (2H, s), 6,17 (1H, d, J = 8,2 Hz), 6,32 (1H, d, J = 8,2 Hz), 7,00 (1H, t, J = 8,2 Hz), 7,09 (1H, s), 7,20 - 7,23 (1H, m), 7,28 - 7,33 (4H, m), 8,97 (1H, m), 9,47 (1H,m).

Ejemplo 1-12

A una solución agitada enfriada (0°C) de 3-(2-amino-6-{2-amino-6-[(4-metoxibencil)oxi]fenil}-3-ciano-4-piridinil)-1-piperidincarboxilato de *terc*-butilo (0,10 g, 0,189 mmol) obtenido en la etapa (1) del ejemplo 1-11 en diclorometano (10 ml), que incluía trietilamina (0,02 g, 0,227 mmol), se añadió anhídrido acético (0,08 g, 0,889 mmol). Se continuó la agitación a 0°C durante 5 horas. Se dejó calentar la mezcla hasta temperatura ambiente y se continuó la agitación durante 30 minutos. Se inactivó la reacción con salmuera y se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo: 2/1 – 1/1 – 1/2), proporcionando 3-(6-{2-(acetilamino)-6-[(4-metoxibencil)oxi]fenil}-2-amino-3-ciano-4-piridinil)-1-piperidincarboxilato de *terc*-butilo en forma de un aceite amarillo pálido (0,102 g, 94,5%).

A continuación se trató el aceite amarillo con ácidos de la misma manera que en la etapa (2) del ejemplo 1-1, proporcionando clorhidrato de N-{2-[6-amino-5-ciano-4-(3-

piperidinil)-2-piridinil]-3-hidroxifenil}acetamida.



Peso molecular: 387,87

Espectrometría de masas: 352 $(M + H)^-$

Grado de actividad in vitro: C

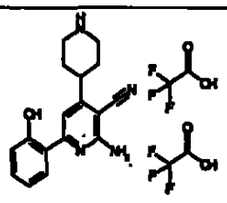
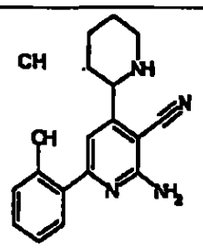
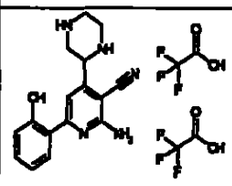
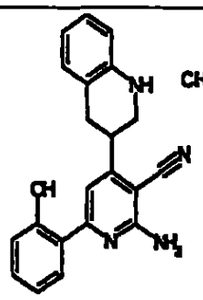
Grado de actividad celular: (A594) C

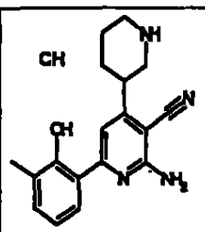
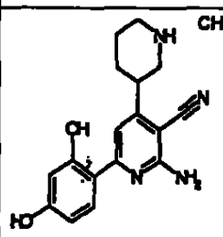
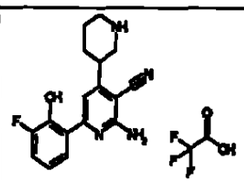
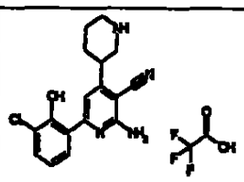
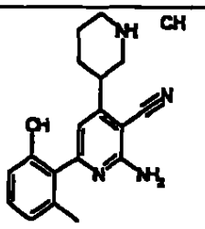
RMN de ^1H (500 MHz, DMSO-d_6): 1,60 - 1,86 (4H, m), 1,90 (3H, s), 2,88 - 2,95 (1H, m), 3,12 - 3,26 (4H, m), 6,78 (1H, d, J = 8,2 Hz), 7,02 (1H, s), 7,23 (1H, t, J = 8,2 Hz), 7,28 - 7,30 (1H, m), 8,90 - 8,92 (1H, m), 9,40 - 9,42 (1H, m), 9,90 (1H, s a).

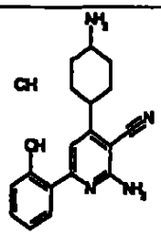
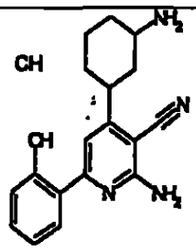
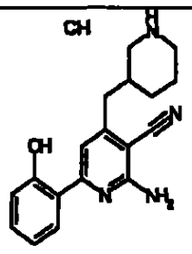
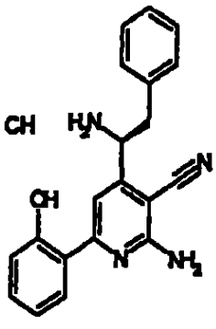
Ejemplos 1-13 a 1-44

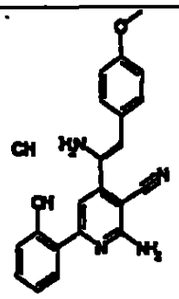
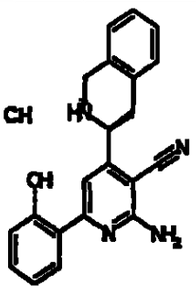
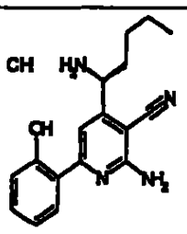
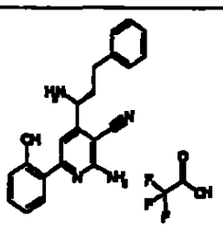
Se sintetizaron de manera similar a la descrita en los ejemplos 1-1 al 1-12 anteriores los compuestos de los ejemplos 1-13 a 1-44 como se muestran en la tabla 1.

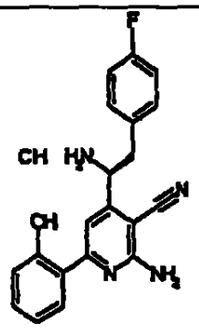
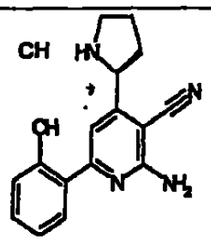
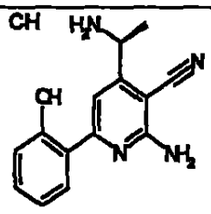
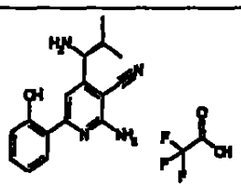
Tabla 1

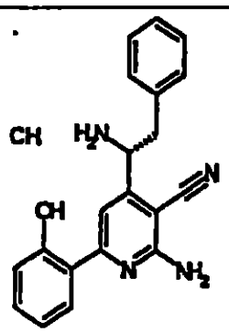
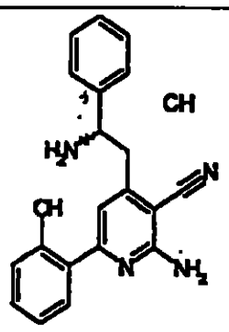
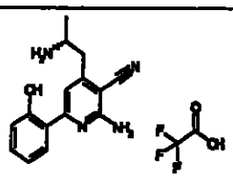
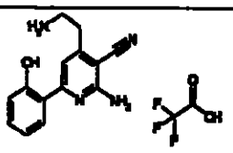
Ej. Nº	Estructura	Peso molecular	Masa	*In vitro*	A549	RMN
I-13		522,41	295	A	A	(300 MHz, DMSO-d_6): 1.99 (4H, m) 3,11 (3H, m), 3,43 (2H, d, J = 13,2 Hz) 6,91 (2H, m), 7,20 (1H, s), 7,35 (3H, m), 7.94 (1H, d, J = 8,5 Hz), 8,46 (1H, a) 8,76 (1H, a), 13,20 (1H, a)
I-14		330,82	295	B	B	(300 MHz, DMSO-d_6): 1,67 - 2.05 (6H, m), 3,19 - 3,26 (1H, m), 3,42 - 3,51 (1H, m), 4,30-4,33 (1H, m), 6,91 - 6,95 (2H, m), 7,35 (2H, m), 7,35 - 7,40 (1H, m), 7.65 (1H, s a), 8,07 (1H, s), 8,18 (1H, d, J = 7,3 Hz), 9,41 - 9,45 (1H, m), 10,27 - 10.30 (1H, m)
I-15		523,40	296	B	B	(300 MHz, DMSO-d_6): 3.00 (3H, m), 3,69 (3H, m), 4,06 (1H, m), 4,55 (1H, d, J = 3,7 Hz), 5,14 (1H, dd, J = 4,0,11,7 Hz), 6,95 (2H, m), 7,38 (1H, t, J = 8,3 Hz), 7,81 (3H, m), 7,98 (1H, d, J = 8,3 Hz), 9,40 (3H, a), 13,5 Hz, (1H, s)
I-16		378,86	343	D		(500 MHz, DMSO-d_6): 2.89 (1H, d, J = 14,8 Hz), 2,92 - 3,19 (2H, m), 3,38 - 3,41 (2H, m), 6,54 (1H, m), 6,59 (1H, d, J = 7,9 Hz), 6,84 - 6,90 (2H, m), 6,94 - 6,97 (2H, m), 7,30 - 7,37 (4H, m), 7,96 (1H, d, J = 8,2 Hz), 13,45 (1H, a)

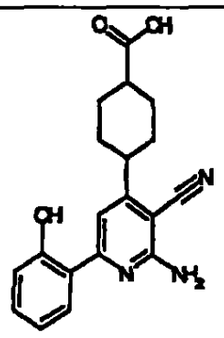
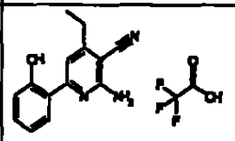
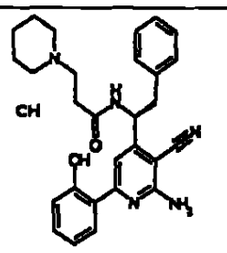
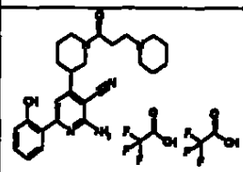
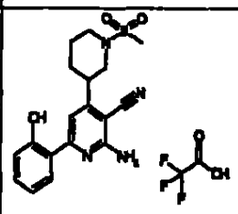
I-17		344,85	309	B	B	(300 MHz, DMSO-d_6): 1,78 - 1,96 (4H m). 2,20 (3H, s), 2,87 - 2,93 (1H, m 3,23 - 3,43 (4H, m), 6,32 (0,7H, s a 6,82 (1H, t, J = 7,5 Hz), 7,25 (1H, d, J = 7,2 Hz), 7,42 (3H, s a), 7,91 (1H, d, J = 8,3 Hz), 13,88 (1H, s a)
I-18		346,82	311	B	B	(300 MHz, DMSO-d_6): 1,76 - 1,95 (4H m). 2,89 (1H, m), 3,22 (1H, m), 3,31 3,39 (3H, m), 6,26 (1H, d, J = 2,3 Hz) 6,36 (1H, dd, J = 2,3,8,7 Hz), 7,24 (1H s), 7,31 (1H, s a), 7,87 (1H, d, J = 8,7 Hz), 8,77 (1H, s a), 9,36 (1H, s a)
I-19		426,37	313	A	A	(500 MHz, DMSO-d_6): 1,76 - 1,97 (4H, m). 2,88 - 2,90 (1H, m), 3,22 - 3,27 (4H, m). 6,88 - 6,94 (1H, m), 7,30 - 7,35 (1H, m). 7,44 (1H, s), 7,55 (2H, s a), 7,88 (1H, d, J = 8,5 Hz), 8,60 (1H, s a), 8,99 (1H, s a), 13,83 (1H, s a)
I-20		442,83	329	A	A	(500 MHz, DMSO-d_6): 1,74 - 1,97 (4H, m), 2,86 - 2,92 (1H, m), 3,23 - 3,45 (4H, m), 6,94 (1H, t, J = 7,8 Hz), 7,47 (1H, s a), 7,55 (1H, dd, J = 7,6,1,4 Hz), 7,59 (2H, s a), 8,07 (1H, dd, J = 8,5,1,4 Hz), 8,60 (1H, s a), 8,99 (1H, s a), 14,58 Hz, (1H, s a)
I-21		344,85	309	C	B	(500 MHz, DMSO-d_6): 1,79 - 1,95 (4H, m). 2,20 (3H, s), 2,90 (1H, dd, J = 10,4,11,3 Hz), 3,23 - 3,42 (4H, m), 6,82 (1H, t, J = 7,6 Hz), 7,26 (1H, d, J = 7,6 Hz), 7,43 (2H, s a), 7,43 (1H, s), 7,91

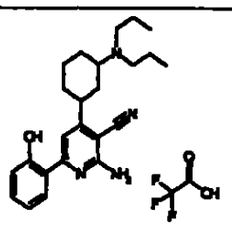
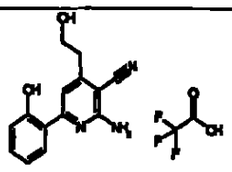
						(1H, d, J = 7,6 Hz), 8,86 (1H, a), 9,51 (1H, a), 13,91 (1H, a)
I-22		344,85	309	A	A	(300 MHz, DMSO-d_6): 1,40 - 2,20 (8H, m), 2,60 - 2,88 (1H, m), 3,10 y 3,48 (1H, s a), 6,75 - 6,95 (2H, m), 7,00 - 7,85 (3H, m), 7,85 - 8,25 (1H, m), 8,14 (1H, s a), 8,37 (1H, s a)
I-23		344,85	309	A	A	(300 MHz, DMSO-d_6): 1,27 - 2,17 (8H, m), 2,75 - 3,00 (1H, m), 3,19 (1H, s a), 6,70 - 7,00 (2H, m), 7,00 -7,80 (3H, m), 7,80 - 8,40 (3H, m)
I-24		344,85	309	A	B	(500 MHz, DMSO-d_6): 1,25 - 1,38 (1H, m), 1,58 - 1,70 (1H, m), 1,72 - 1,84 (2H, m), 2,15 - 2,25 (1H, m), 2,60 - 2,85 (4H, m), 3,10 - 3,22 (2H, m), 6,88 - 6,94 (2H, m), 7,34 (1H, t, J = 7,7 Hz), 7,38 (1H, s), 7,45 (2H, a), 7,95 (1H, d, J = 8,5 Hz), 8,70 (1H, a), 9,05 (1H, a)
I-25		366,85	331	A	B	(300 MHz, DMSO-d_6): 3,20 (1H, dd, J = 9,5,13,2 Hz), 3,22 (1H, dd, J = 5,7,13,2 Hz), 4,54 (1H, a), 6,90 - 6,95 (2H, m), 7,10 - 7,13 (2H, m), 7,22 - 7,51 (7H, m), 8,09 (1H, s), 8,12 (1H, d, J = 7,9 Hz), 9,00 (3H, a)

1-26		396,88	361	A	B	(500 MHz, DMSO-d_6): 3,11 - 3,24 (1H m), 3,27 - 3,45 (1H, m), 3,68 (3H, s) 5,24 (1H, s a), 6,79 (2H, d, J = 8.8 Hz) 6,88 6,99 (2H, m), 7,08 (2H, d, J = 8,8 Hz), 7,33 - 7,41 (3H, m), 7,63 (1H, s) 8,00 (1H, dd, J =1,3,8,2 Hz), 10.14 (1H. s)
1-27		378,86	343	C		(300 MHz, DMSO-d_6): 2,77 - 2.86 (1H. m), 4,82 (1H, d, J = 17,4 Hz), 5,08 (1H. dd, J = 4.2,11,9 Hz), 5,20 (1H, d, J = 17,4 Hz), 6,93 - 700 (2H, m), 7,28 - 7,51 (4H, m), 7,83 (1H, s), 7,94 (1H, s a), 8,07 (1H, dd, J = 7,2,14,9 Hz), 9,53 (1H, s)
1-28		332,84	297	A	C	(300 MHz, DMSO-d_6): 0.85 (3H, t. J = 6,7 Hz), 1,17 - 1,30 (4H, m), 1,88 - 1,94 (1H, m), 1,97 - 2,12 (1H, m), 4,29 (1H, s a), 6,93 (2H, t, J = 6,5 Hz), 7,37 (1H, t, J = 7,6 Hz), 7,60 (1H, s a), 7,92 (1H, s), 8,07 (1H, dd, J = 7,8, 14,5 Hz), 8,99 (2H, s)
1-29		458,44	343	B	C	(300 MHz, DMSO-d_6): 2.08 (1H. m). 5,03 (1H, dd, J = 4,1,6,8 Hz), 6,92 (2H, m), 7,15 - 7,39 (6H, m), 7,70 (3H, d, J = 5,6 Hz), 8,06 (1H, dd, J = 1,3,8,3 Hz), 8,87 (1H, a), 9,25 (1H, m), 10,34 (1H, m), 13,69 (1H, s)

I-30		384,84	349	A	B	(300 MHz, DMSO-d_6): 3,15-3,23 (1H m), 3,47-3,53 (1H, m), 4,47-4,51 (1H m), 6,91-6,98 (2H, m), 7,06-7,20 (4H m), 7,35- 7,48 (1H, m), 8,11 (1H, s) 8,13-8,17 (1H, m), 9,10 (2H, s a)
I-31		316,79	281	B	B	(300 MHz, DMSO-d_6): 1,34-1.53 (1H, m), 2,30-2,47 (3H, m), 3,40-3,67 (2H, m), 5,03-5,14 (1H, m), 6,82-7,00 (2H, m), 7,28-7,44 (1H, m), 7,65 (1H, s), 7,97 (1H, d, J=8,2 Hz), 8,10 (3H, a), 9,85 (1H, s a)
I-32		290,75	255	A	B	(300 MHz, DMSO-d_6): 1,58 (3H, d, J=6,9 Hz), 4,45 (1H, m), 6,91-6,96 (2H, m), 7,34-7,40 (1H, m), 7,90 (1H, s), 8,06 (1H, d, J=8,0 Hz), 8,94 (1H, s a)
I-33		396,37	283	A	B	(300 MHz, DMSO-d_6): 0,64 (3H, d, J=6,8 Hz), 1,08 (3H, d, J=6,9 Hz), 4,96 (1H, s), 6,90-6,95 (2H, m), 7,36 (1H, t, J=8,4m Hz), 7,61 (1H, s), 7,72 (2H, s a), 8,05 (1H, d, J=7,0 Hz), 10,21 (1H, s), 13,65 (1H, s)

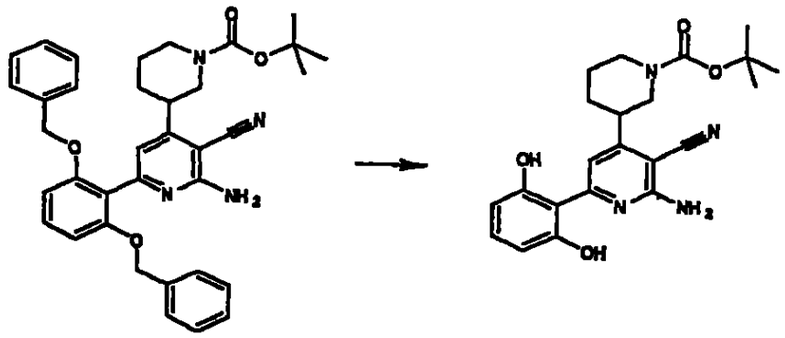
I-34		366,85	331	A	B	(300 MHz, DMSO-d_6): 3,18 (1H, dd J=9,4, 13,2 Hz), 3,21 (1H. dd. J=5,7 13.2 Hz), 4,54 (1H, a), 6,91-6,99 (2H m), 7-10 - 7-13 (2H, m), 7,22-7,29 (4H m), 7,35-7,55 (3H, m), 8,06 (1H, s) 8,12 (1H, d, J=7,9 Hz), 9,02 (3H, a)
I-35		366,85	sin pico	A	B	(300 MHz, DMSO-d_6): 3,26-3.34 (1H m), 3,48-3,57 (1H, m), 4,02-4,80 (1H m), 6,87-6,93 (2H, m), 7.30-7,43 (1H. m), 7,53 (2H, d, J=6,4 Hz), 7,89 (1H, d. J=8,8 Hz), 8,79 (2H, s a)
I-36		382,35	269	A	B	(300 MHz, DMSO-d_6): 1.21 (3H, d. J=6,4 Hz), 2,88-3,08 (2H, m), 3,73 (1H. s a), 6,89 (1H, s), 6,92 (1H, s a), 7,35 (2H, t, J=6,8 Hz), 7,43 (1H, s a), 7,95 (3H, s a), 13,36 (1H, s)
I-37		368,32	255	A	A	(300 MHz, DMSO-d_6): 3.03 (2H, t, J=7,5 Hz), 3,23 (2H, t, J=7,7 Hz), 6,89-6,99 (2H, m), 7,35 (2H, t, J=7,1 Hz), 7,41 (2H, s a), 7,88-7,98 (4H, m), 13,38 (1H, s)

I-38		337,38	338	A	B	(500 MHz, DMSO-d_6): 1,47 (2H, dq, J=3,0 12,8 Hz), 1,72 (2H. dq. J=3,0 12,8 Hz), 1,84 (2H, dd, J=3,0. 12.8 Hz), 2.05 (2H. dd, J= 3,0, 12,8 Hz). 2,33 (2H, tt, J=3,3 12,3 Hz), 2,73 (2H. tt. J=3,2, 12,0 Hz), 6,86-6,93 (2H, m), 7.23-7,38 (4H, m), 8,04 (1H. d, J=7,9 Hz), 12.14 (1H, s a), 13,51 (1H, s á)
I-39		353,30		C	C	
I-40		506,05	470	B	B	(300 MHz, DMSO-d_6): 1.25 (1H. a). 1,60 (5H, m a), 2,69-2,80 (4H, m), 3,04 (2H, d, J=7,5 Hz), 3,12-3,20 (2H, m), 5,19 (1H, dd, J=7,4, 15,4 Hz), 6,91-6,97 (2H, m), 7,21-7,45 (8H, m), 7,56 (1H, s), 7,96-7,99 (1H, m), 9,14 (1H, d, J=8,1 Hz), 9,58 (1H, a), 13,33 (1H, s a)
I-41		661,61		B	B	
I-42		486,47	373	C	B	(300 MHz, DMSO-d_6): 1.85 (4H, m), 3,00 (5H, m), 3,62 (3H, d, J=11,2 Hz), 6,90 (2H, m), 7,37 (3H, m), 8,02 (1H, dd, J=1,4,8,4 Hz), 13,4 (1H, s)

1-43		506,57	393	A	A	(500 MHz, DMSO-d_6): 0.93 (6H, m) 1.68 (8H, m), 2,01 (4H, m), 3,00 (5H m), 6.92 (2H, m), 7,35 (4H, m), 8,02 (1H, d, J=13,2 Hz), 8,84 (1H, a), 13,4 (1H, s)
1-44		369,30	256	B	B	(300 MHz, DMSO-d_6): 3.18 (2H, t, J=6,2 Hz), 4,76 (2H, t, J=6,2 Hz), 6,90 (2H, m), 7,23-7,82 (4H, m), 7.95 (1H, dd, J=1,6,8,4 Hz), 13,39 (1H, s)

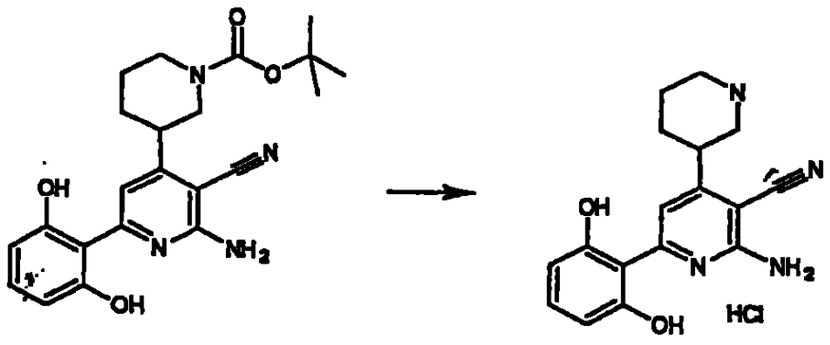
Ejemplo 2-1

(1) Utilizando el compuesto de partida 1E en lugar de 1A, se preparó 3-{2-amino-6-[2,6-bis(benciloxi)fenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (3,54 g, rendimiento: 30%) de manera similar a la descrita en la etapa (1) del ejemplo 1-1.



(2) Se agitó durante 2 días a temperatura ambiente en atmósfera de hidrógeno una suspensión de 3-{2-amino-6-[2,6-bis(benciloxi)fenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (3,46 g, 5,9 mmol) y Pd/C (10%, 600 mg) en acetato de etilo (50 ml), que incluía ácido acético (5 ml). Se diluyó la mezcla de reacción con THF (200 ml) y se filtró a través de Celite®. Se concentró el filtrado a presión reducida,

se lavó el residuo con acetato de etilo y hexano y se secó a presión reducida, proporcionando 3-[2-amino-3-ciano-6-(2,6-dihidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (1,82 g, rendimiento: 76%).



(3) Se trató 3-[2-amino-3-ciano-6-(2,6-dihidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (200 mg, 0,49 mmol) en condiciones ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1. Se recogió el precipitado resultante mediante filtración, se lavó con acetato de etilo y hexano y se secó a presión reducida, proporcionando clorhidrato de 2-amino-6-(2,6-dihidroxifenil)-4-(3-piperidinil)nicotinonitrilo (123 mg, rendimiento: 73%).

Peso molecular: 346,82

Espectrometría de masas: 311 $(M + H)^+$

Grado de actividad in vitro: A

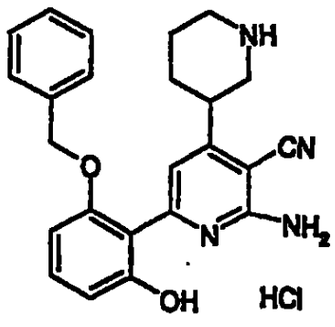
Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 1,66 - 1,99 (5H, m), 2,91 - 3,20 (2H, m), 3,23 - 3,42 (3H, m), 6,41 (2H, d, J = 7,9 Hz), 7,08 (1H, t, J = 7,49 Hz), 7,28 (2H, d a), 7,65 (1H, s), 8,82 (1H, d a), 9,17 (1H, d a).

Ejemplo 2-2

Se agitó durante 2 días a temperatura ambiente una suspensión de 3-[2-amino-3-ciano-6-(2,6-dihidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (300 mg, 0,73 mmol) obtenido en la etapa (2) del ejemplo 2-1, bromuro de bencilo (0,1 ml, 0,80 mmol) y carbonato de potasio (303 mg, 2,19 mmol) en una solución de acetona (15 ml) y THF (15 ml). Se concentró la mezcla de reacción a presión reducida, después se disolvió en acetato de etilo (100 ml) y agua (100 ml). Se extrajo la fase acuosa separada con acetato de etilo (100 ml x 2). Se lavó la fase orgánica reunida con salmuera (100 ml), se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el producto bruto mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo, 4:1-2:1-1:1), proporcionando 3-{2-amino-6-[2-(benciloxi)-6-hidroxifenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (239 mg, rendimiento: 65%).

A una solución de 3-{2-amino-6-[2-(benciloxi)-6-hidroxifenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (239 mg, 0,48 mmol) en dioxano (25 ml), se añadió HCl 4 N/dioxano (25 ml). Se agitó la mezcla de reacción a temperatura ambiente durante la noche. Se recogió el precipitado resultante mediante filtración, se lavó con acetato de etilo y hexano y se secó a presión reducida, proporcionando clorhidrato de 2-amino-6-[2-(benciloxi)-6-hidroxifenil]-4-(3-piperidinil)nicotino-nitrilo (184 mg, rendimiento: 88%).



Peso molecular: 436,95

Espectrometría de masas: 401 $(M + H)^+$

Grado de actividad in vitro: A

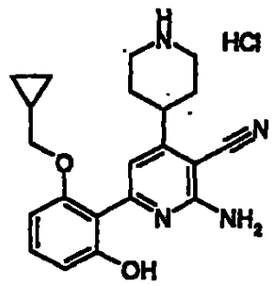
Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 1,07 - 1,14(1H, m), 1,65 - 1,74 (3H, m), 2,57 - 2,73 (2H, m), 3,07 - 3,12 (1H, m), 3,17 - 3,23 (2H, m), 5,07 (1H, d, J = 11,3 Hz), 5,12 (1H, d, J = 11,3 Hz), 6,57 (1H, d, J = 8,3 Hz), 6,73 (1H, d, J = 8,3 Hz), 7,24 - 7,49 (8H, m), 8,72 (1H, d a), 9,01 (1H, d a), 12,54 (1H, s).

Ejemplo 2-3

Utilizando el compuesto de partida 1G en lugar de 1A, y éster *terc*-butílico del ácido 4-formilpiperidin-1-carboxílico preparado de manera similar a la del compuesto de partida 2B, se preparó 4-(2-amino-3-ciano-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-4-piridinil)-1-piperidincarboxilato de *terc*-butilo de manera similar a la de la etapa (1) del ejemplo 1-1.

A una solución agitada de 4-(2-amino-3-ciano-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-4-piridinil)-1-piperidincarboxilato de *terc*-butilo (0,63 g, 1,077 mmol) en 1,4-dioxano (25 ml), se añadió HCl 4 N en 1,4 dioxano (25 ml). Se agitó la mezcla a temperatura ambiente durante 12 horas. Se recogió el sólido resultante por filtración y se lavó con éter diisopropílico, proporcionando clorhidrato de 2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)nicotinonitrilo en forma de un sólido amarillo (0,340 g, rendimiento: 79%).



Peso molecular: 400,91

Espectrometría de masas: 365 $(M + H)^+$

Grado de actividad in vitro: A

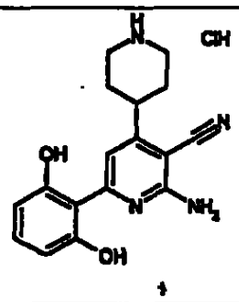
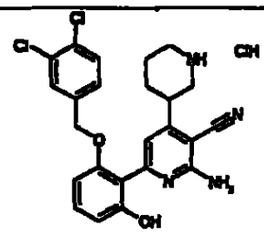
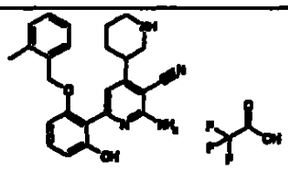
Grado de actividad celular: (A549)A

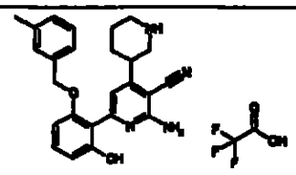
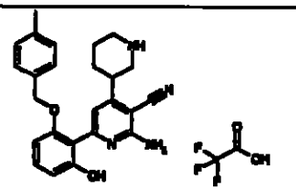
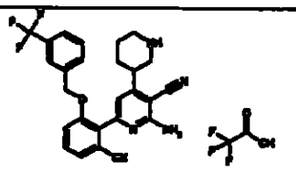
RMN de ^1H (500 MHz, DMSO-d_6): 0,31 - 0,34 (2H, m), 0,55 - 0,59 (2H, m), 1,03 - 1,04 (1H, m), 1,91 - 1,99 (4H, m), 3,06 - 3,14 (3H, m), 3,37 - 3,39 (2H, m), 3,87 (2H, d, J = 7,3), 6,55 (2H, dd, J = 9,9, 8,2 Hz), 7,23 (1H, t, J = 8,2), 9,19 - 9,11 (1H, m), 9,20-9,23 (1H, m).

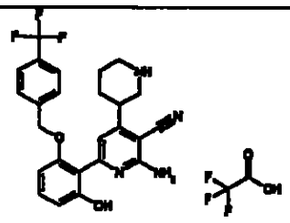
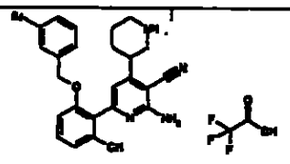
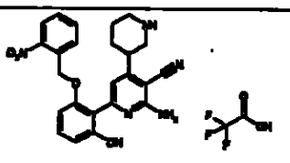
Ejemplos 2-4 a 2-87

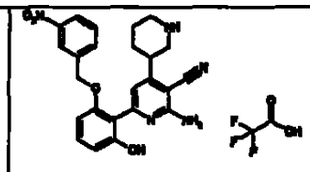
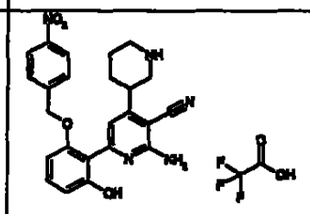
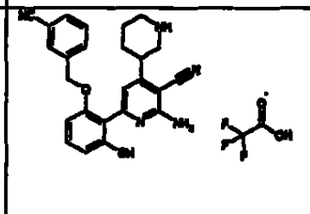
Según un procedimiento sintético similar al de los ejemplos 2-1 a 2-3, se prepararon los compuestos mostrados en la tabla 2.

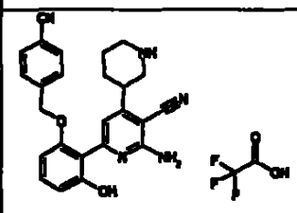
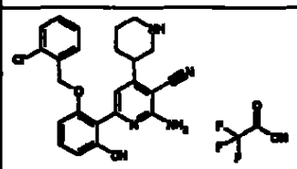
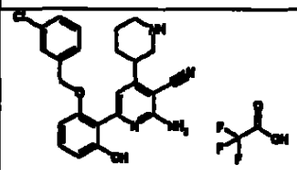
Tabla 2

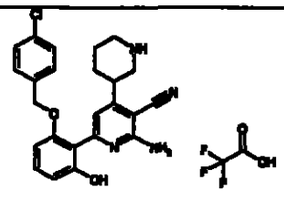
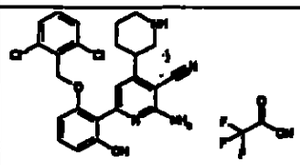
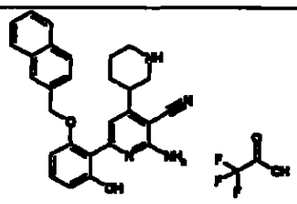
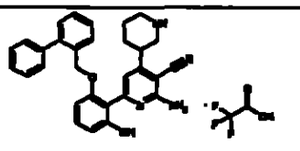
Ej. Nº	Estructura	Peso molecular	Masa	*In vitro*	A549	RMN
2-04		346,82	311			(500 MHz, DMSO-d_6): 1,88-1,98 (4H, m), 3,05-3,10 (3H, m), 3,38-3,57 (2H, m), 6,43 (2H, d, J=8,2 Hz), 7,09 (1H, t, J=8,2 Hz), 7,56-7,60 (1H, s a), 7,60 (1H, s), 8,94-9,01 (2H, m)
2-05		505,84	470	A	B	(500 MHz, DMSO-d_6): 1,26 (1H, a), 1,75 (3H, m), 2,71 (1H, a), 2,88 (1H, a), 3,18 (1H, a), 3,28 (1H, a), 5,07 (1H, d, J=11,7 Hz), 5,12 (1H, d, J=11,7 Hz), 6,59 (1H, m), 6,69 (1H, d, J=8,5 Hz), 7,15 (1H, d, J=8,2 Hz), 7,26 (2H, m), 7,45 (1H, dd, J=1,9, 8,2 Hz), 7,69 (1H, d, J=8,2 Hz), 8,76 (1H, a), 8,92 (1H, a), 9,09 (1H, a), 9,40 (1H, s a)
2-06		526,54	415	A	B	(500 MHz, DMSO-d_6): 0,92 (1H, ddd, J=3,5, 3,5, 12,3 Hz), 1,58-1,72 (3H, m), 2,27 (3H, s), 2,30-2,70 (3H, m), 3,06 (1H, t, J=12,0 Hz), 3,25 (1H, m), 5,08 (1H, d, J=11,0 Hz), 5,13 (1H, d, J=10,8 Hz), 6,56 (1H, d, J=8,2 Hz), 6,77 (1H, d, J=8,2 Hz), 7,23-7,31 (6H, m), 7,43 (1H, d, J=7,6 Hz), 8,59 (1H, a), 8,74 (1H, a), 12,82 (1H, a)

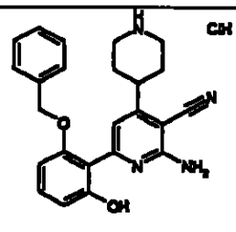
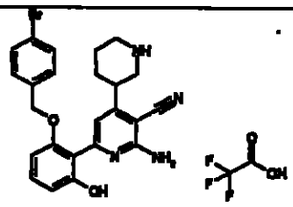
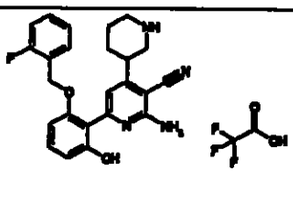
2-07		528,54	415	A	B	(500 MHz, DMSO-d_6): 0,92 (1H, ddd, J=3.8, 4,1. 12,6 Hz), 1,58-1,72 (3H, m), 2,27 (3H, s), 2,30-2,70 (3H, m), 3,07 (1H, m). 3,25 (1H, t, J=9,5 Hz), 5,08 (1H, d, J=10,7 Hz), 5,13 (1H, d, J=10,7 Hz), 6,56 (1H, dd, J=1,0, 8,2 Hz), 6,77 (1H, d, J=8,2 Hz), 7,23-7,31 (6H, m). 7,43 (1H, d. J=7.3 Hz). 8.59 (1H. a). 8.75 (1H. a). 12,83 (1H, a).
2-08		528,54	415	A	A	(500 MHz, DMSO-d_6): 0,85 (1H. m). 1,62-1,95 (3H, m), 2,31 (3H, s), 2,30-2.70 (3H, m), 3,08 (1H, m), 3,20-3,50 (1H, m), 5,02 (1H, d, J=10,7 Hz), 5,07 (1H, d, J=10,7 Hz), 6,55 (1H, dd, J=1,0, 8,2 Hz), 6,72 (1H, d, J=8,2 Hz). 7,22-7,27 (6H, m), 7,37 (1H, d, J=7,9 Hz), 8,58 (1H, a), 8,76 (1H, a), 12,68 (1H, a)
2-09		582,51	469	A	B	(500 MHz, DMSO-d_6): 1,17-1,24 (1H. m), 1,64-1,72 (3H, m), 2,30-2,50 (2H, m), 2,63-2,68 (1H, m), 2,81 (1H, t a, J=11,7 Hz), 3,12 (1H, m), 5,17 (1H, d, J=11,7 Hz), 5,22 (1H, d, J=11,7 Hz), 6,58 (1H, d, J=8,2 Hz), 6,71 (1H, d, J=8,2 Hz), 7,11 (1H, s), 7,17 (2H, s a), 7,25 (1H, t, J=8,2 Hz), 7,64 (1H, dd, J=7,9, 8,2 Hz), 7,71 (2H, m), 7,75 (1H, d, J=7,9 Hz), 8,60 (1H, a), 8,80 (1H, a), 11,9 (1H, a)

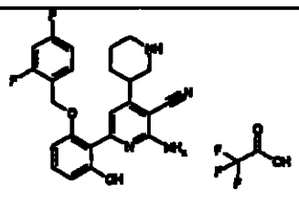
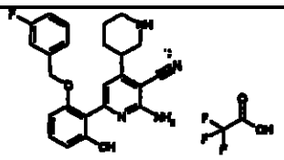
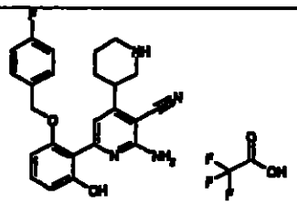
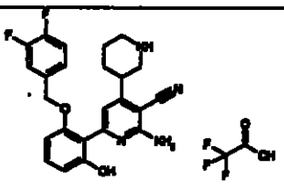
2-10		582,51	469	A	B	(500 MHz, DMSO-d_6): 1,24-1.31 (1H. m), 1,71 (3H, m), 2,60 (2H, m). 2.69 (1H. m), 2,88 (1H, t a, J=12,3 Hz). 3,13 (1H. m), 5.19 (1H, d, J=12,3 Hz), 5,24 (1H. d. J=12.3 Hz), 6,57 (1H, d, J=8,2 Hz). 6.70 (1H, d. J=8,2 Hz), 7,17 (1H, s). 7.19 (2H. s a). 7,24 (1H, t, J=8,2 Hz), 7,66 (2H, d, J=7,9 Hz), 7,77 (2H, d, J=7,9 Hz), 8.66 (2H, a). 11,95 (1H, s)
2-11		593,40	sin pico	A	B	(500 MHz, DMSO-d_6): 1.22 (1H. m). 1,74 (3H, m), 2,69-2.81 (2H. m), 3,13 (1H, t. J=12,3 Hz), 5.07 (1H, d, J=11,4 Hz), 5,12 (1H, d, J=11,4 Hz), 6,57 (1H. d, J=8,5 Hz), 6,69 (1H, d. J=8.5 Hz), 7.16 (1H, s). 7,19 (2H. s a), 7,25 (1H, t, J=8.5 Hz), 7,37 (1H, t. J=7,9 Hz), 7.46 (1H. d, J=7,9 Hz), 7,55 (1H, d. J=7,9 Hz), 7,61 (1H, s a), 8,59 (1H, s a), 8,79 (1H, s a), 12,10 (1H, a).
2-12		559,51	446	A	B	(500 MHz, DMSO-d_6): 1,24 (1H. m). 1,73 (3H, m), 2,30-2.70 (3H. m), 2,80 (1H, m), 3,14 (1H, m), 5,42 (1H, d, J=13,2 Hz), 5,46 (1H, d, J=13,2 Hz), 6,58 (1H, d, J=8,2 Hz), 6,67 (1H, d, J=8,2 Hz), 7,10 (1H, s), 7,19 (2H, s a), 7,24 (1H, t, J=8,2 Hz), 7,64 (1H, dt, J=1,3, 8,2 Hz), 7,71 (1H, d, J=7,6 Hz), 7,78 (1H, d, J=7,6 Hz), 8,11 (2H, d, J=8,2 Hz), 8,56 (1H, a), 8,74 (1H, a), 11,94 (1H, a)

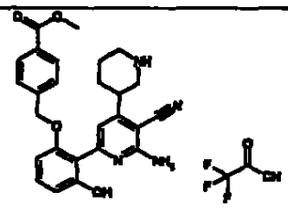
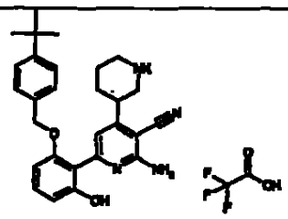
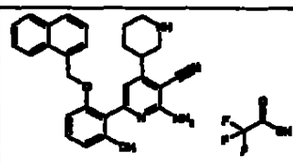
2-13		559,51	446	A	B	(500 MHz, DMSO-d_6): 1.29 (1H, m), 1,71 (3H, m), 2,30-2,50 (2H, m). 2,69 (1H, m), 2,84 (1H, dd, J=11.4, 11,6 Hz), 3,14 (1H, m), 5,23 (1H, d, J=12,3 Hz), 5,28 (1H, d, J=12,3 Hz), 6.59 (1H. dd, J=1.0. 8,5 Hz), 6,71 (1H, d, J=8,5 Hz). 7,12 (1H, s), 7,16 (2H, s a), 7,25 (1H, t, J=8,5 Hz), 7,71 (1H, t, J=7,9 Hz). 7,89 (1H. d. J=7,6 Hz). 8,20 (1H, dd, J=1,3, 8,2 Hz), 8,24 (1H, a), 8,58 (1H, a), 8,82 (1H, a)
2-14		559,51	446	A	A	(500 MHz, DMSO-d_6): 1.38 (1H. m), 1,75 (3H, m), 2,30-2,50 (1H, m), 2,73 (1H, dd, J=10,7, 12,0 Hz), 2,88 (1H, dd, J=10.7, 11,6 Hz), 3,14 (1H, m), 3,29 (1H, m), 5,27 (2H, dd, J=12,9, 16,1 Hz), 6,58 (1H, dd, J=1,0, 8,2 Hz), 6,69 (1H, d, J=8.5 Hz), 7,13 (1H, s), 7,19 (2H, s a), 7,24 (1H, t, J=8,2 Hz), 7,69 (1H, t, J=8,8 Hz), 8,26 (1H, d, J=8,8), 8,54 (1H, s), 8,79 (1H, a), 11,8 (1H, a).
2-15		539,52	426	A	A	(500 MHz, DMSO-d_6): 1,24 (1H, m), 1,68-1,81 (3H, m), 2,30-2,50 (2H, m), 2,72 (1H, dd, J=10,1. 12,3 Hz), 2,82 (1H, dd, J=10,4, 12,0 Hz), 3,13 (1H, m), 5,12 (1H, d, J=11,7 Hz), 5,18 (1H, d, J=11,7 Hz), 6,58 (1H, d, J=8,5 Hz), 6,71 (1H, d, J=8,5 Hz), 7,13 (1H, s), 7,18 (2H, s a), 7,26 (1H, t, J=8,5 Hz), 7,62 (1H, t, J=7,9 Hz), 7,79 (1H, d, J=7,9 Hz), 7,84 (1H, d,

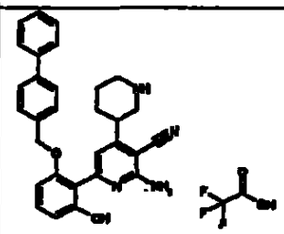
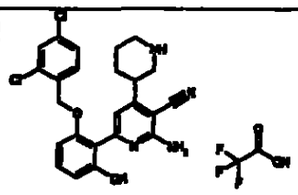
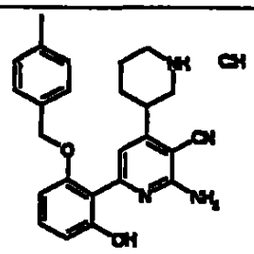
						J=7,9 Hz), 7,88 (1H, s), 8,59 (1H, a), 8.76 (1H. a). 11.95 (1H, a)
2-16		539,52	426	A	A	(500 MHz, DMSO-d_6): 1.31 (1H. m). 1,68-1,91 (3H, m), 2,30-2,50 (2H. m), 2,73 (1H, m), 2,87 (1H, dd, J=11,4, 12,3 Hz)), 3,14 (1H, t, J=12,3 Hz)), 5,19 (1H, d, J=12,6 Hz), 5,22 (1H, d, J=12,6 Hz), 6,57 (1H. d, J=8,2 Hz), 6,68 (1H, d, J=8,2 Hz), 7,13 (1H, s), 7,18 (2H, s a), 7,24 (1H, t, J=8,2 Hz), 7,62 (1H, t, J=8,2 Hz), 7,88 (1H, d, J=8,2 Hz), 8,58 (1H. a), 8,80 (1H, a). 11,84 (1H, s a)
2-17		548,95	435	A	B	(500 MHz, DMSO-d_6): 1.06 (1H, m), 1,60-1.80 (3H, m), 2,50-2,70 (m. 4H), 3,10 (1H, m), 5,13 (1H, d, J=11,4 Hz), 5,21 (1H, d, J=11,4 Hz), 6.58 (1H, dd, J=0,9, 8,2 Hz), 6,74 (1H, d, J=8,2 Hz), 7,21 (1H, s), 7,24 (2H, a), 7,28 (1H, t, J=8,2 Hz), 7,41 (1H, dt, J=1,6, 7,3 Hz), 7,44 (1H, dt, J=1,9, 7,6 Hz), 7.57 (1H, dd, J=1,6, 7,9 Hz), 7,61 (1H, dd, J=1,9, 7,3 Hz), 8,61 (1H, a), 8,77 (1H, a)
2-18		548,95	435	A	B	(500 MHz, DMSO-d_6): 1,22 (1H, m), 1,74 (3H, m), 2,71 (2H, m), 3,13 (1H, t, J=12,3 Hz), 5,08 (1H, d, J=11,3 Hz), 5,13 (1H, d, J=11,3 Hz), 6,57 (1H, d, J=8,2 Hz), 6,70 (1H, d, J=8,2 Hz), 7,17 (1H, s), 7,20 (2H, a), 7,25 (1H, t, J=8,2 Hz), 7,42 (3H, m), 7,48 (1H, s), 8,62 (1H, a), 8,82 (1H, a)

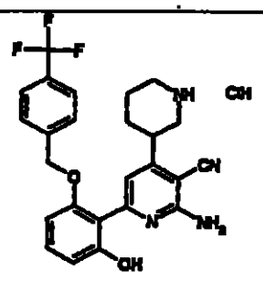
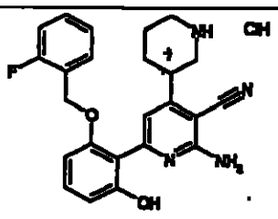
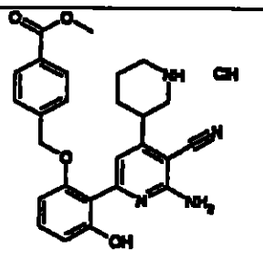
2-19		548,95	435	A	A	(500 MHz, DMSO-d_6): 1,13 (1H, m), 1,73 (3H, m), 2,50-2,80 (3H, m), 3,11 (1H, t, J=12,3 Hz), 5,07 (1H, d, J=11,0 Hz), 5,12 (1H, d, J=11,0 Hz), 6,56 (1H, d, J=8,2 Hz), 6,70 (1H, d, J=8,2 Hz), 7,19 (1H, s), 7,21 (2H, a), 7,25 (1H, t, J=8,2 Hz), 7,49 (4H, dt, J=2,5, 8,8 Hz), 8,61 (1H, a), 8,80 (1H, a), 12,33 (1H, a)
2-20		583,40	470	A	B	(500 MHz, DMSO-d_6): 0,85 (1H, m), 1,53 (1H, d, J=12,6 Hz), 1,69 (2H, m), 3,07 (1H, m), 5,24 (1H, d, J=10,4 Hz), 5,33 (1H, d, J=10,4 Hz), 6,60 (1H, dd, J=0,9, 8,2 Hz), 6,84 (1H, d, J=8,5 Hz), 7,14 (1H, s), 7,29 (2H, a), 7,32 (1H, t, J=8,2 Hz), 7,51 (4H, dd, J=7,6, 8,8 Hz), 7,63 (2H, d, J=7,9 Hz), 8,64 (1H, a), 8,77 (1H, a), 12,95 (1H, a)
2-21		564,57	451	A	A	(500 MHz, DMSO-d_6): 0,82 (1H, m), 1,09 (1H, m), 1,41 (2H, m), 2,08 (1H, m), 2,99 (2H, m), 5,24 (1H, d, J=10,7 Hz), 5,30 (1H, d, J=10,7 Hz), 6,57 (1H, dd, J=1,0, 8,2 Hz), 6,80 (1H, d, J=8,2 Hz), 7,23 (2H, a), 7,26 (1H, s), 7,29 (1H, t, J=8,2 Hz), 7,55 (2H, m), 7,62 (1H, dd, J=1,6, 8,2 Hz), 7,95 (3H, m), 8,03 (1H, s), 8,55 (1H, a), 12,65 (1H, a)
2-22		590,61	477	A	B	(500 MHz, DMSO-d_6): 0,94 (1H, m), 1,63 (3H, m), 3,07 (1H, t, J=11,4 Hz), 4,90 (1H, d, J=10,4 Hz), 4,99 (1H, d, J=10,4 Hz), 6,51 (1H, d, J=8,2 Hz), 6,53

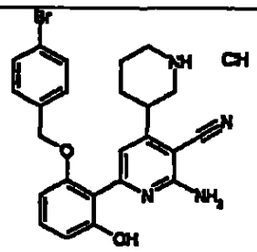
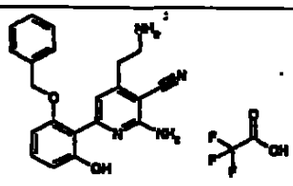
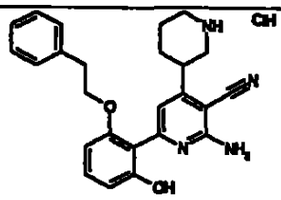
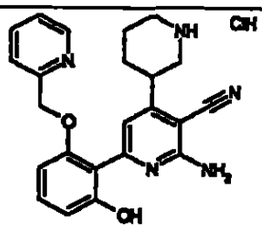
						(1H, d, J=8,2 Hz), 7,19 (1H, t, J=8,2 Hz), 7,26 (2H, a), 7,35 (6H, m), 7,48 (2H, m), 7,66 (1H, d, J=7,3 Hz), 8,60 (1H, a), 8,76 (1H, a)
2-23		436,95	401	A	B	(500 MHz, DMSO-d_6): 1,65-1.89 (4H, m), 2,93-3,10 (3H, m), 3,29 (2H, d, J=12,3 Hz), 5,13 (2H, s), 6,62 (1H, d, J=8,2 Hz), 6,72 (1H, d, J=8,2 Hz), 7,13 (1H, s), 7,28 (1H, t, J=8,2 Hz), 7,33 (1H, t, J= 7.4 Hz), 7,40 (2H, t, J=7,4 Hz), 7,46 (2H, t, J=7,4 Hz), 7,72 (2H, a), 9,10 (1H, s a)
2-24		593,40	480	A	A	(500 MHz, DMSO-d_6): 1,14 (1H, m), 1,74 (3H, m), 2,69 (2H, m), 3,11 (1H, t, J=12,0 Hz), 5,05 (1H, d, J=11,4 Hz), 5,10 (1H, d, J= 11,4 Hz), 6,56 (1H, d, J=8,2 Hz), 6,70 (1H, d, J=8,2 Hz), 7,19 (1H, s), 7,22 (2H, a), 7,25 (1H, t, J=8,2 Hz), 7,44 (2H, d, J=8,2 Hz), 7,61 (2H, d, J=8,2 Hz), 8,60 (1H, a), 8,81 (1H, a), 12,36 (1H, a)
2-25		532,50	419	A	A	(500 MHz, DMSO-d_6): 1,09 (1H, m), 1,71 (3H, m), 2,64 (2H, m), 3,10 (1H, t, J=12,3 Hz), 3,28 (2H, t, J=10,4 Hz), 5,13 (1H, d, J=11,0 Hz), 5,18 (1H, d, J=11,0 Hz), 6,58 (1H, d, J=8,5 Hz), 6,76 (1H, d, J=8,5 Hz), 7,20 (1H, s), 7,26 (4H, m), 7,47 (1H, m), 7,58 (1H, t, J=7,6 Hz), 8,63 (1H, a), 8,82 (1H, a)

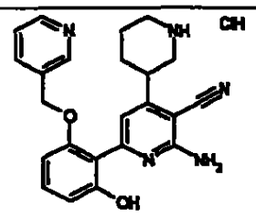
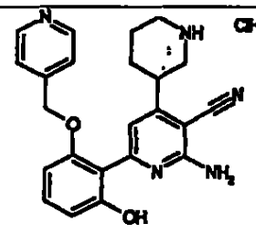
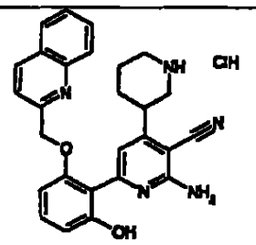
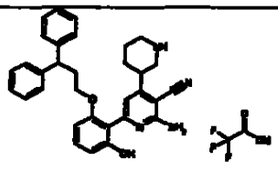
2-26		550,49		A	A	(500 MHz, DMSO-d_6): 1,09 (1H, m), 1,71 (3H, m), 2,64 (2H, m), 3,10 (1H, t, J=12,3 Hz), 3,28 (2H, t, J=10,4 Hz), 5,13 (1H, d, J=11,0 Hz), 5,18 (1H, d, J=11,0 Hz), 6,58 (1H, d, J=8,5 Hz), 6,76 (1H, d, J=8,5 Hz), 7,20 (1H, s), 7,26 (4H, m), 7,47 (1H, m), 7,58 (1H, t, J=7,6 Hz), 8,63 (1H, a), 8,82 (1H, a)
2-27		532,50	419	A	A	(500 MHz, DMSO-d_6): 1,25 (1H, m), 1,73 (3H, m), 2,69 (1H, dd, J=10,8, 11,7 Hz), 2,78 (1H, dd, J=11,7, 11,7 Hz), 3,13 (1H, t, J=12,3 Hz), 5,08 (1H, d, J=11,7 Hz), 5,14 (1H, d, J=11,7 Hz), 6,57 (1H, d, J=8,2 Hz), 6,70 (1H, d, J=8,2 Hz), 7,26 (6H, m), 7,45 (1H, m), 8,60 (1H, a), 8,81 (1H, a), 12,19 (1H, a)
2-28		532,50	419	A	A	(500 MHz, DMSO-d_6): 1,14 (1H, m), 1,71 (3H, m), 2,69 (3H, m), 3,10 (1H, t, J=12,3 Hz), 5,06 (1H, d, J=11,0 Hz), 5,10 (1H, d, J=11,0 Hz), 6,56 (1H, d, J=8,5 Hz), 6,72 (1H, d, J=8,5 Hz), 7,21 (1H, s), 7.25 (5H, m), 7,53 (2H, dd, J=5,7, 8,5 Hz), 8,59 (1H, a), 8,81 (1H, a)
2-29		550,49	437	A	B	(500 MHz, DMSO-d_6): 1,28 (1H, m), 1,73 (3H, m), 2,69 (1H, m), 2,84 (1H, dd, J=11,4, 11,4 Hz), 3,13 (1H, t, J=12,3 Hz), 5,05 (1H, d, J=11,4 Hz), 5,10 (1H, d, J=11,4 Hz), 6,57 (1H, d, J=8,2 Hz), 6,69 (1H, d, J=8,2 Hz), 7,17 (1H, s), 7,20 (2H, a), 7,25 (1H, t, J=8,2 Hz), 7,33 (1H, a),

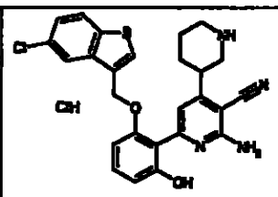
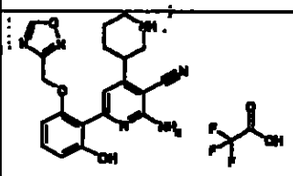
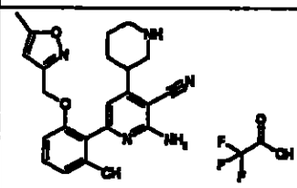
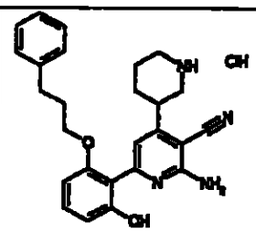
						7,50 (2H, m), 8,60 (1H. a). 8.82 (1H. s). 12.07 (1H. a)
2-30		572,55	459	A	A	(500 MHz, DMSO-d_6): 1.22 (1H. m). 1,70 (3H, m), 2,65 (1H. m). 2.79 (1H, dd. J=11,4. 11,4 Hz), 3.12 (1H. t, J=12.3 Hz), 3,29 (2H, a), 5,17 (1H, d, J=12.0 Hz), 5,22 (1H, d, J=12,0 Hz), 6,57 (1H. d, J=8.2 Hz), 6,69 (1H, d, J=8,2 Hz), 7,17 (1H, s), 7,22 (2H, a), 7,25 (1H, t, J=8,2 Hz), 7,59 (2H, d, J=8,2 Hz), 7,99 (2H, d, J=8,2 Hz), 8,58 (1H, a), 8,80 (1H, a)
2-31		570,62	457	A	A	(500 MHz, DMSO-d_6): 1,67 - 1.78 (3H. m), 2,71 (1H, dd, J=10,4. 11,4 Hz), 2,89 (1H, dd, J=11,4, 11,7 Hz), 3,13 (1H, t, J=12,3 Hz), 5,04 (1H, d, J=11,4 Hz), 5,10 (1H, d, J=11,4 Hz), 6,55 (1H, d, J=8,2 Hz), 6,72 (1H, d, J=8,2 Hz), 7,22 (2H, s a), 7,24 (1H, t, J=8,2 Hz), 7.27 (1H, s), 7,37 (2H, d, J=8,2 Hz), 7,41 (2H, d, J=8,2 Hz), 8,61 (1H, a), 8,84 (1H, a), 12,20 (1H, a)
2-32		564,57	451	A	B	(500 MHz, DMSO-d_6): 0,24 (1H, m), 1,13 (1H, d, J=13,9 Hz), 1,42-1,52 (2H, m), 2,04 (1H, dd, J=11,0, 12,0 Hz), 2,19 (1H, dd, J=11,0, 12,0 Hz), 2,87 (1H, t, J=12,0 Hz), 3,08 (1H, d, J=11,4 Hz), 3,15 (1H, d, J=12,0 Hz), 5,54 (1H, d, J=11,0 Hz), 5,59 (1H, d, J=11,0 Hz), 6,60 (1H, d, J=8,2 Hz), 6,95 (1H, d, J=8,2 Hz), 7,10 (1H, s), 7,23 (2H, s a), 7,34 (1H, t, J=8,2

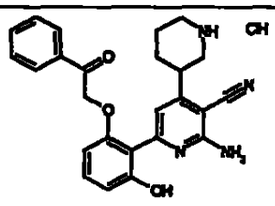
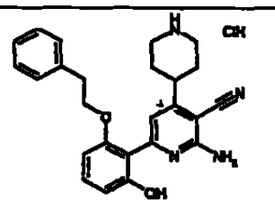
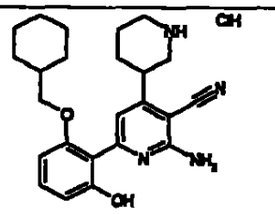
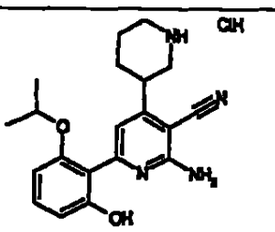
						Hz), 7,56 (3H, m), 7,71 (1H, d, J=6, Hz), 8,00 (3H, m), 8,46 (1H, a), 8,60 (1H a)
2-33		590,61	477	A	B	(500 MHz, DMSO-d_6): 1,17 (1H, m) 1,59-1,68 (3H, m), 2,76 (1H, d, J=11,4 11,7 Hz), 3,07-3,17 (3H, m), 5,13 (1H, d J=11,4 Hz), 5,18 (1H, d, J=11,4 Hz), 6,5 (1H, d, J=8,2 Hz), 6,76 (1H, d, J=8,2 Hz) 7,24-7,94 (4H, m), 7,39 (1H, t, J=7,6 Hz) 7,48 (1H, t, J=7,6 Hz), 7,56 (2H, d, J=8, Hz), 7,69 (2H, d, J=7,9 Hz), 7,73 (2H, d J=7,9 Hz), 8,55 (1H, d a), 8,77 (1H, d a) 12,47 (1H, a)
2-34		583,40	470	A	B	(500 MHz, DMSO-d_6): 1,08 (1H, m) 1,64-1,78 (3H, m), 3,12 (1H, t, J=12, Hz), 3,32 (2H, t, J=12,9 Hz), 5,11 (1H, d J=11,4 Hz), 5,20 (1H, d, J=11,4 Hz), 6,55 (1H, d, J=8,2 Hz), 6,73 (1H, d, J=8,2 Hz), 7,16 (1H, s), 7,25 (2H, a), 7,27 (1H, t, J=8,2 Hz), 7,51 (1H, dd, J=1,9, 8,2 Hz), 7,62 (1H, d, J=8,2 Hz), 7,76 (1H, d, J=1,9 Hz), 8,63 (1H, a), 8,81 (1H, a)
2-35		450,97	415	A	A	(500 MHz, DMSO-d_6): 1,09 (1H, m), 1,68 (3H, m), 2,32 (3H, s), 3,08-3,31 (4H, m), 5,02 (1H, d, J=10,6 Hz), 5,07 (1H, d, J=10,6 Hz), 6,56 (1H, d, J=8,3 Hz), 6,72 (1H, d, J=8,3 Hz), 7,22-7,29 (6H, m), 7,36 (2H, d, J=7,5 Hz), 8,79 (1H, a), 9,16 (1H, a)

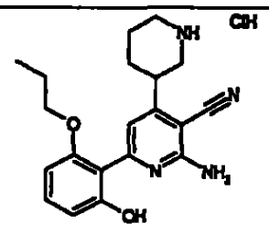
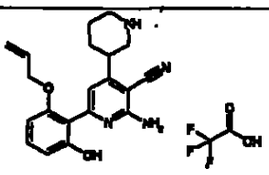
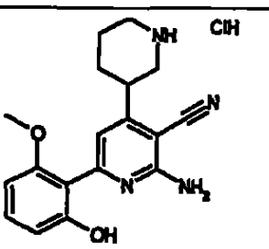
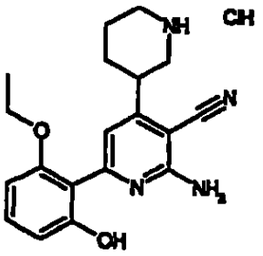
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2-37		454,94	419	A	A	(500 MHz, DMSO-d_6): 1,15-1,20 (1H, m), 1,66-1,77 (3H, m), 2,52-2,73 (2H, m), 3,15-3,28 (3H, m), 5,14 (1H, d, J=11,0 Hz), 5.18 (1H, d, J=11,0 Hz), 6,62 (1H, d. J=8,2 Hz), 6,78 (1H, d, J=8,2 Hz), 7,20 (1H, s), 7,26-7,33 (3H, m), 7,46 (2H, m), 7,58 (2H, dt, J=1,6. 7,6 Hz), 9,00 (1H, d a), 9,50 (1H, d a)
2-38		494,98	459	A	A	(500 MHz, DMSO-d_6): 1,29 (1H, m), 1,73 (3H, m), 2,64 (1H, m), 2,89 (1H, dd, J=1,4, 12,7 Hz), 3,24 (3H, m), 3,86 (3H, s), 5.17 (1H, d, J=12,0 Hz), 5,22 (1H, d, J=12,0 Hz), 6,62 (1H, d, J=8,2 Hz), 6,71 (1H, d, J=8,5 Hz), 7,20 (1H, s), 7,27 (1H, dd, J=8,2, 8,5 Hz), 7,59 (2H, d, J=8,2), 7,99 (2H, d, J=8,2 Hz), 8,95 (1H, d a), 9,41 (1H, d a)

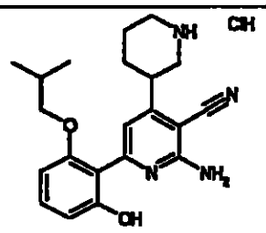
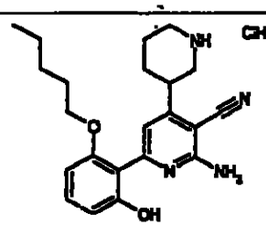
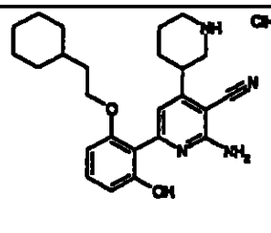
2-39		515,84	479	A	A	(500 MHz, DMSO-d_6): 1.12 (1H, m), 1.73 (3H, m), 2,66 (1H, m), 2.75 (1H, t, J=12,3 Hz), 3,13 (1H, m), 5,05 (1H, d, J=11,0 Hz), 5,10 (1H, d, J=11.0 Hz), 6.56 (1H, d, J=8,2 Hz), 6,70 (1H, d, J=8,2 Hz), 7,19 (1H, s), 7,21 (2H, s a), 7.25 (1H, t, J=8,2 Hz), 7,44 (2H, d, J=8,5 Hz), 7,63 (2H, d, J=8,5 Hz), 9,03 (2H, a), 12.37 (1H, s)
2-40		474,44	361	A	A	(500 MHz, DMSO-d_6): 2.92 (4H, s a), 5,15 (2H, a), 6.55 (1H, d, J=7.2 Hz), 6,68 (1H, d, J=8,5 Hz), 7,22-7.25 (3H, m), 7,30 (1H, s), 7,33-7,35 (1H, m), 7,40-7,45 (4H, m), 7,95 (1H, s a)
2-41		450,97	415	A	A	(500 MHz, DMSO-d_6): 1.63 (1H, m), 1,78-1,90 (3H, m), 2,85 (1H, m), 3.03 (2H, dd, J=6,6, 6,9 Hz), 3.12 (1H, m), 3,26-3,36 (3H, m), 4,20 (2H, dd, J=6,6, 6,9 Hz), 6,62 (1H, d, J=8,2 Hz), 6,63 (1H, d, J=8,5 Hz), 7,18-7,24 (5H, m), 7,23 (1H, s), 7,26 (1H, dd, J=8,2, 8,5 Hz), 7,95 (1H, s a), 9,11 (1H, s a), 9,65 (1H, s a)
2-42		437,93	402	A	B	(500 MHz, DMSO-d_6): 1,42-1.86 (4H, m), 2,80-3,29 (5H, m), 5,27-5,36 (2H, m), 6,64 (1H, d, J=8,2 Hz), 6,72 (1H, d, J=8,5 Hz), 7,26-7,32 (2H, m), 7,51-7,73 (3H, m), 8,15-8,18 (1H, t, J=7,5 Hz), 8,77-8,93 (2H, m), 9,47 (1H, d a, J=10,4 Hz)

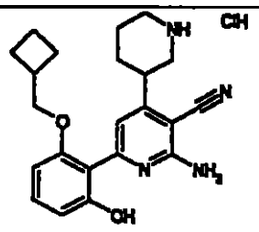
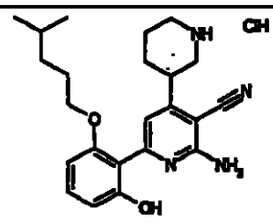
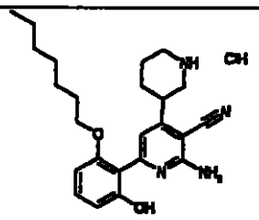
2-43		437,93	402	A	A	(500 MHz, DMSO-d_6): 1,33-1,36 (2H, m), 1,73-1,82 (4H, m), 2,80-3,27 (3H, m), 5,30 (2H, s), 6,64 (1H, d, J=8,2 Hz), 6,74 (1H, d, J=8,5 Hz), 7,13 (1H, s), 7,29 (1H, t, J=8,2 Hz), 7,48 (1H, s a), 7,98 (1H, m), 8,46 (1H, d, J=7,6 Hz), 8,84 (1H, d, 5,4 Hz), 8,89-8,91 (1H, m), 8,95 (1H, s), 9,45 (1H, d a, J=10,1 Hz
2-44		437,93	402	A	A	(500 MHz, DMSO-d_6): 1,52-1,86 (3H, m), 2,79-3,33 (6H, m), 5,42 (2H, s), 6,63 (1H, d, J=8,2 Hz), 6,65 (1H, d, J=8,5 Hz), 7,10 (1H, s), 7,22-7,38 (3H, m), 7,90 (2H, d, J=5,7 Hz), 8,82-8,89 (3H, m), 9,42 (1H, d a, J=10,4 Hz).
2-45		487,99	452	A	A	(500 MHz, DMSO-d_6): 1,27-1,29 (1H, m), 1,49-1,67 (3H, m), 2,90-3,30 (4H, m), 4,61 (2H, s a), 5,41-5,42 (2H, m), 6,63 (1H, d, J=8,2 Hz), 6,75 (1H, d, J=8,5 Hz), 7,25-7,29 (2H, m), 7,66-7,71 (2H, m), 7,85 (1H, t, J=7,6 Hz), 8,08 (2H, t, J=9,3 Hz), 8,57 (1H, d, J=8,8 Hz), 8,81-8,83 (1H, m), 9,29 (1H, d a, J=9,8 Hz)
2-46		618,66	505	A	B	(500 MHz, DMSO-d_6): 1,53-1,66 (3H, m), 1,81 (1H, m), 3,02 (1H, m), 3,15-3,42 (4H, m), 3,73-3,81 (2H, m), 3,90-4,00 (2H, m), 4,04 (1H, m), 6,40 (1H, d, J=8,2 Hz), 6,51 (1H, d, J=8,5 Hz), 7,14 (1H, dd, J=8,2, 8,5 Hz), 7,19-7,28 (10H, m), 7,36 (1H, s), 8,60 (1H, s a), 8,83 (1H, s a)

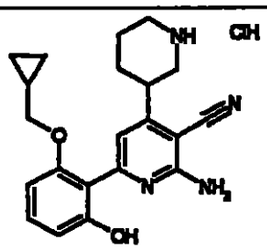
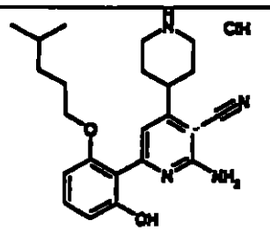
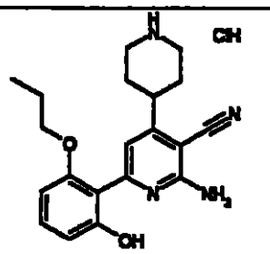
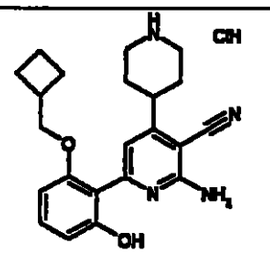
2-47		527,48	490	A	B	(500 MHz, DMSO-d_6): 0,76-0.86 (1H, m). 1.38 (1H, d a, J=12.3 Hz). 3.05 (1H, t, J=10,4 Hz). 3,81 (2H, dd, J=12,0 29.6 Hz), 5,39 (2H, dd, J=11,7, 40.0 Hz), 6.60 (1H, d, J=8,2 Hz), 6,86 (1H, d, J=8,5 Hz), 7,15 (1H, s), 7,29-7,44 (4H, m). 7,79 (1H, d, J=1,9 Hz), 7,99 (1H, s), 8.07 (1H, d, J=8.8 Hz), 8,70-8,80 (1H, m). 9,07 (1H, d, J=10,7 Hz)
2-48		506,45	393	A	A	(500 MHz, DMSO-d_6): 1,62-1.95 (4H, m), 2,87-3,21 (5H, m), 5,41 (2H, s), 6,60 (1H, d, J=8,2 Hz), 6,76 (1H, d, J=8,5 Hz), 7,26-7.30 (2H, m), 7,46 (1H, s), 8,61-8,63 (1H, m), 8,85 (1H, d a, J=10,4 Hz), 9,79 (1H, s)
2-49		519,48	406	A	A	(500 MHz, DMSO-d_6): 1,52-1.91 (4H, m), 2,42 (3H, s), 2,87-3,39 (5H, m), 5,12-5,26 (2H, m), 6,31 (1H, s), 6,58 (1H, d, J=8,2 Hz), 6,71 (1H, d, J=8,5 Hz), 7,24-7,28 (3H, m), 7,36 (1H, s), 6,36-8,65 (1H, m), 8,90-8,93 (1H, d a, J=10,4 Hz)
2-50		465,00	429	A	A	(500 MHz, DMSO-d_6): 1,64-1.76 (3H, m), 1,90 (1H, m), 2,03-2,08 (2H, m), 2,67 (2H, t, J=7,6 Hz), 2,78 (1H, m), 3,06 (1H, m), 3,21-3,27 (2H, m), 3,35 (1H, m), 3,98 (12H, ddd, J=4,1, 6,3, 9,5 Hz), 6,53 (1H, d, J=8,2 Hz), 6,54 (1H, d, J=8,2 Hz), 7,15-7,28 (5H, m), 7,21 (1H, t, J=8,2 Hz), 7,31 (1H, s a), 7,33 (1H, s), 8,74 (1H, b a), 9,10 (1H, s a)

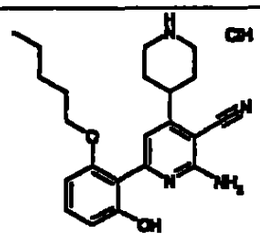
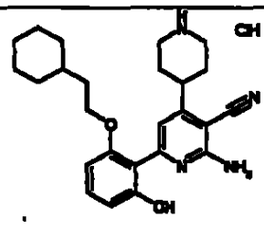
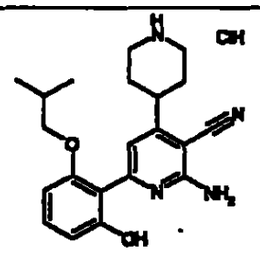
2-51		464,96	429	A	A	(500 MHz, DMSO-d_6): 1,91 (3H, m), 3,03 (1H, m), 5,68 (2H, m), 6,58 (1H, d, J=8,3 Hz), 6,76 (1H, d, J=8,3 Hz), 7,27 (1H, t, J=8,3 Hz), 7,37 (1H, a), 7,60 (2H, t, J=7,2 Hz), 7,73 (1H, t, J=7,2 Hz), 8,11 (2H, d, J=7,2 Hz), 8,18 (1H, a), 8,92 (1H, a), 9,34 (1H, a)
2-52		450,97	415	A	A	(300 MHz, DMSO-d_6): 1,91-1,92 (4H, m), 3,07-3,11 (2H, m), 3,09 (3H, t, J=7,2 Hz), 3,36-3,40 (2H, m), 4,22 (2H, t, J=7,2 Hz), 6,55 (1H, d, J=8,3 Hz), 6,61 (1H, d, J=7,9 Hz), 7,20 (1H, dd, J=7,9, 8,3 Hz), 7,22-7,24 (5H, m), 7,25 (1H, s), 7,28 (1H, s a), 8,86 (2H, s a)
2-53		442,99	407	A	A	(300 MHz, DMSO-d_6): 1,09-1,17 (2H, m), 1,21-1,25 (4H, m), 1,66-1,75 (5H, m), 1,81-1,96 (3H, m), 2,84-2,99 (2H, m), 3,03-3,16 (2H, m), 3,31-3,48 (2H, m), 3,67-3,85 (2H, m), 6.55 (1H, d, J=7,9 Hz), 6,57 (1H, d, J=8,3 Hz), 7,22 (1H, dd, J=7,9, 8,3 Hz), 7,27 (1H, s), 7,45 (1H, s a), 8,98 (1H, s a), 9,44 (1H, s a)
2-54		388,90	353	A	A	(300 MHz, DMSO-d_6): 1.29 (6H, d, J=6,0 Hz), 1,61-1,95 (4H, m), 2,88-3,10 (2H, m), 3,28-3,49 (3H, m). 4,65 (1H, scp, J=6,0 Hz), 6,51 (1H, d, J=7,9 Hz), 6,60 (1H, d, J=8,7 Hz), 7,22 (1H, dd, J=7,9 8,7 Hz), 7,33 (1H, s), 7,42 (1H, s a), 8,87 (1H, s a), 9,24 (1H, s a)

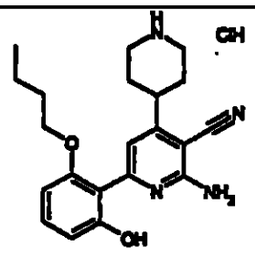
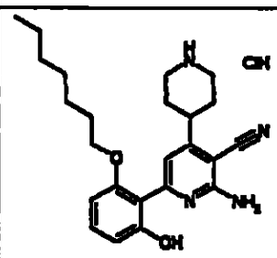
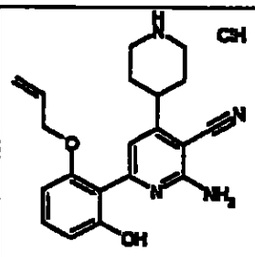
2-55		388,90	353	A	A	(500 MHz, DMSO-d_6): 0,94 (3H, t, J=7.3), 1,67 (1H, m), 1,78 (1H, m), 1,76-1,85 (2H, m), 1,91-1,99 (2H, m), 2,88 (1H, m), 3,06 (1H, m), 3,27 (1H, m), 3,30-3,32 (3H, m), 3,38 (1H, m), 3,96 (2H, t, J=6,0 Hz), 6,54 (1H, d, J=8,2 Hz), 6,58 (1H, d, J= 8,2 Hz), 7,23 (1H, t, J=8,2 Hz), 7,34 (1H, s), 8,88 (1H, s a), 9,31 (1H, s a)
2-56		545,45	351	A	A	(500 MHz, DMSO-d_6): 1,65 (1H, m), 1,78 (1H, m), 1,93 (2H, d, J=11,4 Hz), 2,88 (1H, m), 3,03 (1H, m), 3,21 (1H, m), 3,35 (2H, dd, J=10,25 Hz), 4,57 (2H, d, J=5,7 Hz), 5,33 (2H, m), 6,08 (1H, m), 6,56 (2H, dd, J=8,3, 26 Hz), 7,29 (3H, m), 8,65 (1H, a), 8,97 (2H, a)
2-57		360,85	325	A	A	(500 MHz, DMSO-d_6): 1,67-1,96 (5H, m), 2,72-3,42 (6H, m), 3,79 (3H, s), 6,55 (1H, d, J=8,3 Hz), 6,58 (1H, d, J=8,3 Hz), 7,22 (1H, s), 7,23 (1H, t, J=8,3 Hz), 8,79 (1H, d a), 9,13 (1H, d a)
2-58		374,87	339	A	A	(500 MHz, DMSO-d_6): 1,37 (3H, t, J=6,9 Hz), 1,68 (1H, m), 1,82 (1H, m), 1,92-1,96 (2H, m), 2,91 (1H, m), 3,08 (1H, m), 3,23-3,32 (2H, m), 3,39 (1H, m), 4,06 (2H, q, J=6,6 Hz), 6,54 (1H, d, J=8,2 Hz), 6,58 (1H, d, J=8,5 Hz), 7,24 (1H, dd, J=8,2, 8,5 Hz), 7,40 (1H, s), 7,46 (1H, s a), 8,81 (1H, s a), 9,22 (1H, s a)

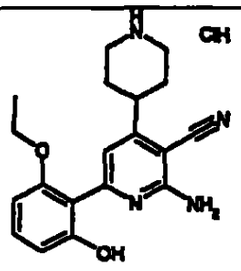
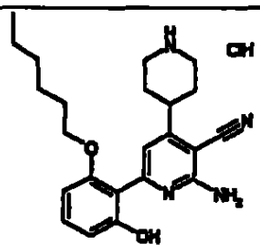
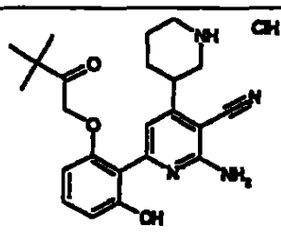
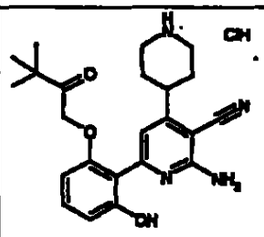
2-59		402,93	367	A	A	(500 MHz, DMSO-d_6): 0,92 (6H, d, J=6,6 Hz), 1,68 (1H, m), 180 (1H, m), 1,91-1,94 (2H, m), 2,04 (1H, sep, J=6,6 Hz), 2,86 (1H, m), 3,07 (1H, m), 3,27-3,36 (3H, m), 3,76 (2H, d, J=6,6 Hz), 6,56 (1H, d, J=7,3 Hz), 6,57 (1H, d, J=8,2 Hz), 7,23 (1H, dd, J=7,3, 8,2 Hz), 7,28 (1H, s), 7,56 (1H, s a), 8,95 (1H, s a), 9,45 (1H, s a)
2-60		416,96	381	A	A	(500 MHz, DMSO-d_6): 0,84-0,86 (2H, m), 1,29-1,30 (4H, m), 1,69-1,73 (2H, m), 1,80-1,95 (3H, m), 2,87 (1H, m), 3,10 (1H, m), 3,29-3,35 (3H, m), 3,48 (1H, m), 3,70 (1H, m), 3,97 (2H, q, J=6,3 Hz), 6,59 (2H, d, J=8,2 Hz), 7,25 (1H, t, J=8,2 Hz), 7,31 (1H, s), 7,75 (1H, s a), 9,07 (1H, s a), 9,60 (1H, s a)
2-61		457,02	421	A	A	(500 MHz, DMSO-d_6): 0,85-0,93 (2H, m), 1,09-1,18 (3H, m), 1,32 (1H, m), 1,60-1,64 (7H, m), 1,71 (1H, m), 1,84 (1H, m), 1,90-1,95 (2H, m), 2,87 (1H, m), 3,09 (1H, m), 3,28 (1H, m), 3,30-3,34 (2H, m), 3,99 (1H, dd, J=6,6, 9,5 Hz), 4,04 (1H, dd, J=6,6, 9,5 Hz), 6,56 (1H, d, J=8,2 Hz), 6,60 (1H, d, J=8,5 Hz), 7,23 (1H, dd, J=8,2, 8,5 Hz), 7,30 (1H, s), 7,59 (1H, s a), 8,99 (1H, s a), 9,46 (1H, s a)

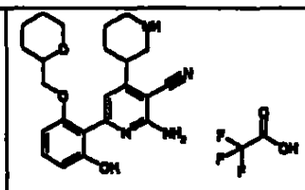
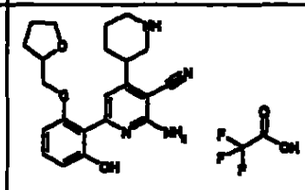
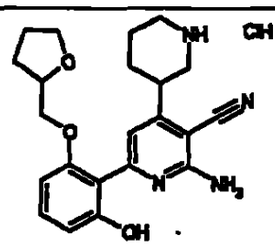
2-62		414,94	379	A	A	(500 MHz, DMSO-d_6): 1,63-1,78 (4H, m), 1,81-1,99 (5H, m), 2,02-2,09 (2H, m), 2,73 (1H, m), 2,88 (1H, m), 3,05 (1H, m), 3,22-3,38 (2H, m), 3,99 (2H, d, J=6,6 Hz), 6,53 (1H, d, J=8,5 Hz), 6,59 (1H, d, J=8,2 Hz), 7,22 (1H, t, 8,2 Hz), 7,27 (1H, s), 7,28 (1H, s a), 8,76 (1H, s a), 9,11 (1H, s a)
2-63		430,98	395	A	A	(500 MHz, DMSO-d_6): 0,84 (6H, d, J=6,6 Hz), 1,17-1,25 (2H, m), 1,52 (1H, scp, J=6,6 Hz), 1,67-1,75 (3H, m), 1,80 (1H, m), 1,86-1,96 (2H, m), 2,87 (1H, m), 3,07 (1H, m), 3,24-3,39 (3H, m), 3,87-4,13 (2H, m), 6,54 (1H, d, J=8,2 Hz), 6,57 (1H, d, J=8,2 Hz), 7,22 (1H, d, J=8,2 Hz), 7,28 (1H, s), 7,43 (1H, s a), 8,87 (1H, s a), 9,27 (1H, s a)
2-64		445,01	409	A	B	(500 MHz, DMSO-d_6): 0,84 (2H, d, J=6,9 Hz), 0,85 (2H, d, J=6,6 Hz), 1,20-1,33 (3H, m), 1,66-1,74 (3H, m), 1,75-1,95 (5H, m), 2,87 (1H, m), 3,10 (1H, m), 3,22-3,47 (4H, m), 3,90 (1H, d, J=6,3 Hz), 3,94-4,02 (2H, m), 6,55 (1H, dd, J=8,2 Hz), 6,58 (1H, d, J=8,2 Hz), 7,23 (1H, t, J=8,2 Hz), 7,32 (1H, s), 7,48 (1H, s a), 8,98 (1H, m), 9,24 (1H, m)

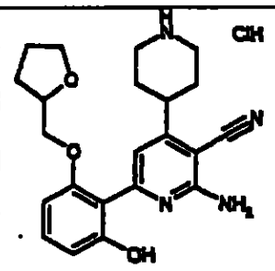
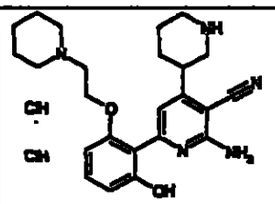
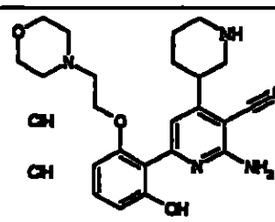
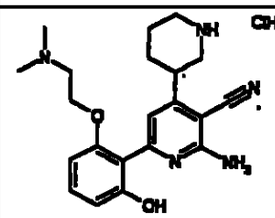
2-65		400,91	365	A	A	(500 MHz, DMSO-d_6): 0,33-0,37 (2H, m), 0,62-0,59 (2H, m), 1,30 (1H, m), 1,67 (1H, m), 1,82 (1H, m), 1,91-1,98 (2H, m), 2,07 (1H, m), 2,88 (1H, m), 3,11 (1H, m), 3,26-3,32 (2H, m), 3,85 (2H, d, J=6,9 Hz), 6,53 (1H, d, J=8,5 Hz), 6,54 (1H, d, J=8,2 Hz), 7,23 (1H, dd, J=8,2, 8,5 Hz), 7,37 (1H, s a), 7,54 (1H, s), 8,94 (1H, m), 9,43 (1H, m)
2-66		430,98	395	A	A	(500 MHz, DMSO-d_6): 0,83 (6H, d, J=6,6 Hz), 1,03 (2H, d, J=6,6 Hz), 1,18-1,22 (2H, m), 1,51-1,53 (1H, m), 1,72-1,77 (3H, m), 1,93-1,95 (4H, m), 2,84-2,85 (1H, m), 3,06-3,22 (3H, m), 3,34-3,37 (2H, m), 3,99 (1H, t, J=6,6 Hz), 6,55-6,59 (2H, m), 7,21-7,26 (2H, m), 9,03-9,12 (1H, s a)
2-67		388,90	353	A	A	(500 MHz, DMSO-d_6): 0,92 (3H, t, J=7,25 Hz), 1,77 (2H, m), 1,90-1,98 (2H, m), 3,06-3,13 (3H, m), 3,38-3,40 (2H, m), 3,97 (2H, t, J=6,3 Hz), 6,57 (2H, dd, J=10,0, 8,3 Hz), 7,23-7,27 (2H, m), 9,06 (2H, s a)
2-68		414,94	379	A	A	(500 MHz, DMSO-d_6): 1,70-1,76 (2H, m), 1,79-1,92 (4H, m), 1,95-1,98 (2H, m), 2,00-2,07 (2H, m), 2,77 (1H, m), 3,07-3,14 (3H, m), 3,39-3,41 (2H, m), 4,00 (2H, d, J=6,6 Hz), 6,56 (1H, d, J=8,2 Hz), 6,60 (1H, d, J=8,2 Hz), 7,19 (1H, s), 7,24 (1H, t, J=8,2 Hz), 7,51 (1H, s a),

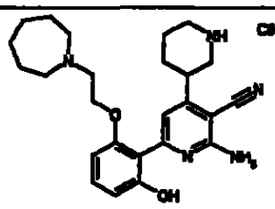
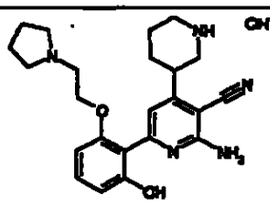
						9,03 (2H, s a)
2-69		416,96	381	A	A	(500 MHz, DMSO-d_6): 0.85 (3H, dd, J=6,6, 7,2 Hz), 1,31-1,33 (4H, m), 1,74-1,78 (2H, m), 1,83-1,91 (2H, m), 1,94-1,99 (2H, m), 3,08-3,12 (3H, m), 3,37-3,39 (2H, m), 4,00 (2H, dd, J=6,3, 6,6 Hz), 6,53 (1H, d, J=8,2 Hz), 6,58 (1H, d, J=8,5 Hz), 7,22 (1H, dd, J=8,2, 8,5 Hz), 7,29 (1H, s), 7,30 (1H, s a), 8,75 (1H, s a), 8,83 (1H, s a)
2-70		457,02	421	A	A	(500 MHz, DMSO-d_6): 0,86-0,93 (2H, m), 1,09-1,23 (3H, m), 1,34 (1H, m), 1,59-1,67 (7H, m), 1,86-1,99 (4H, m), 3,08-3,13 (3H, m), 3,36-3,38 (2H, m), 4,04 (2H, dd, J=6,6, 6,9 Hz), 6,54 (1H, d, J=8,2 Hz), 6,60 (1H, d, J=8,5 Hz), 7,23 (1H, dd, J=8,2, 8,5 Hz), 7,24 (1H, s), 7,36 (1H, s a), 8,91 (2H, s a)
2-71		402,93	367	A	A	(500 MHz, DMSO-d_6): 0.92 (6H, d, J=6,6 Hz), 1,83-1,92 (2H, m), 1,94-1,97 (2H, m), 2,08 (1H, dq, J=6,6 Hz), 3,04-3,13 (3H, m), 3,38-3,41 (2H, m), 3,78 (2H, d, J=6,6 Hz), 6,54 (1H, d, J=8,2 Hz), 6,57 (1H, d, J=8,5 Hz), 7,22 (1H, s), 7,23 (1H, dd, J=8,2, 8,5 Hz), 7,38 (1H, s a), 8,86 (1H, s a), 8,95 (1H, s a)

2-72		402,93	367	A		(500 MHz, DMSO-d_6): 0,89 (3H, dd, J=7,3, 7,6 Hz), 1,37 (2H, dq, J=7,3, 7,6 Hz), 1,75 (2H, dd, J=6,6, 6,9 Hz), 1,86-1,97 (4H, m), 3,06-3,13 (3H, m), 3,37-3,40 (2H, m), 4,02 (2H, t, J=6,6 Hz), 6,54 (1H, d, J=8,2 Hz), 6,59 (1H, d, J=8,2 Hz), 7,23 (1H, t, J=8,2 Hz), 7,28 (1H, s), 7,47 (1H, s a), 8,96 (2H, s a)
2-73		445,01	409	A	A	(300 MHz, DMSO-d_6): 0,84 (3H, t, J=6,8 Hz), 1,22-1,27 (8H, m), 1,73-1,78 (2H, m), 1,87-1,94 (4H, m), 3,07-3,11 (3H, m), 3,35-3,40 (2H, m), 4,01 (2H, t, J=6,4 Hz), 6,54 (1H, d, J=8,3 Hz), 6,58 (1H, d, J=7,9 Hz), 7,23 (1H, dd, J=7,9, 8,3 Hz), 7,28 (1H, s), 7,33 (1H, s a), 8,90 (2H, s a).
2-74		386,88	351	A	A	(300 MHz, DMSO-d_6): 1,78-1,98 (4H, m), 3,06-3,10 (3H, m), 3,38-3,42 (2H, m), 4,61 (2H, d, J=5,3 Hz), 5,29 (1H, dd, J=1,5 10,6 Hz), 5,36 (1H, dd, J=1,5 17,3 Hz), 6,11 (1H, ddt, J=5,3, 10,6, 17,3 Hz), 6,55 (1H, d, J=8,3 Hz), 6,59 (1H, d, J=7,9 Hz), 7,23 (1H, dd, J=7,9, 8,3 Hz), 7,27 (1H, s), 7,33 (1H, s a), 8,74 (2H, s a)

2-75		374,87	339	A	A	(300 MHz, DMSO-d_6): 1,40 (3H, t, J=7,2 Hz), 1,80-2,01 (4H, m), 1,80-2,01 (4H, m), 3,08-3,10 (3H, m), 3,39-3,43 (2H, m), 4,08 (2H, q, J=6,8 Hz), 6,53 (1H, d, J=7,9 Hz), 6,57 (1H, d, J=8,3 Hz), 7,23 (1H, dd, J=7,9, 8,3 Hz), 7,34 (1H, s a), 7,40 (1H, a), 8,80 (2H, s a)
2-76		430,98	395	A	A	(300 MHz, DMSO-d_6): 0,36 (3H. t. J=6,8 Hz), 1,25-1,34 (7H, m), 1,71-1,78 (2H, m), 1,82-1,91 (2H, m), 1,94-1,98 (2H, m), 3,05-3,37 (4H, m), 4,01 (2H, t, J=6,4 Hz), 6,52 (1H, d, J=8,3 Hz), 6,58 (1H, d, J=7,9 Hz), 7,20 (1H, s a), 7,22 (1H, dd, J=7,9, 8,3 Hz), 7,30 (1H, s), 8,61 (1H, s a), 8,75 (1H, s a)
2-77		444,97	409	A	A	(500 MHz, DMSO-d_6): 1,20 (9H. s), 1,81-1,97 (5H, m), 2,98 (1H, m), 3,26-3,31 (2H, m), 3,42 (1H, m), 5,20 (2H, s), 6,55 (1H, d, J=8,2 Hz), 6,61 (1H, d, J=8,2 Hz), 7,25 (1H, t, J=8,2 Hz), 7,36 (2H, s a), 8,13 (1H, s), 8,81 (1H, s a), 9,27 (1H, s a)
2-78		444,97	409	A	A	(300 MHz, DMSO-d_6): 1,17 (9H, s), 1,86-1,95 (4H, m), 3,07-3,10 (3H, m), 3,35-3,40 (2H, m), 5,22 (2H, s), 6,44 (1H, d, J=8,3 Hz), 6,53 (1H, d, J=8,3 Hz), 7,18 (1H, t, J=8,3 Hz), 7,21 (1H, s a), 7,46 (1H, s a), 8,77 (1H, s a)

2-79		522,53	409	A	A	(500 MHz, DMSO-d_6): 1,21-1,30 (2H, m), 1,43-1,51 (3H, m), 1,61 (1H, m), 1,67-1,82 (4H, m), 1,91-1,97 (2H, m), 2,89 (1H, m), 3,05 (1H, m), 3,22 (1H, m), 3,35-3,43 (3H, m), 3,91 (1H, m), 3,96 (1H, m), 6,52 (1H, d, J=8,5 Hz), 6,58 (1H, d, J= 8,5 Hz), 7,22 (1H, t, J= 8,2 Hz), 7,28 (2H, s a), 7,38 (1H, s), 8,67 (1H, s a), 8,88 (1H, s a)
2-80		508,50	395	A	A	(500 MHz, DMSO-d_6): 1,61 (1H, m), 1,66-1,81 (4H, m), 1,85 (1H, m), 1,90-2,04 (4H, m), 2,80 (1H, m), 3,12 (1H, m), 3,23 (1H, m), 3,40 (1H, m), 3,76 (1H, m), 3,87 (1H, m), 4,03 (1H, dd, J=2,8, 3,1 Hz), 4,27 (1H, m), 6,52 (1H, d, J=8,2 Hz), 6,55 (1H, d, J=8,5 Hz), 7,24 (1H, dd, J=8,2, 8,5 Hz), 7,29 (2H, s a), 7,61 (1H, a), 8,62 (1H, s a), 8,92 (1H, s a)
2-81		430,94	395	A	A	(500 MHz, DMSO-d_6): 1,61 (1H, m), 1,71 (1H, m), 1,76-1,86 (3H, m), 1,87-2,03 (3H, m), 2,78 (1H, m), 3,13 (1H, m), 3,25-3,35 (3H, m), 3,75-3,80 (2H, m), 3,88 (1H, m), 4,03 (1H, m), 4,27 (1H, m), 7,51 (1H, d, J=8,2 Hz), 7,56 (1H, d, J=8,2 Hz), 7,24 (1H, t, J=8,2 Hz), 7,53 (1H, s a), 7,58 (1H, s), 8,93 (1H, m), 9,53 (1H, m)

2-82		430,94	395	A	A	(300 MHz, DMSO-d_6): 1,59 (1H, m), 1,76-1,97 (7H, m), 3,07-3,10 (3H, m), 3,37-3,41 (2H, m), 3,70 (2H, dd, J=6,8, 14,7 Hz), 3,92 (1H, dd, J=6,8, 7,2 Hz), 4,01 (1H, dd, J=6,8, 7,2 Hz), 4,22 (1H, m), 6,54 (1H, d, J=8,3 Hz), 6,58 (1H, d, J=8,3 Hz), 7,20 (1H, s a), 7,22 (1H, t, J=8,3 Hz), 7,34 (1H, s), 8,74 (1H, s a), 8,92 (1H, s a)
2-83		494,47	422	B	B	(500 MHz, DMSO-d_6): 1,26-1,38 (1H, m), 1,65-1,93 (10H, m), 2,84-3,39 (8H, m), 4,36-4,43 (3H, m), 6,61 (2H, d, J=8,2 Hz), 7,05 (1H, a), 7,22-7,26 (3H, m), 8,78-8,85 (1H, m), 9,38 (1H, d a, J=10,1 Hz), 10,56 (1H, s a)
2-84		496,44	424	A	B	(500 MHz, DMSO-d_6): 1,71-1,93 (5H, m), 2,95-3,47 (12H, m), 3,75 (1H, s a), 4,36-4,44 (2H, s a), 6,61 (2H, d, J=8,2 Hz), 7,01 (1H, a), 7,16 (2H, s a), 7,23 (1H, t, J=8,4 Hz), 8,76-8,85 (1H, m), 9,29 (1H, d a, J=10,4 Hz), 11,34 (1H, s a)
2-85		417,94	382	B	B	(500 MHz, DMSO-d_6): 1,68-1,83 (2H, m), 1,92 (2H, m), 2,73 (6H, d, J=4,4 Hz), 2,97 (1H, m), 3,17-3,19 (3H, m), 3,22-3,39 (3H, m), 4,36 (2H, a), 6,61 (1H, d, J=8,5 Hz), 6,63 (1H, d, J=8,2 Hz), 7,09 (1H, s), 7,21 (1H, s a), 7,25 (1H, dd, J=8,2, 8,5 Hz), 8,80 (1H, s), 9,37 (1H, s a), 10,6 (1H, s a)

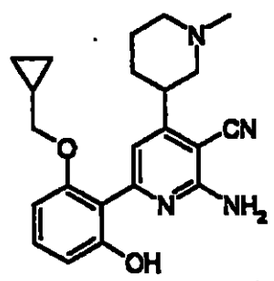
2-86		472,04	436	C	B	(500 MHz, DMSO-d_6): 1,53-1,54 (2H, m), 1,62-1,64 (2H, m), 1,67-1,84 (6H, m), 1,91-1,92 (2H, m), 2,97 (1H, m), 3,05-3,10 (2H, m), 3,17-3,25 (2H, m), 3,29-3,45 (6H, m), 4,39 (2H, a), 6,60 (1H, d, J=8,2 Hz), 6,61 (1H, d, J=8,2 Hz), 7,05 (1H, s), 7,18 (1H, s a), 7,24 (1H, t, J=8,2 Hz), 8,77 (1H, s a), 9,30 (1H, s a), 10,6 (1H, s a)
2-87		443,98	408	C	B	(500 MHz, DMSO-d_6): 1,72-1,85 (5H, m), 1,90-1,93 (3H, m), 2,91-3,17 (3H, m), 3,21-3,39 (4H, m), 3,43-3,44 (2H, m), 3,50-3,51 (2H, m), 4,36 (2H, a), 6,62 (1H, d, J=8,5 Hz), 6,65 (1H, d, J=8,2 Hz), 7,15 (1H, a), 7,26 (1H, dd, J=8,2, 8,5 Hz), 7,53 (1H, s a), 9,00 (1H, s a), 9,64 (1H, s a), 11,2 (1H, s a)

Ejemplo 3-1

(1) Utilizando el compuesto de partida 1G, 2B y otros materiales, se preparó clorhidrato de 2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil-)nicotinonitrilo de manera similar a la descrita en el ejemplo 2-3.

(2) A una solución agitada de clorhidrato de 2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)nicotinonitrilo (200,0 mg, 0,50 mmol) en MeOH, se añadieron formaldehído (0,5 ml) y cianoborohidruro de sodio (40,8 mg, 0,65 mmol) y se agitó durante 2 horas a temperatura ambiente. Se inactivó la reacción mediante la adición de agua, se extrajo con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se

evaporó. Se trituró el residuo con hexano y se secó. Se purificó el producto bruto mediante TLC preparativa sobre gel de silice (MeOH al 5% en diclorometano), proporcionando 2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(1-metil-3-piperidinil)nicotinonitrilo en forma de un sólido amarillo (28,5 mg, rendimiento: 15%).



Peso molecular: 378,48

Espectrometría de masas: 379 $(M + H)^+$

Grado de actividad in vitro: A

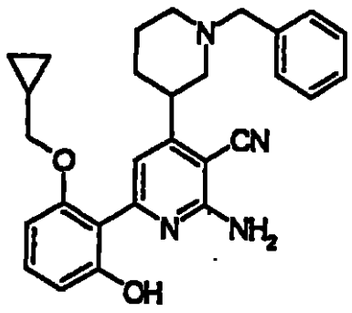
Grado de actividad celular: (A549)A

RMN de ^1H (300 MHz, CDC13): 0,37 - 0,42 (2H, m), 0,67 - 0,73 (2H, m), 0,82 - 0,88 (1H, m), 1,27 - 1,35 (1H, m), 1,76 - 2,09 (4H, m), 2,31 (3H, s), 2,91 - 3,00 (2H, m), 3,14 - 3,23 (1H, m), 3,86 (2H, pent, J= 8,8 Hz), 5,15 (2H, s a), 6,39 (1H, d, J= 8,3 Hz), 6,62 (1H, d, J= 8,3 Hz), 7,20 (1H, t, J=8,3 Hz), 7,95 (1H, s).

Ejemplo 3-2

A una solución agitada de clorhidrato de 2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)nicotinonitrilo (200,0 mg, 0,50 mmol), que se obtuvo en la etapa (1) del ejemplo 3-1, en MeOH, se añadió benzaldehído (0,25 ml, 2,49 mmol), seguido de cianoborohidruro de sodio (40,8 mg, 0,65 mmol) y se continuó la agitación

durante 2 horas a temperatura ambiente. Se inactivó la reacción mediante la adición de agua, se extrajo con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se evaporó. Se trituró el residuo con hexano y se secó. Se purificó el producto bruto mediante TLC preparativa sobre gel de sílice (MeOH al 5% en diclorometano), proporcionando 2-amino-4-(1-bencil-3-piperidinil)-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]nicotinonitrilo en forma de un sólido amarillo (35,7 mg, rendimiento: 16%).



Peso molecular: 454,58

Espectrometría de masas: 455 $(M + H)^+$

Grado de actividad in vitro: C

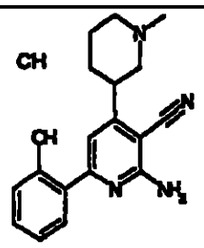
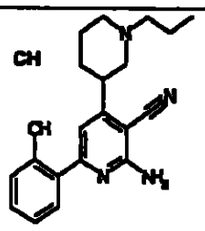
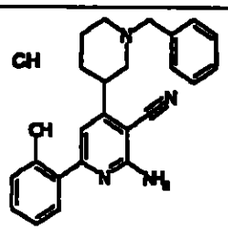
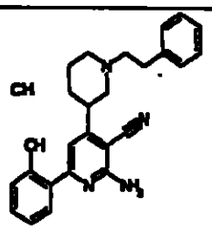
Grado de actividad celular: (A549)C

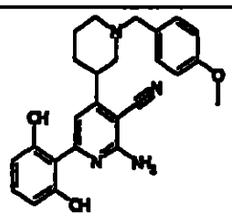
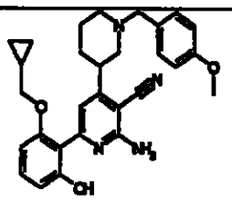
RMN de ^1H (300 MHz, CDC13): 0,35 - 0,37 (2H, m), 0,62 - 0,64 (2H, m), 0,83 - 1,29 (2H, m), 1,75 - 2,21 (5H, m), 2,93 - 3,24 (3H, m), 3,50 - 3,61 (2H, m), 3,78 - 3,88 (2H, m), 5,12 (2H, s a), 6,39 (1H, d, J= 8,3 Hz), 6,60 (1H, d, J= 8,3 Hz), 7,16 - 7,32 (6H, m), 7,93 (1H, s), 13,33 (1H, s a).

Ejemplos 3-3 a 3-8

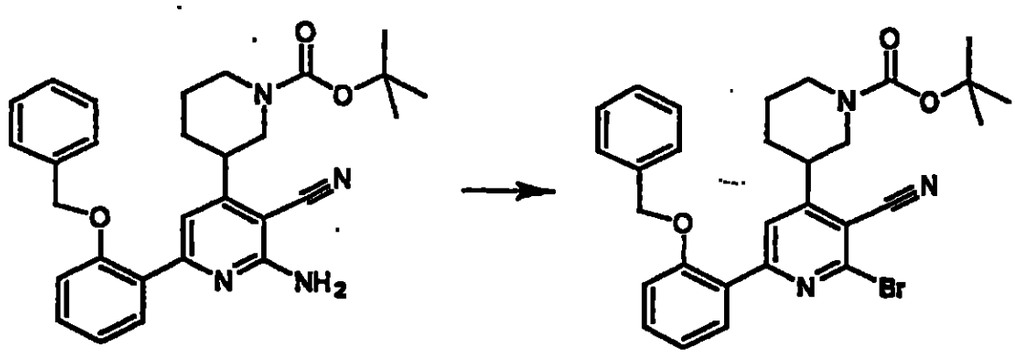
Según un procedimiento sintético similar al de los ejemplos 3-1 a 3-2, se prepararon los compuestos mostrados en la tabla 3.

Tabla 3

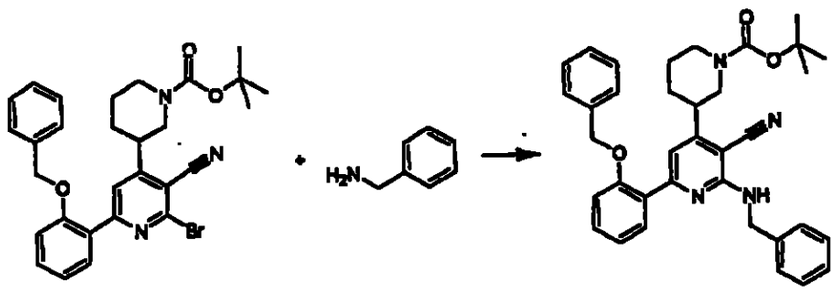
Ej. Nº	Estructura	Peso molecular	Masa	*In vitro*	A549	RMN
3-03		344,85	309	A	A	(500 MHz, DMSO-d_6): 1,70-1.96 (4H, m), 2,73 (3H, d, J=1,8 Hz), 2,93-2,98 (1H, m), 3,35-3,49 (4H, m), 6,90-6,95 (2H, m), 7,33-7,46 (3H, m), 8,02 (1H, dd, J=8,5, 1,3 Hz), 10,62 (1H, s a)
3-04		372,90	337	A	B	(300 MHz, DMSO-d_6): 0.92 (3H. t. J=7,4 Hz), 1,71-1,76 (3H, m), 1,81-1,98 (3H, m), 2,92-3,04 (3H, m), 6,90-6,95 (2H, m), 7,34-7,38 (2H, m), 7,45 (1H, s a), 8,01 (1H, d, J=7,4 Hz), 9,80 (1H, s a)
3-05		420,95	385	A	A	(300 MHz, DMSO-d_6): 1,81-1,96 (4H, m), 2,72-2,73 (1H, m), 3,31-3,50 (4H, m), 4,26-4,35 (2H, m), 6,89-6,95 (2H, m), 7,34-7,51 (6H, m), 7,59-7,62 (2H, m), 8,00-8,02 (1H, m), 10,57 (1H, s a)
3-06		434,97	399	B	B	(300 MHz, DMSO-d_6): 1,78-2,01 (5H, m), 3,04-3,15 (4H, m), 3,30-3,67 (2H, m), 6,90-6,95 (2H, m), 7,24-7,49 (11H, m), 8,03 (1H, d, J=7,5 Hz), 10,58 (1H, s a)

3-07		430,51	431	A	B	(500 MHz, DMSO-d_6): 1,39 (1H, dd, J=3,5, 11,7 Hz), 1,59 (1H, m), 1,73 (1H, d, J=12,9 Hz), 1,88 (1H, d, J=11,7 Hz), 1,95 (1H, t, J= 10,4 Hz), 2,02 (1H, t, J=11,0 Hz), 2,84 (1H, d, J=11,0 Hz), 2,89 (1H, d, J=10,4 Hz), 2,97 (1H, t, J=11,0 Hz), 3,45 (2H, m), 3,72 (3H, s), 6,36 (2H, d, J=8,2 Hz), 6,86 (2H, d, J=8,5 Hz), 7,06 (1H, t, J=8,2 Hz), 7,16 (2H, a), 7,21 (1H, d, J=8,5 Hz), 7,78 (1H, s), 11,91 (2H, s)
3-08		484,60	485	C	C	(300 MHz, DMSO-d_6): 0,33-0,38 (2H, m), 0,60-0,66 (2H, m), 1,24-2,21 (8H, m), 2,94-3,25 (2H, m), 3,52 (2H, s a), 3,79-3,84 (5H, m), 5,16 (2H, s a), 6,39 (1H, d, J=8,3 Hz), 6,60 (1H, d, J=8,3 Hz), 6,84 (2H, d, J=8,7 Hz), 7,16-7,26 (3H, m), 7,93 (1H, s)

Ejemplo 4-1

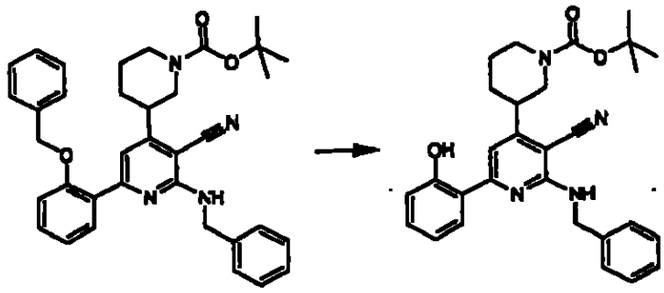


(1) Se agitó a 65°C durante 15 minutos una mezcla de bromuro de cobre (II) (1,106 g, 4,593 mmol) y nitrito de *terc*-butilo (0,736 ml, 6,191 mmol) en acetonitrilo (30 ml). Se añadió gota a gota a la mezcla una solución de 3-{2-amino-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (2,000 g, 4,127 mmol) que se obtuvo en la etapa (1) del ejemplo 1-1, en acetonitrilo (20 ml). Se agitó la mezcla a 65°C durante 2 horas. Después de enfriar hasta temperatura ambiente se diluyó la mezcla de reacción con acetato de etilo. Se lavó la fase orgánica separada con una solución acuosa de HCl 1 N y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. Se recristalizó el residuo en éter dietílico proporcionando 3-{2-bromo-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo en forma de un sólido blanco (1,010 g, rendimiento: 45%).

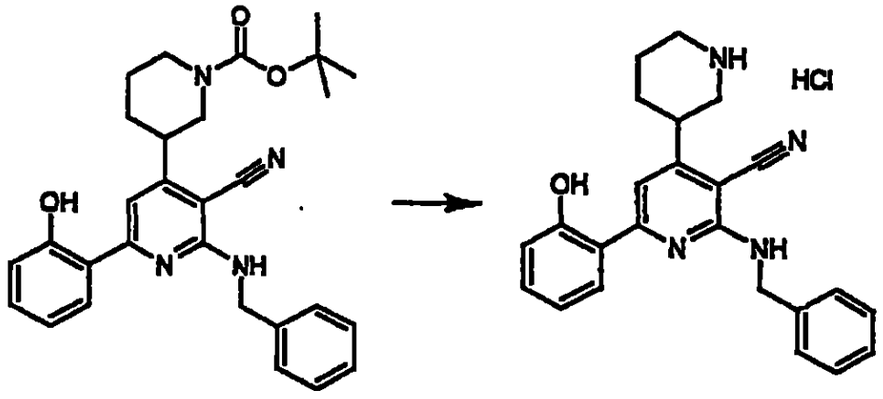


(2) A una solución agitada de 3-{6-[2-(benciloxi)fenil]-2-bromo-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,300 g, 0,547 mmol) en DMSO, se añadieron trietilamina (0,229 ml, 1,341 mmol) y bencilamina (0,147 g, 1,367 mmol). Se agitó la mezcla a 70°C durante 12 horas. Después de enfriar hasta temperatura ambiente se inactivó la mezcla de reacción con agua y se extrajo con acetato de etilo. Se lavó la fase orgánica separada con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo: 4/1-2/1), proporcionando 3-{6-[2-(benciloxi)fenil]-2-bencilamino-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo en forma de un

sólido amorfo amarillo (0,290 g, rendimiento: 92%).



(3) Se retiró a continuación el resto bencilo de la misma manera que se describió en la etapa (2) del ejemplo 1-1. Se suspendió el residuo en etanol y se filtró, proporcionando 3-[2-(bencilamino)-3-ciano-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo en forma de un sólido blanco (0,150 g, rendimiento: 61%).



(4) Se trató 3-[2-(bencilamino)-3-ciano-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,145 g, 0,299 mmol) en condiciones ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1. Se recogió el sólido resultante por filtración y se secó a presión reducida, proporcionando clorhidrato de 2-(bencilamino)-6-(2-hidroxifenil)-4-(3-piperidinil)nicotinonitrilo (0,075 g, rendimiento: 60%).

Peso molecular: 420,95

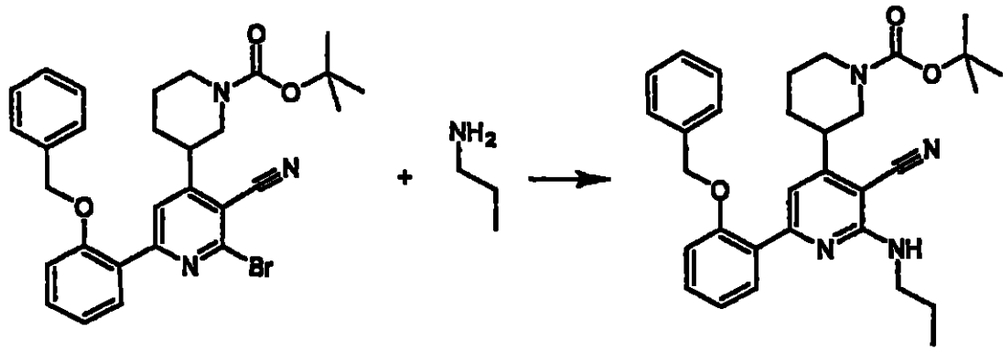
Espectrometría de masas: 385 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-B/Jurkat-B

RMN de ^1H (300 MHz, MSO-d6): 1,80 - 1,92 (4H, m), 2,90 - 2,93 (1H, m), 3,31 - 3,40 (4H, m), 4,59 (2H, d, J=5,6 Hz), 6,84 - 6,92 (2H, m), 7,19 - 7,31 (5H, m), 7,47 (1H, s), 8,00 (1H, d, J=6,8 Hz), 8,11 - 8,15 (1H, m), 8,91 (1H, s a), 9,52 (1H, s a), 12,59 (1H, s a), 12,90 (1H, s a).

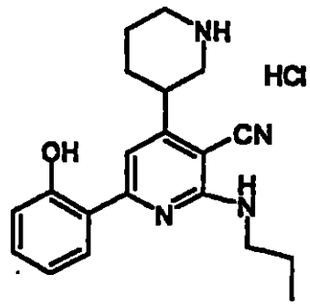
Ejemplo 4-2



A una solución agitada de 3-{6-[2-(benciloxi)fenil]-2-bromo-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,100 g, 0,182 mmol), que se obtuvo en la etapa (1) del ejemplo 4-1, en DMSO (2 ml), se añadieron propilamina (0,108 g, 1,823 mmol) y trietilamina (0,038 ml, 0,273 mmol). Se agitó la mezcla a 40°C durante 12 horas. Se inactivó la reacción con agua y se extrajo la mezcla de reacción resultante con acetato de etilo. Se secó la fase orgánica sobre Na_2SO_4, se filtró y se concentró. Se purificó el concentrado mediante columna de gel de sílice (hexano/acetato de etilo= 4/1), proporcionando 3-{6-[2-(benciloxi)fenil)]-3-ciano-2-propilamino-4-piridinil}-1-piperidincarboxilato de *terc*-butilo en forma de un aceite incoloro (0,104 g, rendimiento: cuantitativo).

A continuación se retiró el resto bencilo de la misma manera que se describió en la etapa (2) del ejemplo 1-1. Se lavó el residuo con éter dietílico, proporcionando el producto deseado en forma de un sólido blanco (0,112 g, rendimiento: cuantitativo).

A continuación se trató 3-[3-ciano-6-(2-hidroxifenil)-2-(propilamino)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,110 g, 0,252 mmol) en condiciones ácidas de la misma manera que se describió en la etapa (3) del ejemplo 1-1. Se recogió el sólido resultante por filtración y se secó a presión reducida, proporcionando clorhidrato de 6-(2-hidroxifenil)-4-(3-piperidinil)-2-(propilamino)nicotinonitrilo (0,062 g, rendimiento: 66%).



Peso molecular: 372,90

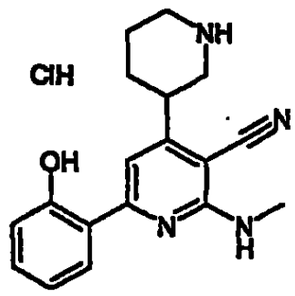
Espectrometría de masas: 337$(M + H)^+$

Grado de actividad in vitro: C

Grado de actividad celular: (A549)-C

RMN de ^1H (300 MHz, DMSO-d_6): 0,92 (3H, t, J=7,4 Hz), 1,62 (2H, m), 1,80 - 1,95 (4H, m), 2,89 - 2,93 (1H, m), 3,33 - 3,46 (6H, m), 6,91 - 6,97 (2H, m), 7,34 - 7,40 (1H, m), 7,48 (1H, a), 7,57 (1H, s a), 8,08 - 8,17 (1H, m), 8,97 - 9,07 (1H, m), 9,67 - 9,71 (1H, m).

Ejemplo 4-3



De manera similar a la del ejemplo 4-2, se preparó clorhidrato de 6-(2-hidroxifenil)-2-metilamino)-4-(3-piperidinil)nicotinonitrilo.

Peso molecular: 344,85

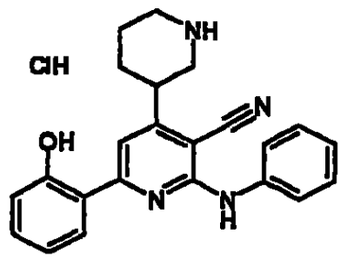
Espectrometría de masas: 309 $(M + H)^+$

Grado de actividad in vitro: C

Grado de actividad celular: (A549)-C

RMN de ^1H (300 MHz, DMSO-d_6): 1,83 - 1,96 (4H, m), 3,31 (4H, s), 3,30 - 3,56 (4H, m), 6,90 - 6,96 (2H, m), 7,34 - 7,37 (1H, m), 7,39 (1H, s), 7,55 (1H, s a), 8,10 (1H, d, J=7,9 Hz), 8,87 - 8,90 (1H, m), 9,52 - 9,54 (1H, m), 13,80 (1H, s a).

Ejemplo 4-4



De manera similar a la del ejemplo 4-2, se preparó clorhidrato de 2-anilino-6-(2-hidroxifenil)-4-(3-piperidinil)nicotinonitrilo.

Peso molecular: 406,92

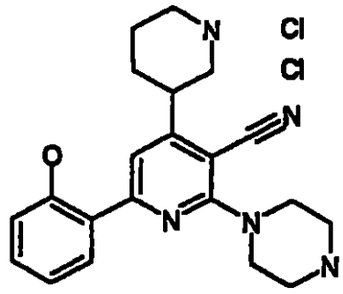
Espectrometría de masas: 371$(M + H)^+$

Grado de actividad in vitro: D

Grado de actividad celular: (A549)-B

RMN de ^1H (300 MHz, DMSO-d_6): 1,87 - 2,00 (4H, m), 2,91 - 2,95 (1H, m), 3,34 (1H, m), 6,79 (1H, d, J=8,3 Hz), 6,91 (1H, t, J=7,2 Hz), 7,18 - 7,44 (1H, s a), 7,66 (1H, s), 8,06 (1H, d, J=6,8 Hz), 8,84 (1H, m), 9,43 (2H, m), 12,42 (1H, s a).

Ejemplo 4-5



De manera similar a la del ejemplo 4-2, se preparó diclorhidrato de 6-(2-hidroxifenil)-2-(1-piperazinil)-4-(3-piperidinil)nicotinonitrilo.

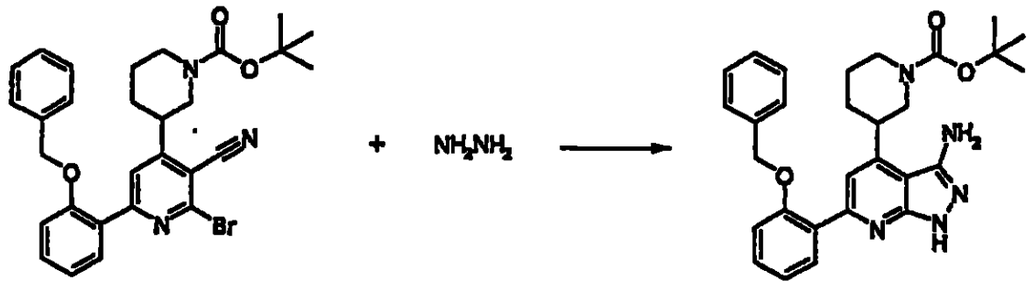
Peso molecular: 436,39

Espectrometría de masas: 364 $(M + H)^+$

Grado de actividad in vitro: D

RMN de ^1H (500 MHz, DMSO-d_6): 1,81 - 1,83 (2H, m), 1,90 - 1,95 (2H, m), 2,93 - 2,95 (1H, m), 3,76 - 3,78 (4H, m), 6,98 (1H, t, J=7,3 Hz), 7,37 - 7,40 (1H, m), 7,84 (1H, s), 8,03 - 8,05 (1H, m), 8,78 - 8,81 (1H, m), 9,14 (1H, s a), 9,24 - 9,27 (1H, m), 12,10 (1H, s).

Ejemplo 5-1

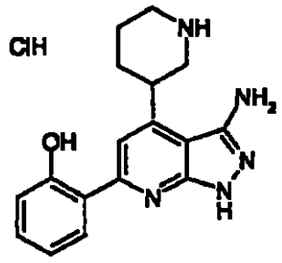


(1) Se agitó a 100°C durante 1,5 horas una mezcla de 3-{6-[2-(benciloxi)fenil]-2-bromo-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,300 g, 0,547 mmol), que se obtuvo en la etapa (1) del ejemplo 4-1, hidrazina monohidratada (3 ml) y 1,4-dioxano (1 ml). Se inactivó la reacción con agua y se extrajo con acetato de etilo. Se lavó la fase orgánica con salmuera y se secó sobre Na_2SO_4, se filtró y se concertró. Se recristalizó el residuo en etanol proporcionando {3-[3-amino-6-(2-benciloxifenil)-1H-pirazolo[3,4-b]piridin-4-il]-1-piperidincarboxilato de *terc*-butilo en forma de un sólido amarillo (0,210 g, rendimiento: 72%).

(2) A continuación se retiró el resto bencilo de la misma manera que se describió en la etapa (2) del ejemplo 1-1. Se purificó el residuo mediante columna de gel de sílice (hexano/acetato de etilo = 2/1 –1/1), proporcionando 3-[3-amino-6-(2-hidroxifenil)-1H-pirazolo[3,4-b]piridin-4-il]-1-piperidincarboxilato de *terc*-butilo en forma de un sólido naranja (0,080 g, rendimiento: 49%).

A una solución agitada de 3-[3-amino-6-(2-hidroxifenil)-1H-pirazolo[3,4-b]piridin-4-il]-1-piperidincarboxilato de *terc*-butilo (0,075 g, 0,183 mmol) en 1,4-dioxano (3 ml), se añadió HCl 4 N en 1,4-dioxano (3 ml). Se agitó la mezcla a temperatura ambiente

durante 12 horas. Se recogió el sólido resultante por filtración proporcionando clorhidrato de 2-[3-amino-4-(3-piperidinil)-1H-pirazolo[3,4-b]piridin-6-il]fenol (0,062 g, rendimiento: 98%).



Peso molecular: 345,83

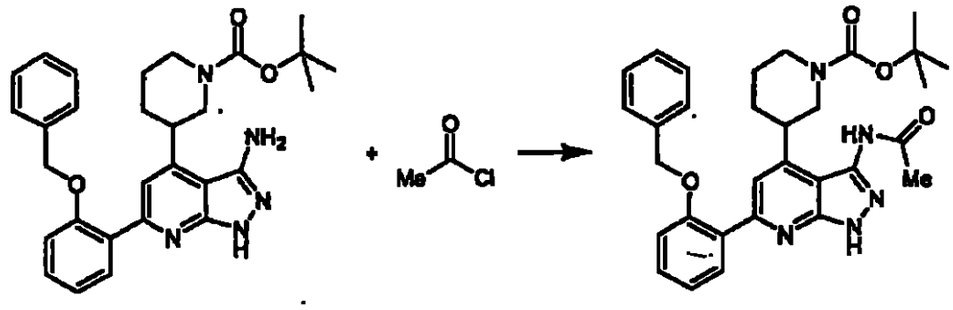
Espectrometría de masas: 310 $(M + H)^-$

Grado de actividad in vitro: C

Grado de actividad celular: A549-B

RMN de ^1H (300 MHz, DMSO-d_6): 1,97 - 2,27 (4H, m), 2,95 - 3,11 (1H, m), 3,12 - 3,23 (1H, m), 3,30 - 3,39 (3H, m), 6,94 - 6,99 (2H, m), 7,32 - 7,38 (1H, m), 7,73 (1H, s), 8,12 (1H, d, J=7,2 Hz).

Ejemplo 5-2

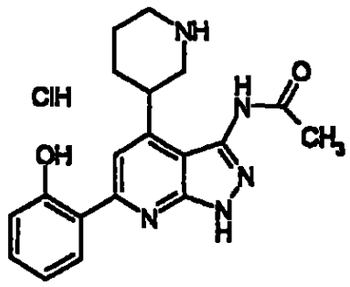


A una solución agitada enfriada (0°C) de 3-{3-amino-6-[2-(benciloxi)fenil]-1H-pirazolo[3,4-b]piridin-4-il}-1-piperidincarboxilato de *terc*-butilo (0,200 g, 0,400 mmol)

obtenido en la etapa (1) del ejemplo 5-1 en THF (3 ml), se añadieron piridina (1 ml) y cloruro de acetilo (0,035 g, 0,440 mmol). Se agitó la mezcla a 0°C durante 1 hora. Se inactivó la reacción con agua y se extrajo con acetato de etilo. Se lavó la fase orgánica con salmuera saturada, se secó sobre Na_2SO_4, se filtró y se concentró. Se recristalizó el residuo con éter diisopropílico proporcionando un sólido blanco (0,180 g, rendimiento: 83%).

A continuación se retiró el resto bencilo de la misma manera que se describió en la etapa (2) del ejemplo 1-1. Se suspendió el residuo en etanol y se filtró, proporcionando el producto deseado en forma de un sólido blanco (0,120 g, rendimiento: 82%).

Se trató 3-[3-(acetilamino)-6-(2-hidroxifenil)-1H-pirazolo[3,4-b]piridin-4-il]-1-piperidincarboxilato de *terc*-butilo (0,115 g, 0,260 mmol) en condiciones ácidas de la misma manera que se describió en la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de N-[6-(2-hidroxifenil)-4-(3-piperidinil)-1H-pirazolo[3,4-b]piridin-3-il]acetamida (0,097 g, rendimiento: 96%).



Peso molecular: 387,87

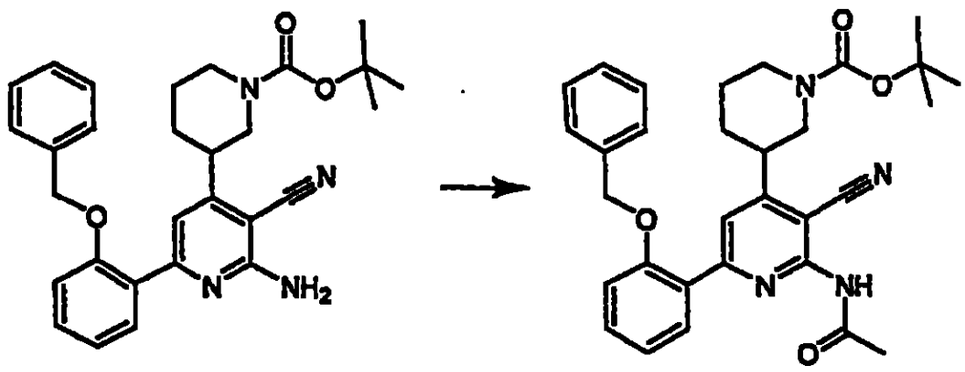
Espectrometría de masas: 352 $(M + H)^+$

Grado de actividad in vitro: D

Grado de actividad celular: A549-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,80 - 1,91 (4H, m), 1,95 (3H, s), 2,82 - 2,92 (1H, m), 3,34 - 3,44 (4H, m), 6,92 - 6,95 (2H, m), 7,36 - 7,39 (1H, m), 7,66 (1H, s), 8,12 (1H, d, J=8,2 Hz), 8,83 - 8,85 (1H, m), 9,48 - 9,49 (1H, m), 9,56 (1H, s), 10,21 (1H, a), 13,59 (1H, s a).

Ejemplo 6-1

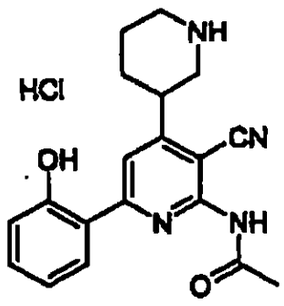


A una solución agitada enfriada (0°C) de 3-{2-amino-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo, que se obtuvo en la etapa (1) de ejemplo 1-1, (0,500 g, 1,032 mmol) en piridina (10 ml), se añadió cloruro de acetilo (0,477 ml, 6,70 mmol). Se agitó la mezcla de 0°C a temperatura ambiente durante 3 horas y se continuó la agitación a temperatura ambiente durante 5 horas. Se inactivó la mezcla de reacción con agua y se extrajo con acetato de etilo. Se secó la fase orgánica sobre Na_2SO_4, se filtró y se concentró. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo: 9/1- 4/1- 2/1), proporcionando una mezcla del producto deseado, 3-{2-(acetilamino)-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo, y el correspondiente compuesto diacilado. Se disolvió la mezcla obtenida en THF (5 ml), se trató con una solución acuosa de NH_3 1N (1 ml) y se agitó a temperatura ambiente durante 1 hora. Se extrajo la

mezcla de reacción con acetato de etilo. Se lavó la fase orgánica con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró, proporcionando 3-{2-(acetilamino)-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo en forma de un sólido amorfo blanco (0,432 g, rendimiento: 80%).

A continuación se retiró el resto bencilo de la misma manera que se describió en la etapa (2) del ejemplo 1-1. Se recristalizó el residuo en etanol proporcionando el producto deseado en forma de un sólido amarillo (0,110 g, rendimiento: 31%).

Se trató 3-[2-(acetilamino)-3-ciano-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,100 g, 0,229 mmol) en condiciones ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1. Se recogió el precipitado resultante por filtración, se lavó con 1,4-dioxano y se secó a presión reducida, proporcionando clorhidrato de N-[3-ciano-6-(2-hidroxifenil)-4-(3-piperidinil)-2-piridinil]acetamida (0,101 g, rendimiento: cuantitativo).



Peso molecular: 372,86

Espectrometría de masas: 337 $(M + H)^+$

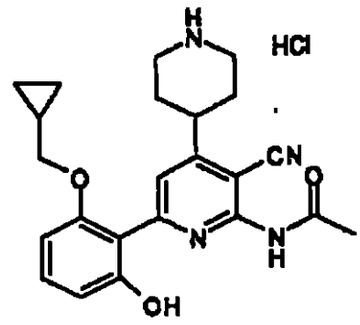
Grado de actividad in vitro: A

Grado de actividad celular: (A549)-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,86 - 1,97 (4H, m), 2,19 (3H, a), 2,91 - 2,94 (1H,

m), 3,33 - 3,47 (4H, m), 6,96 - 6,99 (2H, m), 7,38 - 7,41 (1H, m), 8,11 - 8,13 (2H, m), 8,94 - 8,96 (1H, m), 9,62 - 9,64 (1H, m), 10,97 (1H, s).

Ejemplo 6-2



Utilizando el compuesto de partida 1G y éster *terc*-butílico del ácido 4-formilpiperidin-1-carboxílico y otros materiales, se preparó clorhidrato de N-[3-ciano-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(4-piperidinil)-2-piridinil]acetamida de manera similar a la del ejemplo 6-1.

Peso molecular: 442,95

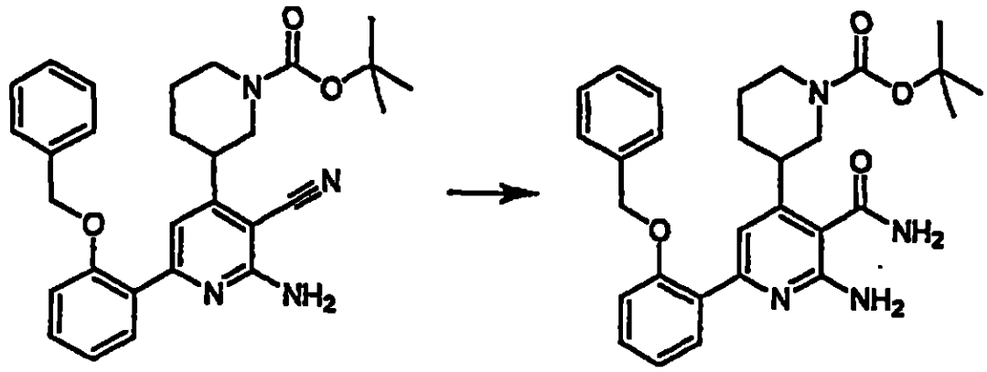
Espectrometría de masas: 407 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,28 - 0,31 (2H, m), 0,55 - 0,58 (2H, m), 1,32 (1H, m), 1,98 - 2,01 (2H, m), 2,16 (3H, s), 3,09 - 3,13 (2H, m), 3,24 - 3,28 (1H, m), 3,40 - 3,42 (2H, m), 3,87 (2H, d, J=6,9 Hz), 6,57 (2H, dd, J=8,5, 2,8 Hz), 7,24 (1H, t, J=8,5 Hz), 7,92 (1H, s), 9,06 - 9,15 (2H, m), 10,93 (1H, s).

Ejemplo 7-1

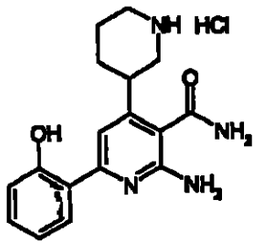


(1) A una suspensión agitada de 3-{2-amino-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,300 g, 0,619 mmol), que se obtuvo en la etapa (1) del ejemplo 1-1, en etanol (10 ml), se añadió una solución de hidróxido de potasio (0,695 g, 12,381 mmol) en etanol (20 ml). Se agitó la mezcla de reacción a 70°C durante 50 horas. Después de enfriar hasta temperatura ambiente se vertió la mezcla de reacción en agua y el sólido resultante se filtró y secó a presión reducida, proporcionando 3-{2-amino-6-[2-(benciloxi)fenil]-3-carbamoil-4-piridinil}-1-piperidincarboxilato de *terc*-butilo en forma de un sólido amorfo blanco (0,226 g, rendimiento: 73%).

(2) A continuación se retiró el resto bencilo de la misma manera que se describió en la etapa (2) del ejemplo 1-1. Se suspendió el residuo en etanol y se filtró proporcionando 3-[2-amino-3-(carbamoil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidin-carboxilato de *terc*-butilo en forma de un sólido blanco (0,045 g, rendimiento: 46%).

(3) Se trató 3-[2-amino-3-(carbamoil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidin-carboxilato de *terc*-butilo (0,040 g, 0,097 mmol) en condiciones ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de 2-amino-6-(2-hidroxifenil)-4-(3-piperidinil)nicotinamida en forma de un sólido amarillo

(0,008 g, rendimiento: 24%).



Peso molecular: 348,84

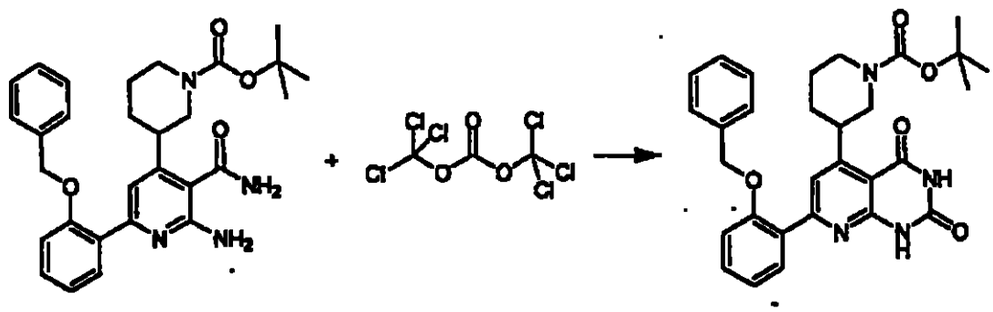
Espectrometría de masas: 313 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-B

RMN de ^1H (300 MHz, DMSO-d_6): 1,68 - 1,92 (4H, m), 2,90 - 2,93 (1H, m), 3,17 - 3,34 (4H, m), 6,89 - 6,97 (2H, m), 7,29 - 7,34 (2H, m), 7,80 - 7,86 (2H, m), 8,09 (1H, s a), 8,80 - 8,82 (1H, m), 9,34 - 9,37 (1H, m).

Ejemplo 7-2

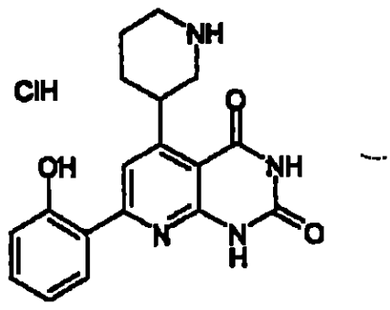


A una solución agitada enfriada (0°C) de 3-{2-amino-6-[2-(benciloxi)fenil]-3-carbamoil-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,400 g, 0,800 mmol), que se obtuvo en la etapa (1) del ejemplo 7-1, en THF (10 ml), se añadieron trietilamina (0,50 ml, 3,58 mmol) seguida de trifosgeno (0,354 g, 1,19 mmol). Se agitó la mezcla de

reacción a temperatura ambiente durante 12 horas. Se inactivó la reacción con agua y se extrajo con acetato de etilo. Se lavó la fase orgánica con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo= 2/1-1/1) y se recristalizó en etanol proporcionando 3-{7-[2-(benciloxi)fenil]-2,4-dioxo-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-5-il}-1-piperidincarboxilato de *terc*-butilo en forma de un sólido blanco (0,406 g, rendimiento: 97%).

A continuación se retiró el resto bencilo de la misma manera que se describió en la etapa (2) del ejemplo 1-1. Se lavó el residuo con etanol proporcionando 3-[7-(2-hidroxifenil)-2,4-dioxo-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-5-il]-1-piperidin-carboxilato de *terc*-butilo en forma de un sólido blanco (0,036 g, 29%).

Se trató 3-[7-(2-hidroxifenil)-2,4-dioxo-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-5-il]-1-piperidincarboxilato de *terc*-butilo (0,036 g, 0,80 mmol) en dioxano (3 ml) en condiciones ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de 7-(2-hidroxifenil)-5-(3-piperidinil)pirido[2,3-d]pirimidin-2,4-(1H,3H)-diona en forma de un sólido amarillo (0,016 g, rendimiento: 52%).



Peso molecular: 374,83

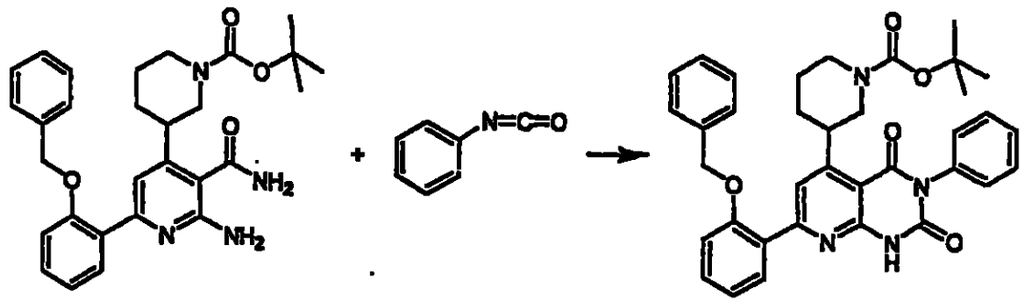
Espectrometría de masas: 339 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-C

RMN de ^1H (500 MHz, DMSO-d_6): 1,78 - 1,83 (2H, m), 1,94 - 1,95 (2H, m), 2,90 - 2,92 (1H, m), 4,68 - 4,69 (1H, m), 6,97 - 6,99 (2H, m), 7,39 - 7,42 (1H, m), 7,85 (1H, a), 8,16 (1H, dd, J=8,4, 1,4 Hz), 8,75 (1H, s a), 9,43 (1H, m), 11,45 (1H, d, J=1,4 Hz), 12,05 (1H, d, J=1,4 Hz), 12,44 (1H, s a).

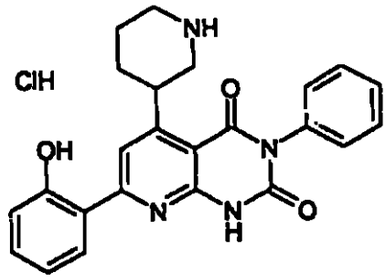
Ejemplo 7-3



A una solución agitada de 3-{2-amino-6-[2-(benciloxi)fenil]-3-carbamoil-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,100 g, 0,199 mmol), que se obtuvo en la etapa (1) del ejemplo 7-1, en éter fenílico (1 ml), se añadió isocianato de fenilo (0,047 g, 0,398 mmol). Se agitó la mezcla a 140°C durante 12 horas. Después de enfriar hasta temperatura ambiente se retiró el sólido resultante (urea) por filtración. Se concentró el filtrado a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice proporcionando 3-[7-(2-benciloxifenil)-2,4-dioxo-3-fenil-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-5-il]-1-piridincarboxilato de *terc*-butilo en forma de un sólido amorfo blanco (0,900 g, rendimiento: 78%).

A continuación se retiró el resto bencilo de la misma manera que se describió en la etapa (2) del ejemplo 1-1. Se lavó el residuo con etanol proporcionando el producto deseado en forma de un sólido blanco (0,600 g, rendimiento: 83%).

Se trató 3-[7-(2-hidroxifenil)-2,4-dioxo-3-fenil-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-5-il]-1-piperidincarboxilato de *terc*-butilo (0,050 g, 0,100 mmol) en condiciones ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de 7-(2-hidroxifenil)-3-fenil-5-(3-piperidinil)pirido[2,3-d]pirimidin-2,4-(1H,3H)-diona en forma de un sólido amarillo (0,016 mg, rendimiento: 37%).



Peso molecular: 450,93

Espectrometría de masas: 415 $(M + H)^+$

Grado de actividad in vitro: B

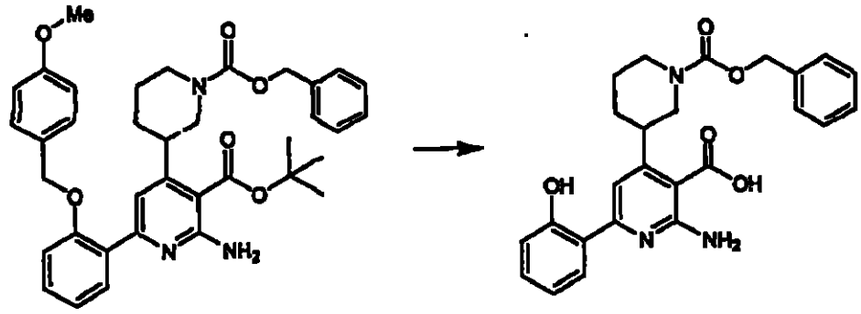
Grado de actividad celular: (A594)-C

RMN de ^1H (300 MHz, DMSO-d_6): 1,71 - 1,96 (4H, m), 2,71 - 2,91 (1H, m), 3,27 - 3,53 (3H, m), 4,56 (1H, m), 6,98 - 7,03 (2H, m), 7,34 - 7,53 (6H, m), 7,89 (1H, s), 8,18 - 8,21 (1H, m), 8,69 - 8,70 (1H, m), 9,24 - 9,25 (1H, m), 12,47 (1H, s).

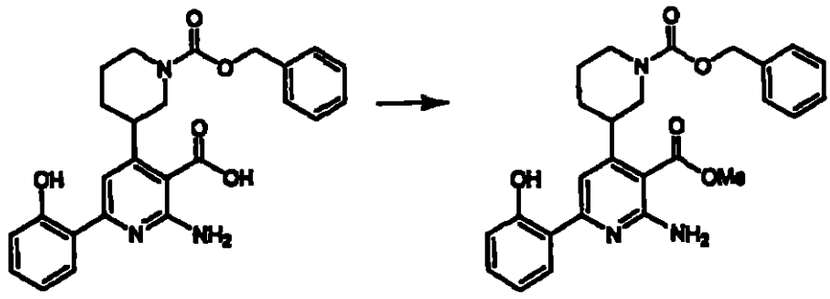
Ejemplo 8-1

(1) Se agitó a reflujo durante 3,5 horas una solución de 1-{2-[(4-

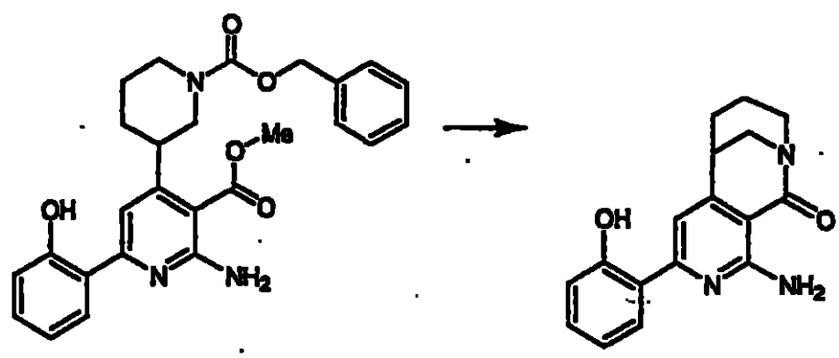
metoxibencil)oxi]fenil}etanona (14,2 g, 55,4 mmol) (compuesto de partida 1D), 3-formil-1-piperidincarboxilato de bencilo (13,7 g, 55,4 mmol) (compuesto de partida 2C), cianoacetato de *terc*-butilo (7,8 g, 55,4 mmol) y acetato de amonio (9,8 g, 166,1 mmol) en 1,2-dimetoxietano (60 ml). Después de enfriar hasta temperatura ambiente, se repartió la mezcla entre acetato de etilo y agua. Se lavó la fase orgánica separada con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (acetato de etilo:hexano 1:2), proporcionando 2-amino-4-{1-[(benciloxi)carbonil]-3-piperidinil}-6-{2-[(4-metoxibencil)oxi]fenil}nicotinato de *terc*-butilo en forma de un aceite amarillo pálido (4,89 g, rendimiento: 14%).



(2) A una solución de 2-amino-4-{1-[(benciloxi)carbonil]-3-piperidinil}-6-{2-[(4-metoxibencil)oxi]fenil}nicotinato de *terc*-butilo (0,95 g, 1,67 mmol) en CH_2Cl_2 (10 ml), se añadió ácido trifluoroacético (10 ml), y se continuó la agitación a temperatura ambiente durante una noche. Se concentró la mezcla a presión reducida. Se diluyó el residuo con tolueno, después se concentró a presión reducida para retirar el exceso de ácido trifluoroacético mediante destilación azeotrópica, proporcionando ácido 2-amino-4-{1-[(benciloxi)carbonil]-3-piperidinil}-6-(2-hidroxifenil)nicotínico (1,1 g, rendimiento; cuantitativo).



(3) A una solución de ácido 2-amino-4-{1-[(benciloxi)carbonil]-3-piperidinil}-6-(2-hidroxifenil)nicotínico (1,1 g, 2,5 mmol) en THF (10 ml) y MeOH (5 ml), se añadió gota a gota trimetilsilildiazometano (4,0 ml) a temperatura ambiente. Se agitó la mezcla de reacción a temperatura ambiente durante 1,5 horas, y se inactivó la reacción con ácido acético. Se repartió la mezcla entre acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo 3:1) seguida de recristalización en una mezcla de CH_2Cl_2 y hexano, proporcionando 2-amino-4-{1-[(benciloxi)carbonil]-3-piperidinil}-6-(2-hidroxifenil)nicotinato de metilo en forma de un sólido amarillo (0,39 g, rendimiento: 34%).



(4) A una solución de 2-amino-4-{1-[(benciloxi)carbonil]-3-piperidinil}-6-(2-hidroxifenil)nicotinato de metilo (60 mg, 0,130 mmol) en metanol (2,0 ml) y THF (1,0

ml), se añadió Pd-C al 10% (200 mg). Se agitó la mezcla a temperatura ambiente en atmósfera de hidrógeno (1 atm) durante 6,5 horas. Se filtró la mezcla a través de celite® y se lavó con MeOH y THF sucesivamente. Se concentró el filtrado a presión reducida. Se purificó el residuo mediante TLC preparativa (hexano:acetato de etilo, 2:1), proporcionando 6-amino-4-(2-hidroxifenil)-5,9-diazatriciclo-[7.3.1.$0^{2,8}$]trideca-2(7),3,5-trien-8-ona en forma de un sólido amarillo (16 mg, rendimiento 40%).

Peso molecular: 295,34

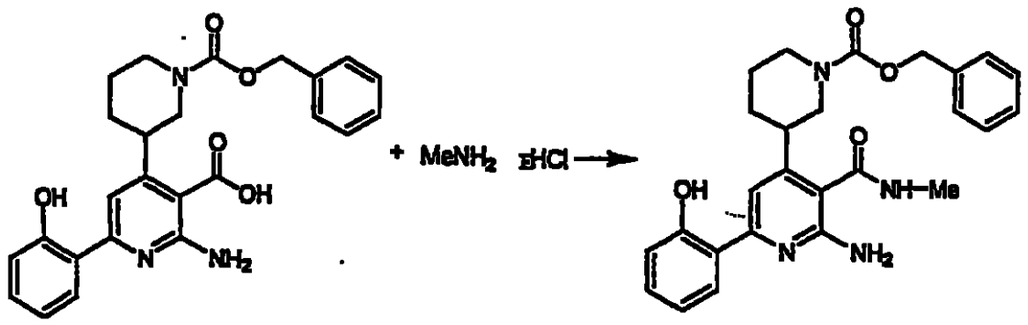
Espectrometría de masas: 296 $(M + H)^+$

Grado de actividad in vitro: B

Grado de actividad celular: (A549)-B

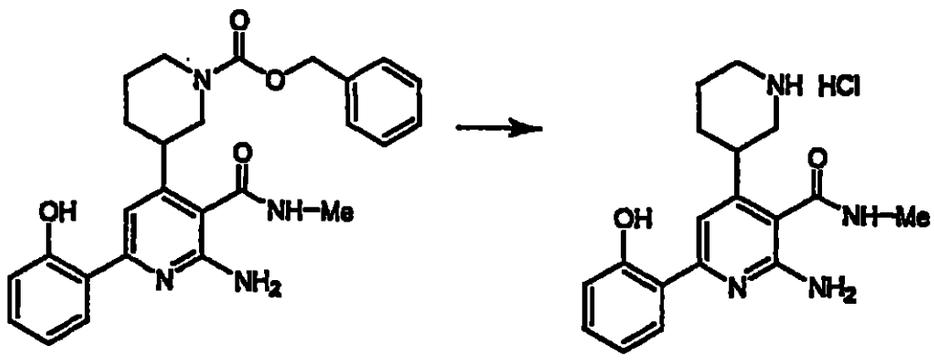
RMN de ^1H (300 MHz, DMSO-d_6): 1,42 (1H, d, J=14,3 Hz), 1,84 (1H, m), 1,92 (1H, d, J=13,6 Hz), 2,17 (1H, m), 2,85 (1H, s), 3,16 (1H, td, J=3,0, 12,7 Hz), 3,35 (1H, dd, J=1,9, 12,2 Hz), 3,63 (1H, d, J=13,2 Hz), 3,92 (1H, dd, J=4,5, 12,8 Hz), 6,88 (1H, td, J=1,1, 8,3 Hz), 6,99 (1H, dd, J=1,1, 8,3 Hz), 7,04 (1H, s), 7,32 (1H, td, J=1,1, 8,3 Hz), 7,75 (1H, dd, J=1,5, 8,0 Hz).

Ejemplo 8-2



A una solución de ácido 2-amino-4-{1-[(benciloxi)carbonil]-3-piperidinil}-6-(2-

hidroxifenil)nicotínico (750 mg, 1,676 mmol), que se obtuvo en la etapa (2) del ejemplo 8-1, clorhidrato de metilamina (230 mg, 3,352 mmol), trietilamina (340 mg, 3,35 mmol) y 1-hidroxibenzotriazol (360 mg, 2,68 mmol), se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (390 mg, 2,0 mmol) a 0°C en atmósfera de argón. Se agitó la mezcla a temperatura ambiente durante la noche. Se extrajo la mezcla de reacción con acetato de etilo, se lavó con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo, 2:1), proporcionando 3-{2-amino-6-(2-hidroxifenil)-3-(N-metilcarbamoíl)-4-piridinil}-1-piperidincarboxilato de bencilo en forma de un sólido amarillo pálido (337 mg, 44%).



A una solución de 3-{2-amino-6-(2-hidroxifenil)-3-(N-metilcarbamoíl)-4-piridinil}-1-piperidincarboxilato de bencilo (130 mg, 0,274 mmol) en MeOH (2 ml) y THF (2 ml), se añadió Pd-C (180 mg). Se agitó la mezcla a temperatura ambiente en atmósfera de hidrógeno durante la noche. Se filtró la mezcla de reacción a través de celite®, se lavó con THF y después se concentró a presión reducida. Se diluyó el residuo con acetato de etilo y se añadió HCl 4 N en 1,4-dioxano. Se lavó el precipitado amarillo resultante con acetonitrilo. Se secó el sólido recogido a presión reducida proporcionando clorhidrato de 2-amino-6-(2-hidroxifenil)-N-metil-4-(3-piperidinil)nicotinamida (10 mg, rendimiento: 81%).

Peso molecular: 362,86

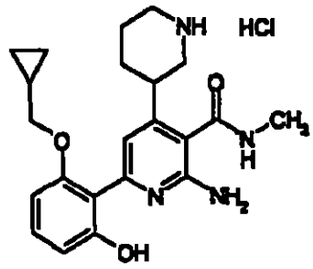
Espectrometría de masas: 327 $(M + H)^+$

Grado de actividad in vitro: B

Grado de actividad celular: (A549)-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,69 - 1,77 (2H, m), 1,82 - 1,86 (2H, m), 2,80 (3H, d, J=4,4 Hz), 2,88 (1H, m), 3,03 (1H, m), 3,19 - 3,29 (3H, m), 6,89 - 6,93 (3H, m), 7,29 - 7,32 (2H, m), 7,85 (1H, a), 8,50 (1H, a), 8,85 (1H, a), 9,16 (1H, a).

Ejemplo 8-3



Utilizando el compuesto de partida 1G (en lugar de 1D), 2C y otros materiales, se preparó clorhidrato de 2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-N-metil-4-(3-piperidinil)-nicotinamida de manera similar a la del ejemplo 8-1 y 8-2.

Peso molecular: 432,95

Espectrometría de masas: 397 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

RMN de ^1H (300 MHz, DMSO-d_6): 0,29 - 0,34 (2H, m), 0,49 - 0,55 (2H, m), 1,21 (1H, m), 1,74 - 1,89 (5H, m), 2,84 (3H, d, J=4,5 Hz), 3,10 - 3,11 (2H, m), 3,25 - 3,28 (2H,

m), 3,78 - 3,90 (2H, m), 6,59 (1H, d, J=8,3 Hz), 6,65 (1H, d, J=8,3 Hz), 7,20 (1H, s), 7,26 (1H, t, J=8,3 Hz), 7,56 (1H, s a), 8,76 (1H, s a), 9,08 (1H, s a), 13,8 (1H, s a).

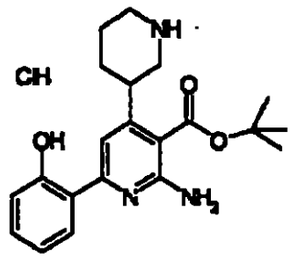
Ejemplo 9-1

(1) Se calentó a reflujo durante 3,5 horas una mezcla del compuesto de partida 1A (3,500 g, 15,47 mmol), el compuesto de partida 2B (3,299 g, 15,47 mmol), cianoacetato de *terc*-butilo (2,184 g, 15,47 mmol), acetato de amonio (3,577 g, 46,40 mmol) y 1,2-dimetoxietano (17 ml). Después de enfriar hasta temperatura ambiente, se concentró la mezcla a presión reducida, y se repartió el residuo entre acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía ultrarrápida sobre gel de sílice (hexano:acetato de etilo, 4:1), proporcionando 2-amino-6-[2-(benciloxi)fenil]-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]nicotinato de *terc*-butilo (1,892 g, rendimiento: 22%).

(2) A continuación se retiró el resto bencilo de manera similar a la descrita en la etapa (2) del ejemplo 1-1. Se suspendió el sólido resultante en etanol, se recogió por filtración, se lavó con etanol y se secó a presión reducida proporcionando 2-amino-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]-6-(2-hidroxifenil)nicotinato de *terc*-butilo (0,322 g, rendimiento: 38%).

(3) Se trató 2-amino-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]-6-(2-hidroxifenil)-nicotinato de *terc*-butilo (0,050 g, 0,106 mmol) en condiciones ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de 2-amino-6-

(2-hidroxifenil)-4-(3-piperidinil)nicotinato de *terc*-butilo (0,034 g, rendimiento: 79%).



Peso molecular: 405,92

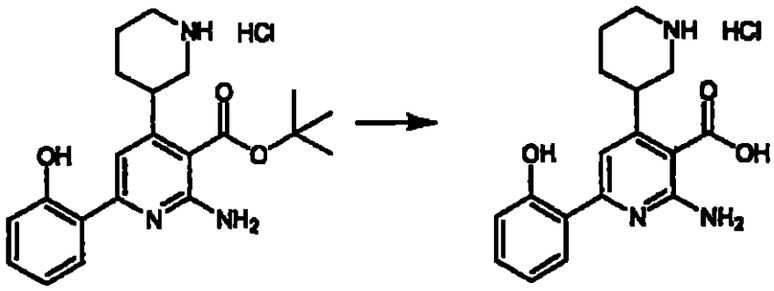
Espectrometría de masas: 370 $(M + H)^-$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,60 (9H, s), 1,76 - 1,95 (4H, m), 1,90 - 2,97 (1H, m), 3,20 - 3,46 (4H, m), 6,89 - 6,94 (2H, m), 7,31 - 7,36 (1H, m), 7,38 (1H, s), 8,02 (1H, dd, J=1,3, 8,2 Hz), 9,09 (1H, a), 9,29 (1H, a), 13,78 (1H, a).

Ejemplo 9-2



A una solución de clorhidrato de 2-amino-6-(2-hidroxifenil)-4-(3-piperidinil)nicotinato de *terc*-butilo (0,023 g, 0,057 mmol), que se obtuvo en el ejemplo 9-1, en cloruro de metileno (1,0 ml), se añadió ácido trifluoroacético (TFA) (1,0 ml). Después de agitarse

durante 6 horas, se concentró la mezcla a presión reducida. Se disolvió el residuo en 1,4-dioxano (3,0 ml) y después se trató con una solución de HCl en 1,4-dioxano (4 N, 0,2 ml). Se recogieron los precipitados resultantes por filtración en atmósfera de argón, se lavaron con 1,4-dioxano y acetonitrilo y se secaron a presión reducida, proporcionando clorhidrato de ácido 2-amino-6-(2-hidroxifenil)-4-(3-piperidinil)nicotínico (0,020 g, rendimiento: cuantitativo).

Peso molecular: 349,82

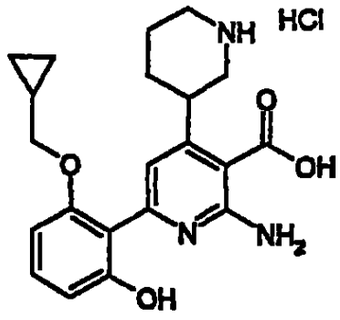
Espectrometría de masas: 314$(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,75 - 1,93 (4H, m), 2,92 (1H. m a), 2,92 - 3,39 (3H, m), 3,63 - 3,67 (1H, m a), 6,91 - 6,96 (2H, m), 7,32 - 7,36 (1H, m), 7,37 (1H, s), 7,95 (1H, d, J=7,9 Hz), 8,84 (1H, a), 9,41 (1H, a), 13,80 (1H, a) .

Ejemplo 9-3



Utilizando 1-(2-benciloxi-6-ciclopropilmetoxifenil)etanona preparada de manera similar a la del compuesto de partida 1G, el compuesto de partida 2B y otros materiales, se preparó clorhidrato de ácido 2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-

piperidinil)nicotínico de manera similar a la descrita en el ejemplo 9-2.

Peso molecular: 419,91

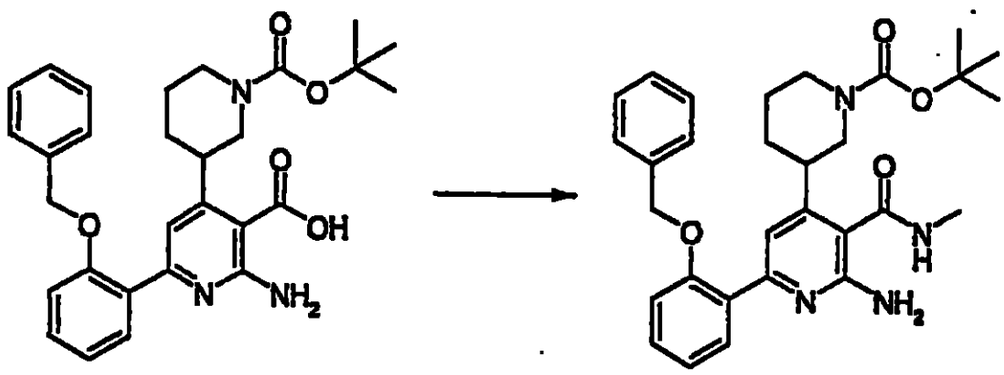
Espectrometría de masas: 384 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-C

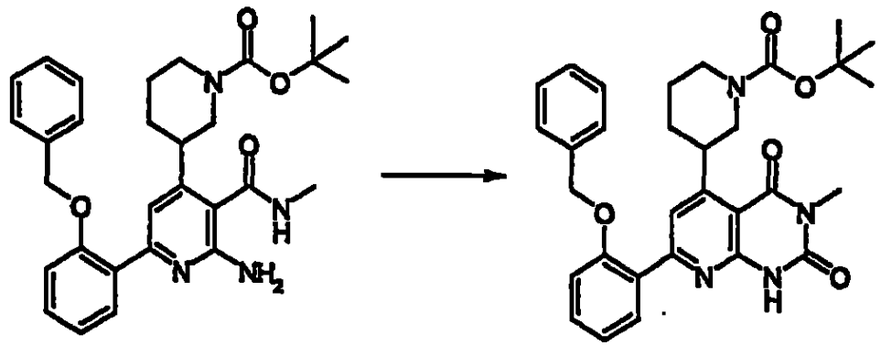
RMN de ^1H (500 MHz, DMSO-d_6): 0,31 - 0,32 (2H, m), 0,51 - 0,53 (2H, m), 1,20 (1H, m), 1,70 - 1,74 (2H, m), 1,89 - 1,91 (2H, m), 2,89 (1H, m), 3,18 (1H, m), 3,26 - 3,28 (3H, m), 3,83 (2H, dd, J=6,9, 7,3 Hz), 6,58 (1H, d, J=8,2 Hz), 6,65 (1H, d, J=8,5 Hz), 7,28 (1H, dd, J=8,2, 8,5 Hz), 7,30 (1H, s), 7,81 (1H, s a), 8,92 (1H, s a), 9,37 (1H, s a).

Ejemplo 10-1



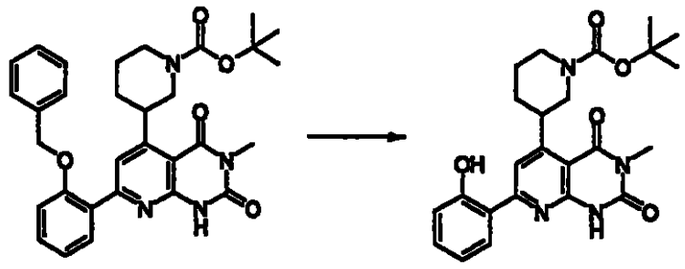
(1) A una solución de ácido 2-amino-6-[2-(benciloxi)fenil]-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]nicotínico (0,500 g, 0,993 mmol) que derivaba del producto de la etapa (1) del ejemplo 9-1, clorhidrato de metilamina (0,134 g, 1,896 mmol), trietilamina (0,277 ml, 1,986 mmol) y 1-hidroxibenzotriazol (0,215 g, 1,589 mmol) en diclorometano (10,0 ml) a 0°C en atmósfera de argón, se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0,228 g, 1,191 mmol). Se agitó la mezcla a

temperatura ambiente durante la noche. Se concentró la mezcla a presión reducida, después se extrajo con acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre $MgSO_4$, se filtró y después se concentró a presión reducida. Se purificó el residuo resultante mediante cromatografía en columna sobre gel de sílice (diclorometano/metanol= 19/1), proporcionando 3-{2-amino-6-[2-(benciloxi)fenil]-3-[(metilamino)carbonil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo en forma de un aceite amarillo (0,11 g, 21%).

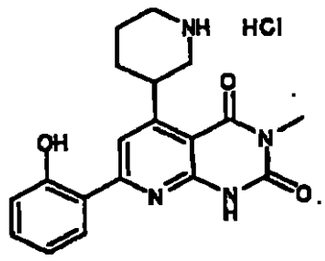


(2) A una solución enfriada (-20°C) de 3-{2-amino-6-[2-(benciloxi)fenil]-3-[(metilamino)carbonil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,120 g, 0,232 mmol) y trietilamina (0,213 g, 2,090 mmol) en tetrahidrofurano (10 ml), se añadió trifosgeno (0,069 g, 0,232 mmol) en atmósfera de argón. Se continuó la agitación de 0°C a temperatura ambiente durante la noche. Se extrajo la mezcla de reacción con acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. Se purificó el residuo resultante mediante TLC preparativa (hexano/acetato de etilo: 2/1), proporcionando 3-{7-[2-(benciloxi)fenil]-3-metil-2,4-dioxo-1,2,3,4-tetrahidro-pirido[2,3-d]pirimidin-5-il}-1-piperidincarboxilato de *terc*-butilo en forma de un sólido amarillo pálido (0,0655 g,

52%).



(3) Se trató 3-{7-[2-(benciloxi)fenil]-3-metil-2,4-dioxo-1,2,3,4-tetrahidropiridio[2,3-d]pirimidin-5-il}-1-piperidincarboxilato de *terc*-butilo (0,065 g, 0,120 mmol) de manera similar a la de la etapa (2) del ejemplo 1-1. Se purificó el residuo mediante TLC preparativa (hexano/acetato de etilo: 1/1), proporcionando 3-[7-(2-hidroxifenil)-3-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-5-il]-1-piperidincarboxilato de *terc*-butilo (0,010 g, 18%), que se trató entonces como se describió en la etapa (3) del ejemplo 1-1, obteniéndose clorhidrato de 7-(2-hidroxifenil)-3-metil-5-piperidin-3-il-1H-pirido[2,3-d]pirimidin-2,4-diona.



Peso molecular: 388,86

Espectrometría de masas: 353 $(M + H)^+$

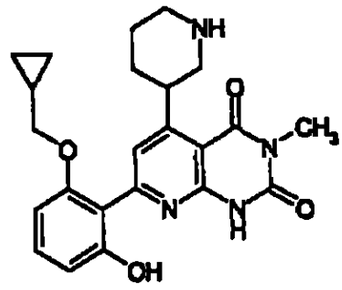
Grado de actividad in vitro: A

Grado de actividad celular: A549-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,81 - 1,85 (2H, m), 1,96 - 1,98 (2H, m), 2,91 (1H, m), 3,26 (3H, s), 3,31 - 3,40 (3H, m), 4,70 (1H, m), 6,97 - 7,00 (2H, m), 7,39 (1H, m),

7,86 (1H, s), 8,16 (1H, m), 8,73 (1H, a), 9,17 (1H, a), 12,37 (1H, s)

Ejemplo 10-2



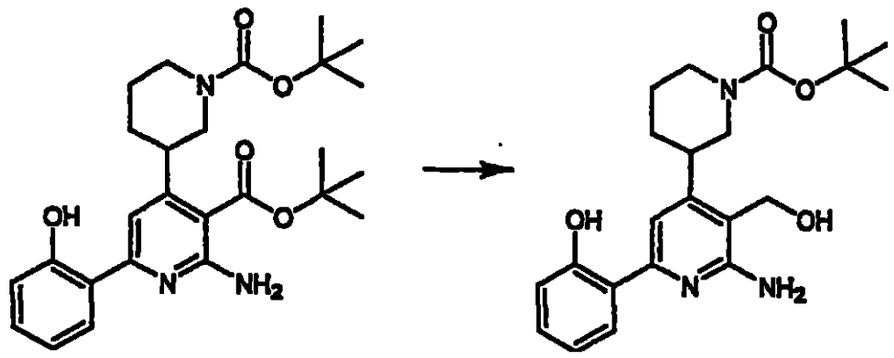
Utilizando 1-(2-benciloxi-6-ciclopropilmetoxifenil)etanona preparada de manera similar a la del compuesto de partida 1G, el compuesto de partida 2B y otros materiales, se preparó 7-(2-ciclopropilmetoxi-6-hidroxifenil)-3-metil-5-piperidin-3-il-1H-pirido[2,3-d]pirimidin-2,4-diona de manera similar a la del ejemplo 10-1.

Peso molecular: 458,95

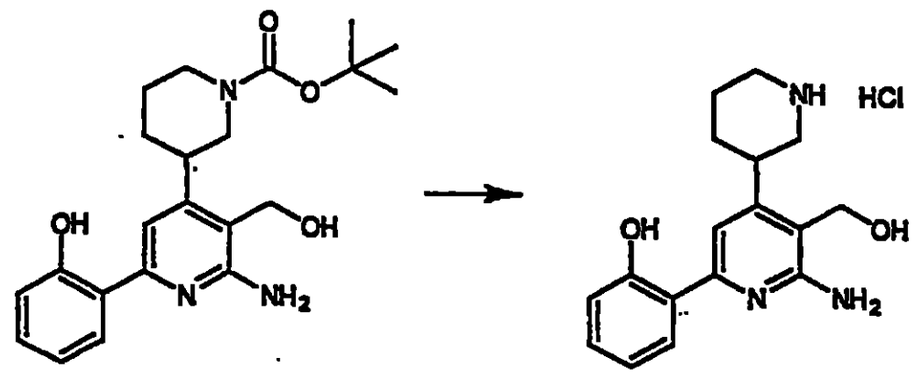
Grado de actividad in vitro: A

RMN de ^{1}H (500 MHz, DMSO-d_6): 0,31 - 0,34 (2H, m), 0,56 - 0,60 (2H, m), 1,27 (1H, m), 1,67 (1H, m), 1,79 (1H, m), 1,91 - 2,01 (2H, m), 2,87 (1H, m), 3,06 (1H, m), 3,27 (3H, s), 3,30 (1H, m), 3,39 (1H, m), 3,83 (1H, dd, J=7,3, 9,8 Hz), 3,91 (2H, dd, J=6,9, 9,8 Hz), 4,65 (1H, m), 6,58 (2H,d, J=8,2, 8,5 Hz), 7,25 (1H, dd, J=8,2, 8,5 Hz), 7,91 (1H, s), 8,83 (1H, s a), 9,32 (1H, s a), 12,2 (1H, s a).

Ejemplo 11-1



(1) A una solución fría (0°C) de 2-amino-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]-6-(2-hidroxifenil)nicotinato de *terc*-butilo, obtenido en la etapa (2) del ejemplo 9-1, (0,200 g, 0,426 mmol) en THF (3,0 ml) en atmósfera de argón, se añadió $LiBH_4$ (0,019 g, 0,85 mmol). Después de agitar a temperatura ambiente durante la noche, se inactivó la mezcla con agua y después se extrajo con acetato de etilo y HCl 0,5 N. Se lavó la fase orgánica separada con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo, 1:1), proporcionando 3-[2-amino-3-(hidroximetil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidin-carboxilato de *terc*-butilo (0,161 g, rendimiento: 95%).



Se trató 3-[2-amino-3-(hidroximetil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidin-carboxilato de *terc*-butilo (0,160 g, 0,401 mmol) en 1,4-dioxano (3,0 ml) en condiciones

ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de 2-[6-amino-5-(hidroximetil)-4-(3-piperidinil)-2-piridinil]fenol (0,132 g, rendimiento: 98%).

Peso molecular: 335,84

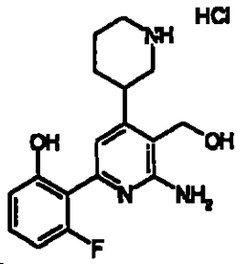
Espectrometría de masas: 300 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 1,75 - 1,98 (4H, m), 2,90 (1H, a), 3,14 - 3,33 (3H, m), 3,56 - 3,60 (1H, a), 4,58 (2H, dd, J=13,0, 20,2 Hz), 6,96 (1H, t, J=7,6 Hz), 7,06 (1H, d, J=7,9 Hz), 7,19 (1H, s), 7,37 (1H, t a, J=7,3 Hz), 7,65 (1H, d a, J=7,6 Hz), 9,03 (1H, a), 9,32 (1H, a), 13,59 (1H, a).

Ejemplo 11-2



Utilizando el compuesto de partida 1I y 2B y otros materiales se preparó clorhidrato de 2-[6-amino-5-(hidroximetil)-4-(3-piperidinil)-2-piridinil]-3-fluorofenol de manera similar a la del ejemplo 11-1.

Peso molecular: 353,83

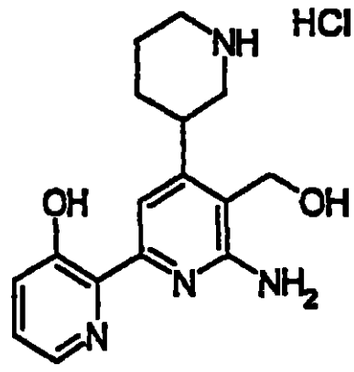
Espectrometría de masas: 318$(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 1,03 (3H, t, J=7,6 Hz), 1,83 (4H, m), 3,00 (2H, m), 3,31 (2H, m), 3,71 (1H, m), 4,56 (2H, dd, J=13,1, 19,4 Hz), 5,16 (1H, a), 6,79 (2H, m), 7,12 (1H, s), 7,32 (1H, m), 8,52 (1H, d, J=9,8 Hz), 8,86 (1H, d, J=9,8 Hz), 14,0 (1H, a).

Ejemplo 11-3



Utilizando el compuesto de partida 1F, el compuesto de partida 2B y otros materiales se preparó clorhidrato de 6'-amino-5'-(hidroximetil)-4'-(3-piperidinil)-2,2'-bipiridin-3-ol de manera similar a la del ejemplo 11-1.

Peso molecular: 336,82

Espectrometría de masas: 301 $(M + H)^+$

Grado de actividad in vitro: A

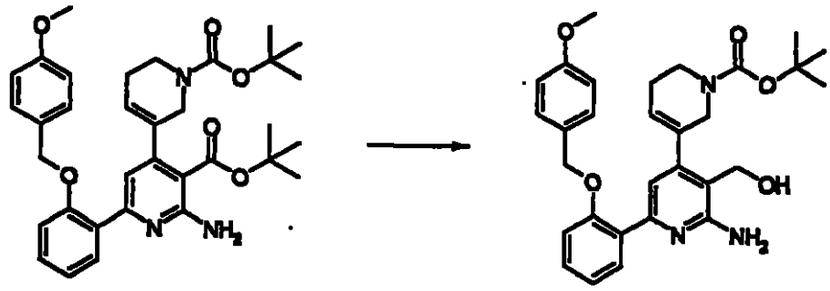
Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 1,81 - 1,95 (3H, m), 2,46 - 2,64 (1H, m), 3,00 - 3,06 (2H, m), 3,28 - 3,39 (2H, m), 3,54 - 3,60 (1H, m), 4,56 (1H, d, J=13,0 Hz), 4,59 (1H, d, J=13,0 Hz), 7,41 - 7,50 (2H, m), 7,81 (1H, s), 8,24 (1H, d, J=3,8 Hz), 8,92 (1H, a), 9,07

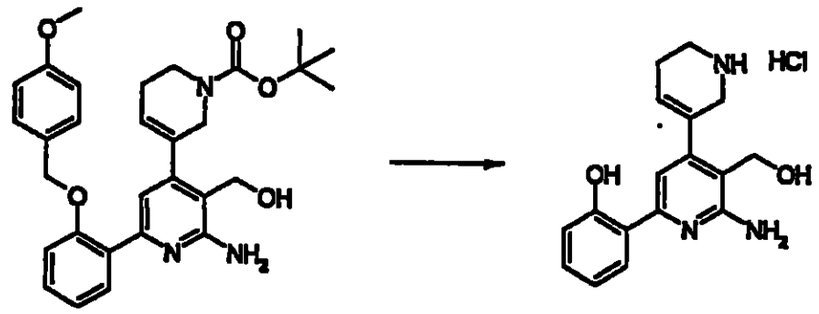
(1H, a).

Ejemplo 11-4

(1) Utilizando el compuesto de partida 1D en lugar de 1A y 2H en lugar de 2B, se preparó 2'-amino-6'-{2-[(4-metoxibencil)oxi]fenil}-5,6-dihidro-3,4'-bipiridin-1,3'-(2H)-dicarboxilato de di(*terc*-butilo) de manera similar a la de la etapa (1) del ejemplo 9-1.



(2) A una solución enfriada (0°C) de 2'-amino-6'-{2-[(4-metoxibencil)oxi]fenil}-5,6-dihidro-3,4'-bipiridin-1,3'-(2H)-dicarboxilato de di(*terc*-butilo) (50,0 mg, 0,09 mmol) en THF (4,5 ml), se añadió gota a gota hidruro de bis-(2-metoxietoxi)aluminio y sodio (0,10 ml), después se agitó durante 1 hora a 0°C. Se inactivó la reacción mediante la adición de una solución saturada de NH_4Cl, se filtró y se lavó con acetato de etilo. Se lavó la fase orgánica reunida con salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó. Se purificó el producto bruto mediante TLC preparativa con gel de sílice (acetona al 15% en cloroformo), proporcionando 2'-amino-3'-(hidroximetil)-6'-{2-[(4-metoxibencil)oxi]fenil}-5,6-dihidro-3,4'-bipiridin-1(2H)-carboxilato de *terc*-butilo en forma de una espuma blanca (25 mg, rendimiento: 57%).



(3) Se trató 2'-amino-3'-(hidroximetil)-6'-{2-[(4-metoxibencil)oxi]fenil}-5,6-dihidro-3,4'-bipiridin-1(2H)-carboxilato de *terc*-butilo (25,0 mg, 0,05 mmol) con HCl 2 N en dioxano (4,0 ml) durante la noche a temperatura ambiente. Se recogió el sólido resultante por filtración, se lavó con éter y se secó a presión reducida, proporcionando clorhidrato de 2-[6'-amino-5'-(hidroximetil)-1,2,5,6-tetrahidro-3,4'-bipiridin-2'-il]fenol (14 mg, rendimiento: 87%).

Peso molecular: 333,82

Espectrometría de masas: 298 $(M + H)^+$

Grado de actividad in vitro: A

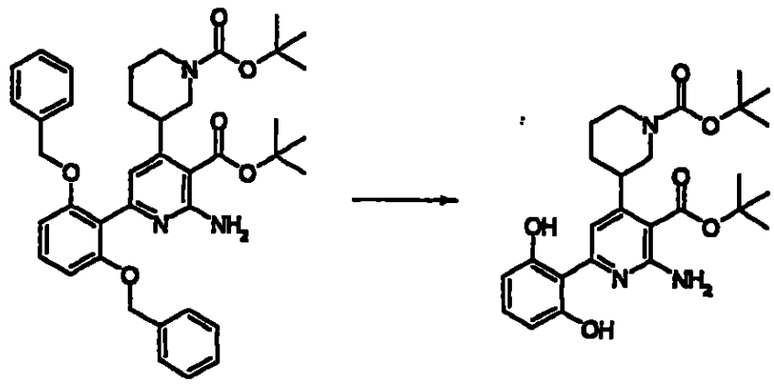
Grado de actividad celular: (A549)-A

RMN de ^1H (300 MHz, DMSO-d_6): 2,51 (2H, s a), 3,35 (2H, s a), 3,83 (2H, s), 4,58 (2H, s), 6,04 (1H, s a), 6,93 - 7,01 (3H, m), 7,34 - 7,47 (2H, m).

Ejemplo 12-1

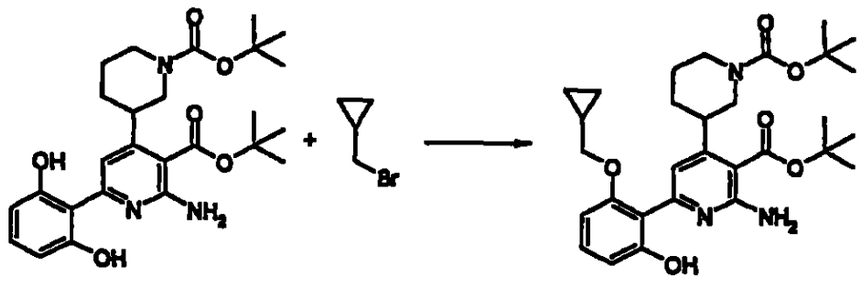
(1) Se agitó a 100°C en un tubo sellado durante la noche una mezcla de 1-[2,6-bis(benciloxi)fenil]etanona (8,00 g, 24,067 mmol) (compuesto de partida 1E), 3-formil-1-piperidincarboxilato de *terc*-butilo (5,133 g, 24,067 mmol) (compuesto de partida

2B), cianoacetato de *terc*-butilo (3,398 g, 24,067 mmol) y acetato de amonio (5,432 g, 72,202 mmol) en 1,2-dimetoxietano (24 ml). Después de enfriar hasta temperatura ambiente se repartió la mezcla de reacción entre acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. Se diluyó el residuo con 30 ml de diclorometano y se añadió MnO_2 a la mezcla, después se agitó la mezcla a temperatura ambiente durante 5 horas. Se filtró la mezcla a través de celite® y se concentró a presión reducida. Se purificó el residuo resultante (líquido) mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo: 2/1), proporcionando 2-amino-6-[2,6-bis(benciloxi)fenil]-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]nicotinato de *terc*-butilo en forma de un aceite amarillo pálido (2,5 g, rendimiento: 16%).



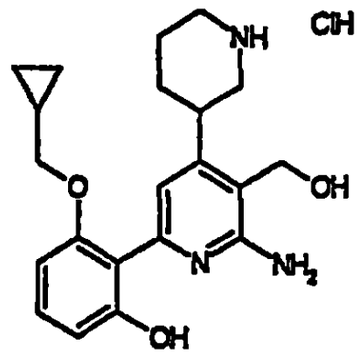
(2) Se agitó a temperatura ambiente en atmósfera de hidrógeno (1 atm) durante la nocha una suspensión de 2-amino-6-[2,6-bis(benciloxi)fenil]-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]nicotinato de *terc*-butilo (1,00 g, 1,052 mmol) y paladio-carbón al 10% (0,500 g) en 20 ml de acetato de etilo. Después se retiró el paladio-carbón mediante filtración a través de celite®, y se concentró el filtrado a presión reducida proporcionado 2-amino-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]-6-(2,6-dihidroxifenil)nicotinato de *terc*-butilo en forma de un aceite marrón (0,710 g,

rendimiento: 97%).



(3) A una solución de 2-amino-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]-6-(2,6-dihidroxifenil)nicotinato de *terc*-butilo (1,280 g, 2,636 mmol) y K_2CO_2 (3,643 g, 26,36 mmol) en DMF (100 ml), se añadió (bromometil)ciclopropano (0,268 ml, 2,768 mmol). Se continuó la agitación a 50°C durante 20 horas. Después de retirar el disolvente mediante evaporación, se extrajo el residuo con acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre $MgSO_4$, se filtró y después se concentró a presión reducida. Se purificó el residuo resultante mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo:3/1), proporcionando 2-amino-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]nicotinato de *terc*-butilo en forma de un sólido marrón (0,820 g, rendimiento: 58%).

Se trató 2-amino-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]nicotinato de *terc*-butilo de manera similar a la de la etapa (1) del ejemplo 11-1 y después de manera similar a la de la etapa (3) del ejemplo 1-1, obteniendo clorhidrato de 2-[6-amino-5-(hidroximetil)-4-(3-piperidinil)-2-piridinil]-3-(ciclopropilmetoxi)fenol.



Peso molecular:405,93

Espectrometría de masas: 370 $(M + H)^+$

Grado de actividad in vitro: A

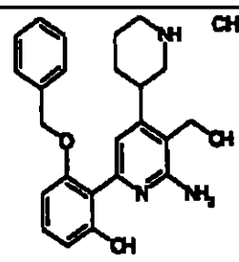
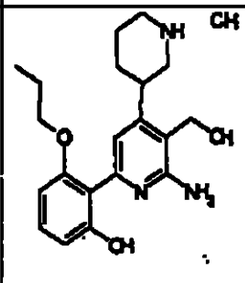
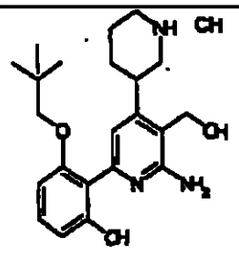
Grado de actividad celular: (A549)-A

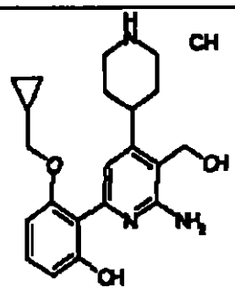
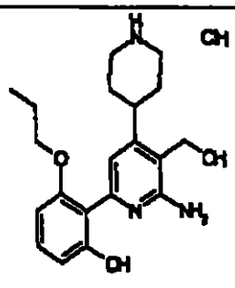
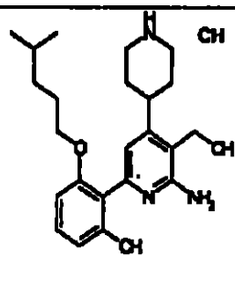
RMN de ^1H (300 MHz, DMSO-d_6): 0,26 - 0,29 (2H, m), 0,47 - 0,52 (2H, m), 1,13 (1H, m), 1,75 - 1,83 (5H, m), 2,90 - 2,93 (2H, m), 3,04 - 3,17 (2H, m), 3,81 - 3,86 (2H, m), 4,60 (2H, s), 6,55 (1H, d, J=8,3 Hz), 6,60 (1H, d, J=8,3 Hz), 7,06 (1H, s), 7,27 (1H, t, J=8,3 Hz), 7,59 (1H, a), 8,96 (1H, a), 9,25 (1H, a), 13,58 (1H, a).

Ejemplos 12-2 a 12-7

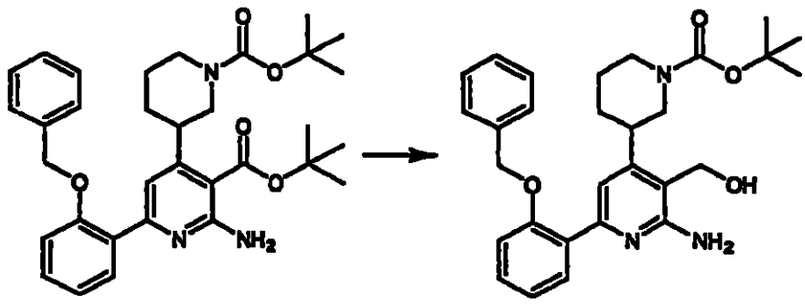
Se prepararon los compuestos mostrados en la tabla 4 según un procedimiento sintético similar al del ejemplo 12-1.

Tabla 4

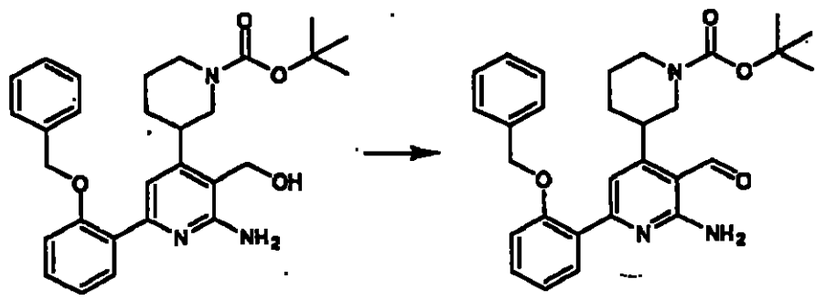
Ej. Nº	Estructura	Peso molecular	Masa	*In vitro*	A549	RMN
12-02		441,96	406	A	B	(500 MHz, DMSO-d_6): 1,56-1,88 (4H, m), 2,84 - 3,20 (3H, m), 4,54 (1H, d, J=13,2 Hz), 4,57 (1H, d, J=13,2 Hz), 5,08 (2H, s), 6,70 (1H, d, J=8,2 Hz), 6,76 (1H, d, J=8,5 Hz), 7,05 (1H, s), 7,29-7,41 (6H, m), 7,60 (1H, a), 8,95 (1H, a), 9,25 (1H, a), 10,42 (1H, a), 13,67 (1H, a)
12-03		393,92	358	A	A	(500 MHz, DMSO-d_6): 0,87 (3H, t, J=7,2 Hz), 1,64 (2H, q, J=6,9 Hz), 1,88-1,90 (3H, m), 2,07 (1H, a), 2,88 (1H, m), 3,05 (1H, m), 3,22-3,24 (2H, m), 3,56 (1H, m), 3,92 (2H, t, J=6,6 Hz), 4,59 (2H, d, J=3,1 Hz), 4,96 (1H, a), 6,62 (1H, d, J=8,2 Hz), 6,66 (1H, d, J=8,2), 7,00 (1H, s), 7,29 (1H, t, J=8,2 Hz, 7,58 (1H, a), 8,92 (1H, a), 9,21 (1H, a), 13,57 (1H, a)
12-04		421,97	386	A	A	(500 MHz, DMSO-d_6): 0,83 (9H, s), 0,82-1,05 (4H, m), 1,75-1,93 (4H, m), 2,87 (1H, a), 3,02-3,07 (4H, m), 4,61 (2H, dd, J=13,2, 18,6 Hz), 4,99 (1H, a), 6,60 (1H, d, J=8,5 Hz), 6,67 (1H, d, J=8,2 Hz), 6,79-6,89 (1H, m), 6,98 (1H, s), 7,07 (1H, a), 7,07 (1H, a), 7,27-7,29 (1H, a), 7,62 (1H, a), 13,72 (1H, a)

12-05		405,93	370	A	A	(500 MHz, DMSO-d_6): 0,29-0,32 (2H, m), 0,46-0,50 (2H, m), 1,19 (1H, m), 1,89-2,05 (2H, m), 3,01-3,07 (2H, m), 3,34-3,48 (3H, m), 3,84 (2H, d, J=6,9 Hz), 4,61 (2H, s), 6,59 (1H, d, J=8,5 Hz), 6,69 (1H, d, J=8,2 Hz), 6,80 (1H, s), 7,27 (1H, dd, J=8,2, 8,5 Hz), 7,75 (1H, s a), 9.14-9,25 (2H, m), 13,6 (1H, a)
12-06		393,92	358	A	A	(500 MHz, DMSO-d_6): 0.85 (3H, t, J=7,3 Hz), 1,63-1,67 (2H, m), 1,82-1,85 (2H, m), 1,90-1,95 (2H, m), 3,03-3,08 (2H, m), 3,34-3,45 (4H, m), 3,92 (2H, t, J=6,6 Hz), 4,60 (2H, s), 6,62 (1H, d, J=8,2 Hz), 6,68 (1H, d, J=8,2 Hz), 6,75 (1H, s), 7,28 (1H, t, J=8,2 Hz), 7,63 (1H, a), 8,98 (2H, a)
12-07		436,00	400	A	A	(500 MHz, DMSO-d_6): 0,79-0,82 (7H, m), 1,12-1,16 (2H, m), 1,42-1,49 (1H, m), 1.60-1,66 (2H, m), 1,82-1,84 (2H, m), 1,93-1,98 (2H, m), 3,93-3,95 (2H, m), 4,60 (2H, s), 6,61 (1H, d, J=8,2 Hz), 6,68 (1H, d, J=8,2 Hz), 6,74 (1H, s), 7,28 (1H, t, J=8,2 Hz), 7,68 (2H, s), 9,07 (2H, s), 10,38 (1H, s a)

Ejemplo 13-1

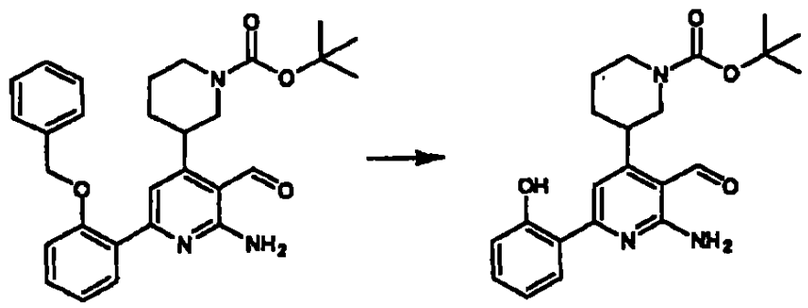


(1) A una solución fría (0°C) de 2-amino-6-[2-(benciloxi)fenil]-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]nicotinato de *terc*-butilo, que se obtuvo en la etapa (1) del ejemplo 9-1, (2,590 g, 4,627 mmol) en THF (25 ml), se añadió $LiBH_4$ (0,202 g, 9,255 mmol). Se agitó la mezcla a temperatura ambiente durante 5 horas, y después se inactivó con agua. Se extrajo la mezcla con acetato de etilo y agua. Se lavó la fase orgánica separada con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo, 2:3), proporcionando 3-[2-amino-6-[2-(benciloxi)fenil]-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,904 g, rendimiento: 40%).

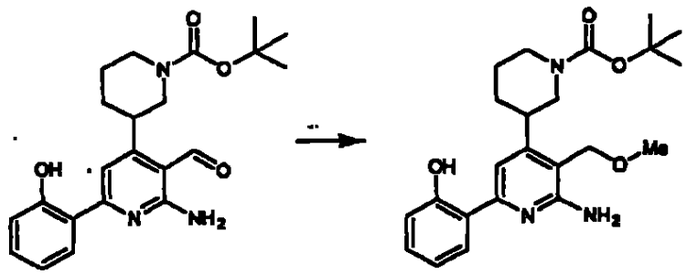


(2) A una solución de 3-[2-amino-6-[2-(benciloxi)fenil]-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,900 g, 1,838 mmol) en cloruro de metileno (20 ml), se añadió óxido de manganeso (IV) (3,20 g, 36,8 mmol). Después de agitar a

temperatura ambiente durante 40 minutos, se filtró la mezcla para retirar la sal de manganeso. Se concentró el filtrado a presión reducida. Se purificó el sólido resultante mediante recristalización en una mezcla de acetato de etilo y hexano, proporcionando 3-[2-amino-6-[2-(benciloxi)fenil]-3-formil-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,651 g, rendimiento: 73%).

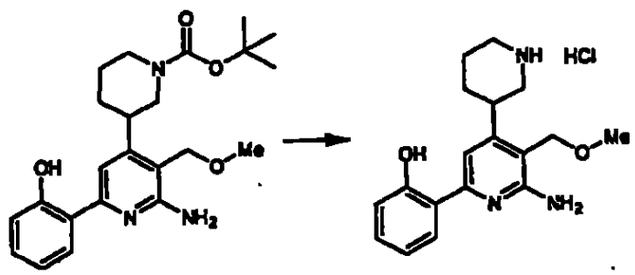


(3) A continuación se retiró el resto bencilo de manera similar a la descrita en la etapa (2) del ejemplo 1-1. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo, 2:1), proporcionando 3-[2-amino-3-formil-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,536 g, rendimiento: cuantitativo).



(4) A una solución de 3-[2-amino-3-formil-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,100 g, 0,252 mmol) en 1,4-dioxano (2,0 ml) en atmósfera de argón, se añadió una solución de HCl en 1,4-dioxano (4 N, 2,0 ml), y se

continuó la agitación a temperatura ambiente durante 1 hora. Se diluyó la mezcla con Et_2O y se decantó el sobrenadante. Se lavaron los precipitados dos veces con Et_2O y se secaron a presión reducida, proporcionado un sólido amarillo pálido, que se disolvió entonces en metanol (2,0 ml). Se dejó enfriar la mezcla en baño de agua con hielo. Después se añadió cianoborohidruro de sodio (0,047 g, 0,76 mmol) a la mezcla en atmósfera de argón. Se dejó calentar la mezcla hasta temperatura ambiente y se continuó la agitación durante la noche. Se concentró la mezcla resultante a presión reducida. Se disolvió el residuo en una mezcla de cloruro de metileno (2,0 ml) y THF (2,0 ml). Se añadió a la mezcla trietilamina (0,140 ml, 1,006 mmol) seguida de dicarbonato de di-*terc*-butilo (0,110 g, 0,503 mmol) y se continuó la agitación durante 2 horas. Se repartió la mezcla resultante entre acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo, 2:1), proporcionando 3-[2-amino-6-(2-hidroxifenil)-3-(metoximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,033 g, rendimiento: 47%).



(4) Se trató 3-[2-amino-6-(2-hidroxifenil)-3-(metoximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,025 g, 0,060 mmol) en condiciones ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de 2-[6-amino-5-(metoximetil)-4-(3-piperidinil)-2-piridinil]fenol.

Peso molecular: 349,86

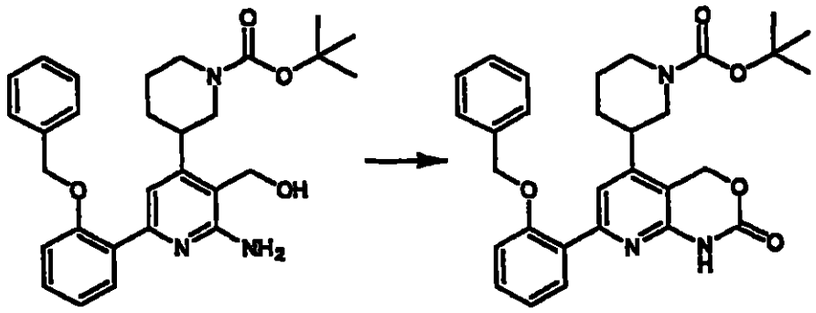
Espectrometría de masas: 314 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

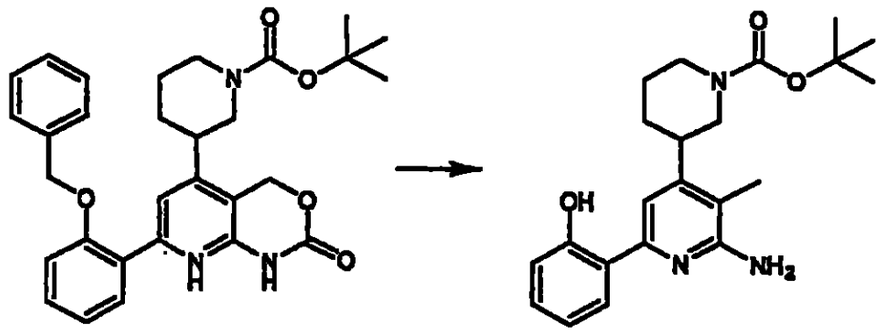
RMN de ^1H (500 MHz, DMSO-d_6): 1,40 – 1,74 (4H, m), 2,80 – 2,92 (2H, m), 4,03 – 4,13 (2H, m), 4,42 (1H, d, J=11,5 Hz), 4,50 (1H, d, J=11,5 Hz), 6,22 – 6,32 (2H, m), 6,81 – 6,85 (2H, m), 7,17 (1H, s), 7,21 (1H, t a, J=7,3 Hz), 7,93 (1H, d a, J=7,6 Hz), 14,30 (1H, a).

Ejemplo 14-1

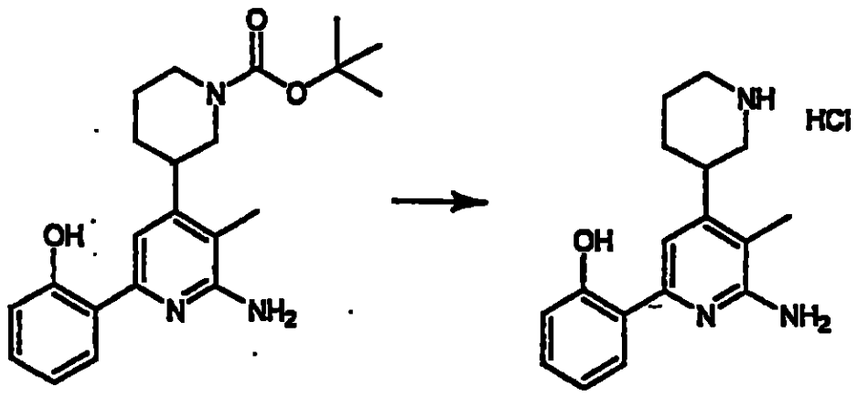


A una solución fría (0°C) de 3-[2-amino-6-[2-(benciloxi)fenil]-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,104 g, 0,212 mmol) obtenido en la etapa (1) del ejemplo 13-1 en THF (2,0 ml), que incluía trietilamina (0,089 ml, 0,64 mmol), se añadió trifosgeno (0,044 g, 0,15 mmol). Después de agitar durante 30 minutos, se dejó calentar la mezcla hasta temperatura ambiente y se continuó la agitación durante 1 hora adicional. Se inactivó la mezcla resultante con agua y se extrajo con acetato de etilo. Se lavó la fase orgánica separada con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo, 5:3),

proporcionando 3-{7-[2-benciloxi]fenil]-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]-oxazon-5-il}-1-piperazincarboxilato de *terc*-butilo (0,058 g, rendimiento: 53%).



Se sometió a hidrogenación a 1 atm. en presencia de paladio sobre carbono (10%, 0,10 g) durante la noche una solución de 3-{7-[2-benciloxi]fenil]-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il}-1-piperazincarboxilato de *terc*-butilo (0,050 g, 0,097 mmol) en acetato de etilo (3,0 ml). Se filtró la mezcla resultante a través de celite® y se lavó con acetato de etilo y THF. Se concentró el filtrado reunido a presión reducida y se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo, 2:1), proporcionando 3-[2-amino-6-(2-hidroxifenil)-3-metil-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,027 g, rendimiento: 73%).



Se trató 3-[2-amino-6-(2-hidroxifenil)-3-metil-4-piridinil]-1-piperidincarboxilato de

terc-butilo (0,025 g, 0,065 mmol) en condiciones ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de 2-[6-amino-5-metil-4-(3-piperidinil)-2-piridinil]fenol (0,017 g, rendimiento: 82%).

Peso molecular: 319,84

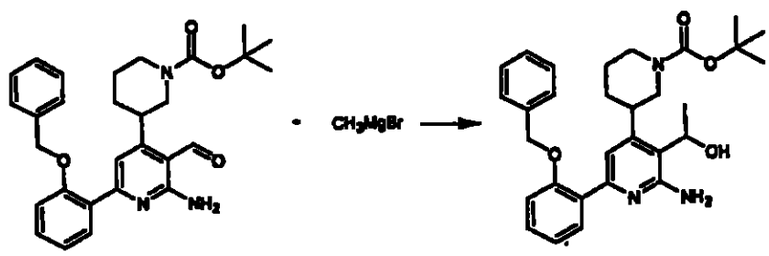
Espectrometría de masas: 284 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)/Jurkat-B

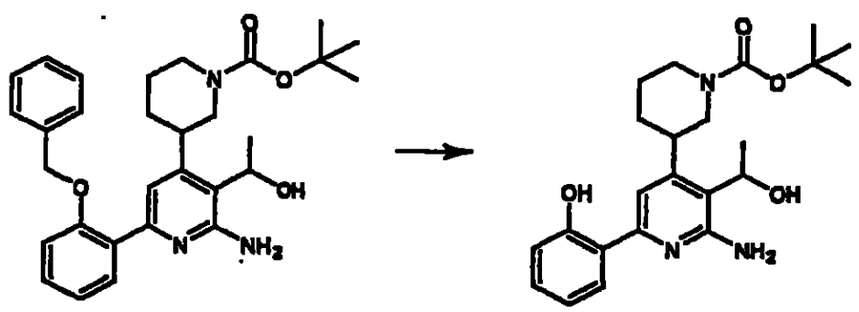
RMN de ^1H (500 MHz, DMSO-d_6): 1,08 – 1,75 (4H, m), 2,10 (3H, s), 2,55 – 2,98 (3H, m), 4,12 (1H, a), 6,19 (2H, d a, J=15,1 Hz), 6,79 –6,83 (2H, m), 7,12 (1H, s), 7,18 (1H, t a, J=7,9 Hz), 7,88 (1H, a).

Ejemplo 15-1

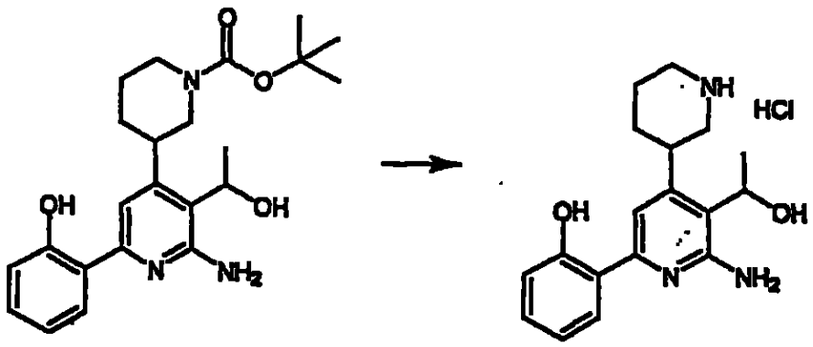


(1) A una solución fría (-20°C) de 3-{2-amino-6-[2-(benciloxi)fenil]-3-formil-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (400 mg, 0,82 mmol), que se obtuvo en la etapa (2) del ejemplo 13-1, en THF (2,0 ml); se añadió gota a gota una solución de bromuro de metilmagnesio en THF (7,38 ml, 7,38 mmol). Se agitó la mezcla a -20°C durante 2 horas, se inactivó con una solución acuosa saturada de NH_4Cl y se extrajo con acetato de etilo. Se lavó la fase orgánica separada con agua y salmuera, se secó sobre Na_2SO_4; se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo, 3:2)

proporcionando 3-[2-amino-6-[2-(benciloxi)fenil]-3-(1-hidroxietil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo en forma de un aceite amarillo (356 mg, rendimiento: 86%).



(2) A continuación se retiró el resto bencilo de manera similar a la descrita en la etapa (2) del ejemplo 1-1, proporcionando 3-[2-amino-3-(1-hidroxietil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo en forma de un aceite amarillo pálido (147 mg, rendimiento: 96%).



(3) Se trató 3-[2-amino-3-(1-hidroxietil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (30 mg, 0,07 mmol) en condiciones ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de 2-[6-amino-5-(1-hidroxietil)-4-(3-piperidinil)-2-piridinil]fenol en forma de un sólido amarillo (20 mg, rendimiento: 78%).

Peso molecular: 349,86

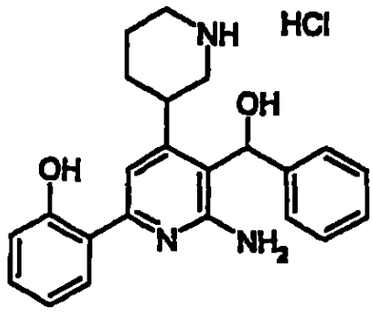
Espectrometría de masas: 296 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,83 – 1,92 (7H, m), 2,90 – 2,91 (1H, m), 3,13 – 3,15 (1H, m), 3,57 (3H, s), 5,29 – 5,39 (1H, m), 6,89 – 6,99 (1H, m), 7,05 – 7,10 (1H, m), 7,17 (1H, d, J=3,16 Hz), 7,27 - 7,40 (2H, m), 7,62 (1H, d, J=5,0 Hz), 7,68 – 7,87 (2H, m), 13,50 (1H, s a).

Ejemplo 15-2



De manera similar a la del ejemplo 15-1, se preparó clorhidrato de 2-[6-amino-5-[hidroxi(fenil)metil]-4-(3-piperidinil)-2-piridinil]fenol.

Peso molecular: 411,94

Espectrometría de masas: 376 $(M + H)^+$

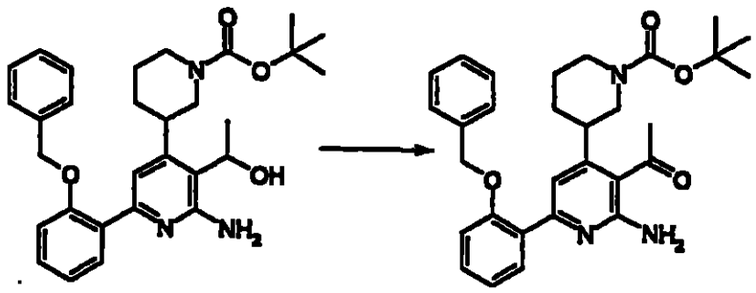
Grado de actividad in vitro: A

Grado de actividad celular: (A549)-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,67 – 1,74 (2H, m), 1,89 – 1,99 (2H, m), 2,88 – 2,93 (1H, m), 3,14 – 3,24 (4H, m), 6,32 (1H, s), 6,91 (1H, d, J=2,2 Hz), 6,92 – 7,01 (2H,

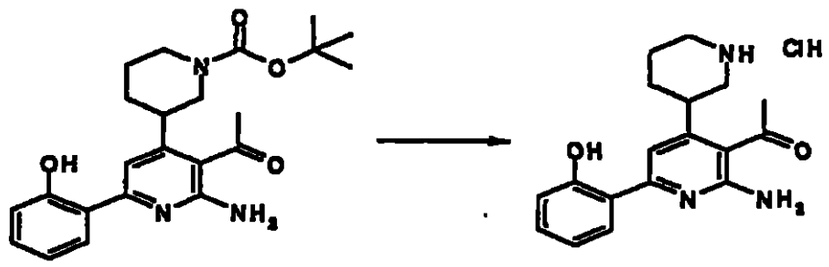
m), 7,24 – 7,32 (3H, m), 7,34 – 7,40 (6H, m), 7,42 – 7,44 (1H, m), 7,75 (1H, d, J=7,9 Hz).

Ejemplo 15-3



A una solución agitada de 3-[2-amino-6-[2-(benciloxi)fenil]-3-(1-hidroxietil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,100 g, 0,199 mmol) obtenido en la etapa (1) del ejemplo 15-1 en diclorometano (1 ml), se añadió MnO_2 (0,350 g, 3,971 mmol). Se agitó la mezcla a temperatura ambiente durante 2 horas, se filtró la mezcla a través de celite® y se concentró a presión reducida, proporcionando 3-{3-acetil-2-amino-6-[2-(benciloxi)fenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo.

Se trató a continuación el 3-{3-acetil-2-amino-6-[2-(benciloxi)fenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,090 g, 0,169 mmol) de manera similar a la de la etapa (2) del ejemplo 1-1. Se recristalizó el residuo en alcohol etílico proporcionando 3-[3-acetil-2-amino-6-(2-hidroxifenil)-4-piridinil]-1-piperidin-carboxilato de *terc*-butilo en forma de un sólido amarillo pálido (0,019 g, rendimiento: 27%).



A continuación se trató 3-[3-acetil-2-amino-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,020 g, 0,044 mmol) de manera similar a la de la etapa (3) del ejemplo 1-1. Se recogió por filtración el precipitado resultante, se lavó con acetonitrilo y se secó a presión reducida, proporcionando clorhidrato de 1-[2-amino-6-(2-hidroxifenil)-4-(3-piperidinil)-3-piridinil]etanona (0,014 g, rendimiento 89%).

Peso molecular: 347,85

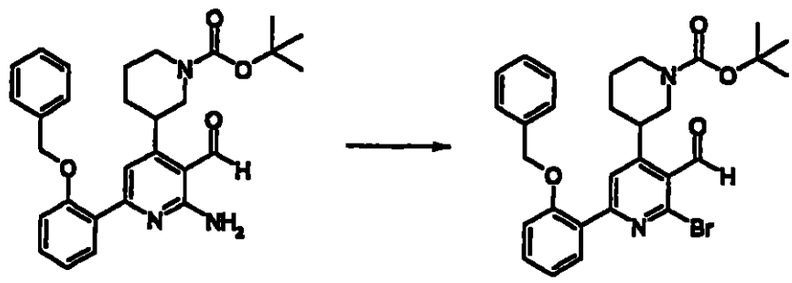
Espectrometría de masas: 312 $(M + H)^+$

Grado de actividad in vitro: A

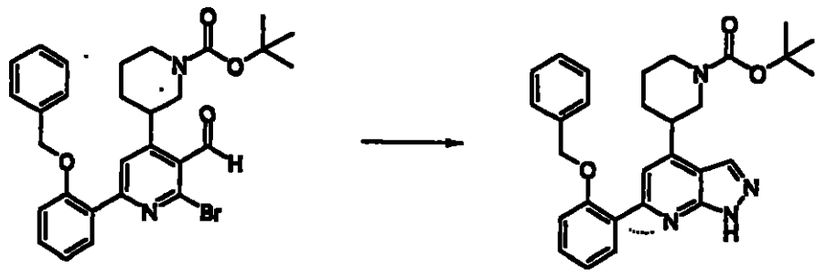
Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 1,17 – 1,87 (4H, m), 2,92 – 2,98 (1H, m), 2,56 (3H, s), 3,00 - 3,29 (4H, m), 6,98 – 6,91 (4H, m), 7,30 (1H, dd, J=7,3, 7,9 Hz), 7,37 (1H, s), 8,73 (1H, d, J=7,6 Hz), 13,73 (1H, s a).

Ejemplo 16-1



A una solución de bromuro de cobre (II) (0,82 g, 3,692 mmol) en acetonitrilo (10 ml), se añadió nitrato de *terc*-butilo (0,550 ml, 4,614 mmol). Se agitó la mezcla a 65°C durante 15 minutos. Se añadió a la mezcla una solución de 3-{2-amino-6-[2-(benciloxi)fenil]-3-formil-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (1,50 g, 3,076 mmol), que se obtuvo en la etapa (2) del ejemplo 13-1, en acetonitrilo (10 ml), y se agitó a 65°C durante 3 horas. Después de enfriar hasta temperatura ambiente, se diluyó la mezcla de reacción con agua y se extrajo con acetato de etilo. Se secó la fase orgánica sobre sulfato de sodio, se filtró y se concentró a presión reducida. Se purificó el residuo resultante mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo: 4/1 – 2/1 – 1/1), proporcionando 3-{6-[2-(benciloxi)fenil]-2-bromo-3-formil-4-piridinil}-1-piperidincarboxilato de *terc*-butilo en forma de un sólido blanco (0,260 g, rendimiento: 15%).



A una solución agitada de 3-{6-[2-(benciloxi)fenil]-2-bromo-3-formil-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,150 g, 0,272 mmol) en 1,4-dioxano (1 ml), se

añadió hidrazina monohidratada (0,5 ml). Se agitó la mezcla de reacción a 90°C durante 15 horas. Después de enfriar hasta temperatura ambiente se inactivó la reacción con agua y se extrajo con acetato de etilo. Se secó la fase orgánica sobre sulfato de sodio, se filtró y se concentró a presión reducida. Se recristalizó el residuo en éter dietílico proporcionando 3-{6-[2-(benciloxi)fenil]-1H-pirazolo[3,4-b]piridin-4-il}-1-piperidincarboxilato de *terc*-butilo en forma de un sólido blanco (0,030 g, 23%). Después se trató el 3-{6-[2-(benciloxi)fenil]-1H-pirazolo[3,4-b]piridin-4-il}-1-piperidincarboxilato de *terc*-butilo de manera similar a la de la etapa (2) del ejemplo 1-1 y después la etapa (3) del ejemplo 1-1, obteniendo clorhidrato de 2-(4-piperidin-3-il-1H-pirazolo[3,4-b]piridin-6-il)fenol.



Peso molecular: 330,82

Espectrometría de masas: 295 $(M + H)^+$

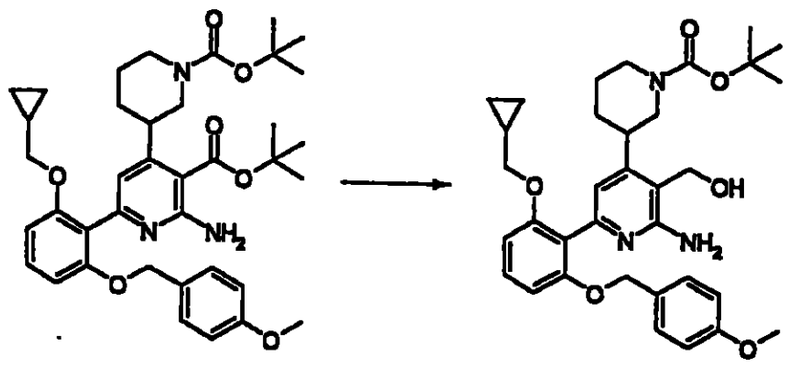
Grado de actividad in vitro: B

Grado de actividad celular: (A549)-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,91 – 2,05 (4H, m), 6,97 – 7,00 (2H, m), 7,35 - 7,87 (1H, m), 7,87 (1H, s), 8,16 (1H, d, J=7,3 Hz), 8,42 (1H, s), 8,96 (1H, s a), 9,26 (1H, s a).

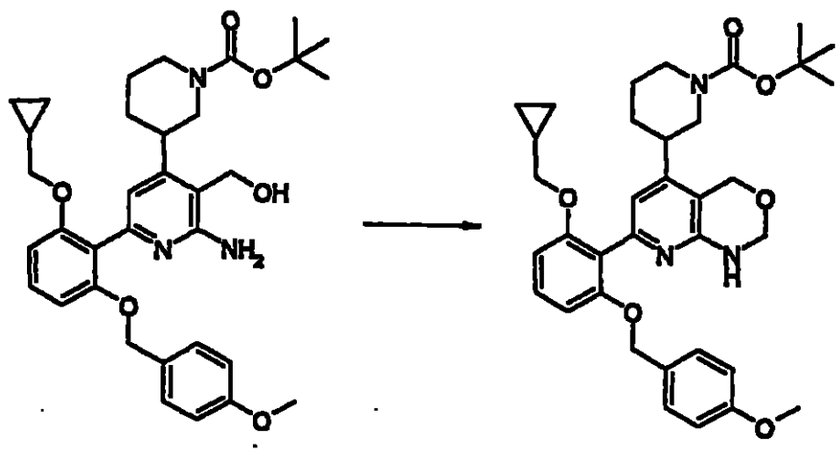
Ejemplo 17-1

(1) Se agitó a 90°C durante la noche una mezcla de compuesto de partida 1G (10,00 g, 30,368 mmol), 2B (13,069 g, 61,275 mmol), cianoacetato de *terc*-butilo (8,650 g, 61,275 mmol) y acetato de amonio (6,902 g, 91,913 mmol) en dioxano (10 ml). Después de enfriar hasta temperatura ambiente se diluyó la mezcla de reacción con acetato de etilo (100 ml). Se añadió a la mezcla cloranilo (1,507 g, 6,128 mmol) y se agitó a temperatura ambiente. Después de agitar durante 1,5 horas se añadió ácido ascórbico (1,079 g, 6,128 mmol) a la mezcla. Después de agitar durante 1,5 horas se repartió la mezcla entre acetato de etilo y agua. Se lavó la fase orgánica con salmuera, se secó sobre $MgSO_4$, se filtró y después se concentró a presión reducida. Se purificó el residuo resultante mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo: 2/1), proporcionando 2-amino-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]-6-{2-(ciclopropilmetoxi)-6-[(4-metoxi-bencil)oxi]fenil}-nicotinato de *terc*-butilo en forma de una espuma marrón pálido (4,9 g, 24%).

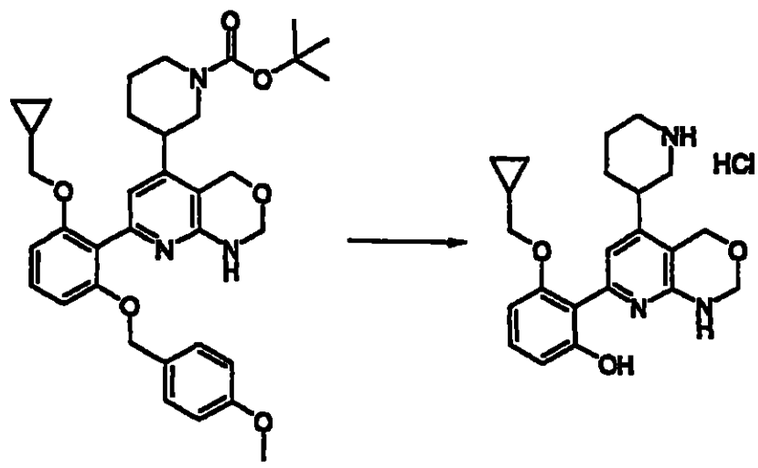


(2) A una solución enfriada de 2-amino-4-[1-(*terc*-butoxicarbonil)-3-piperidinil]-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}nicotinato de *terc*-butilo (4,9 g, 7,426 mmol) en tetrahidrofurano (60 ml), se añadió gota a gota Vitride® (10 ml) en atmósfera de argón. Se continuó la agitación a 0°C durante 1 hora. Después de inactivar mediante una solución acuosa saturada de NH_4Cl, se añadió tartrato de potasio y sodio acuoso

saturado a la mezcla, después se agitó vigorosamente la mezcla. Se extrajo la mezcla con acetato de etilo, se lavó con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida, proporcionando 3-[2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo, que se utilizó para la siguiente etapa sin purificación adicional (4,38 g, rendimiento: cuantitativo).



(3) A una solución agitada de 3-[2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,501 g, 0,850 mmol) en 1,4-dioxano, se añadió una solución de formaldehído al 37% (5,000 ml) y HCl 1 N (5,000 ml). Se agitó la mezcla a temperatura ambiente durante 2 horas. Se extrajo la mezcla de reacción con acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el residuo resultante mediante cromatografía en columna sobre gel de silice (acetato de etilo/hexano= 3/2), proporcionando 3-{7-[2-(ciclopropilmetil)oxi]-6-({[4-(metiloxi)fenil]-metil}oxi)fenil]-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il}-1-piperidin-carboxilato de dimetiletil(*terc*-butilo) en forma de una espuma incolora (0,319 g, rendimiento: 62%).



(4) A una solución agitada de 3-{7-[2-(ciclopropilmetil)oxi]-6-({[4-(metiloxi)fenil]-metil}oxi)fenil]-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il}-1-piperidin-carboxilato de dimetiletil(*terc*-butilo) (0,050 g, 0,083 mmol) en 1,4-dioxano, se añadió HCl 4 N en 1,4-dioxano (2,000 ml). Se agitó la mezcla a temperatura ambiente durante 6 horas. Se concentró la mezcla de reacción a presión reducida. Se lavó el residuo resultante con acetonitrilo proporcionando clorhidrato de 3-(ciclopropilmetoxi)-2-[5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-7-il]fenol en forma de un sólido incoloro (0,033 g, rendimiento: 95%).

Peso molecular: 417,94

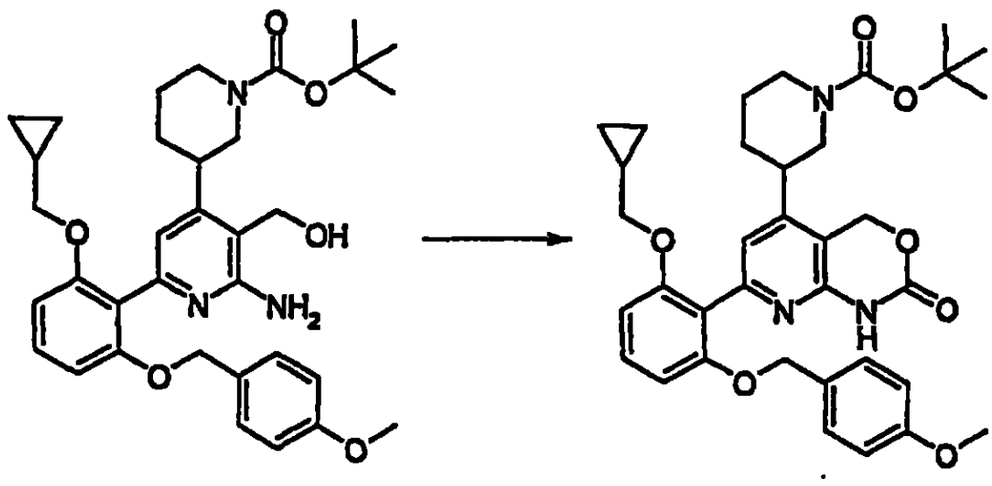
Espectrometría de masas: 382 $(M + H)^+$

Grado de actividad in vitro: A

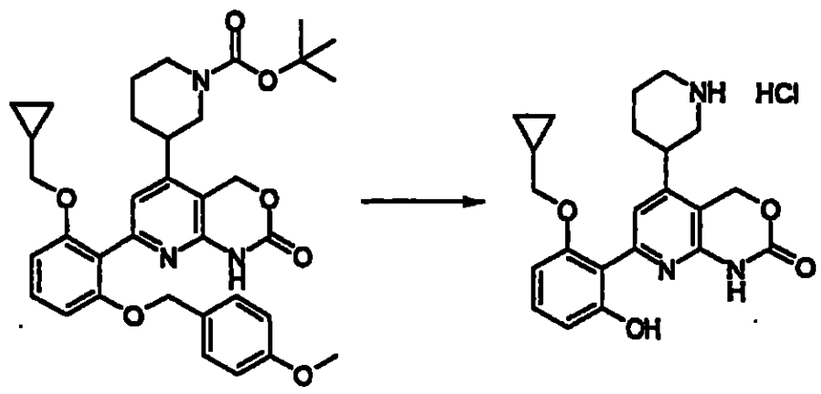
Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,30 (2H, s a), 0,51 (2H, s a), 1,17 (1H, m), 1,84 (4H, m), 2,86 (1H, m), 4,91 (2H, a), 5,01 (2H, a), 6,58 (1H, d, J=7,9 Hz), 6,64 (1H, a), 7,16 (1H, a), 7,26 (1H, t, J=7,9 Hz), 8,30 (1H, a), 9,14 (1H, a), 9,29 (1H, a), 13,95 (1H, a).

Ejemplo 18-1



A una solución enfriada (0°C) de 3-[2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (5,0 g, 8,478 mmol), que se obtuvo en la etapa (2) del ejemplo 17-1, y diisopropiletilamina (4,12 ml, 25,435 mmol) en tetrahidrofurano (200 ml) en atmósfera de argón, se añadió gota a gota una solución de trifosgeno (1,258 g, 4,239 mmol) en tetrahidrofurano (100 ml). Se dejó calentar la mezcla hasta temperatura ambiente y se continuó la agitación durante 3 horas. Después de inactivar con agua se extrajo la mezcla con acetato de etilo. Se lavó la fase orgánica separada con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. Se purificó el residuo resultante mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo: 1:1), proporcionando 3-(7-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il)-1-piperidincarboxilato de *terc*-butilo en forma de una espuma blanca (3,2 g, rendimiento: 61%).



A una solución de 3-(7-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il)-1-piperidincarboxilato de *terc*-butilo (2,0 g, 3,248 mmol) en dioxano (15 ml), se añadió HCl 4 N en dioxano (30 ml) a temperatura ambiente. Se continuó la agitación durante 3 horas. Después de retirar el disolvente por evaporación, se trituró el sólido resultante con acetonitrilo, se recogió por filtración y se lavó con acetonitrilo. Se secó el sólido a presión reducida proporcionando clorhidrato de 7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-2-ona en forma de un sólido blanco (0,865 g, rendimiento: 62%).

Peso molecular: 431,92

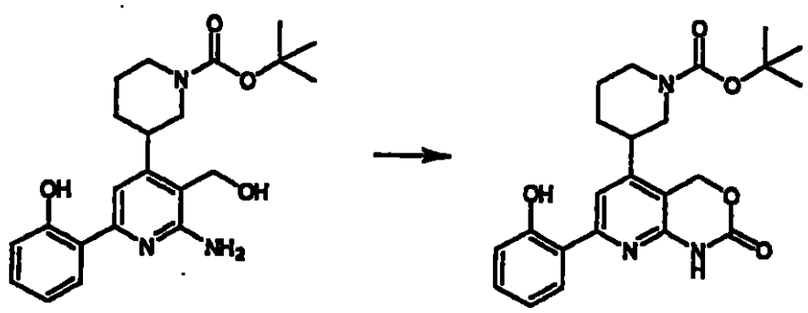
Espectrometría de masas: 396 $(M + H)^+$

Grado de actividad in vitro: A

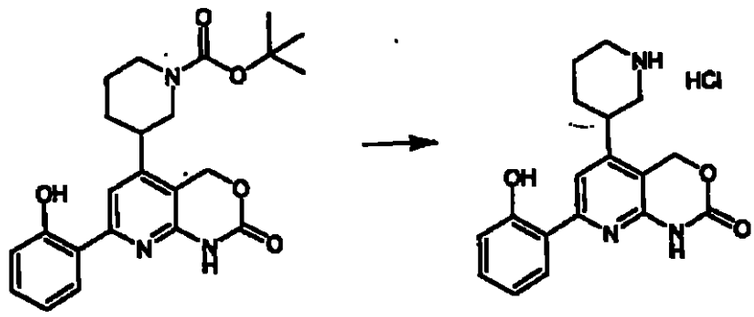
Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,26 - 0,37 (2H, m), 0,51 – 0,63 (2H, m), 1,20 - 1,31 (1H, m), 1,72 - 1,95 (4H, m), 2,80 – 2,96 (2H, m), 3,17 - 3,37 (3H, m), 3,79 – 3,88 (2H, m), 5,48 (1H, d, J=14,2 Hz), 5,53 (1H, d, J=14,2 Hz), 6,54 (2H, d, J=8,2 Hz), 7,17 (1H, t, J=8,2 Hz), 7,77 (1H, s), 9,06 (1H, a), 9,27 (1H, a), 10,96 (1H, a).

Ejemplo 18-2



A a una solución fría (0°C) de 3-[2-amino-3-(hidroximetil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,297 g, 0,74 mmol), que se obtuvo en la etapa (1) del ejemplo 11-1 en THF (3,00 ml), que incluía trietilamina (0,226 g, 2,23 mmol), se añadió trifosgeno (0,221 g, 0,74 mmol). Después de 30 minutos, se dejó calentar la mezcla hasta temperatura ambiente y se continuó la agitación durante 1 hora. Se inactivó la reacción con una solución acuosa de $NaHCO_3$ y se extrajo con acetato de etilo. Se lavó la fase orgánica con una solución acuosa de NH_4Cl, agua y salmuera sucesivamente. Se secó la fase orgánica sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el residuo resultante mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo, 3:2), proporcionando 3-[7-(2-hidroxifenil)-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]-oxazin-5-il]-1-piperidincarboxilato de *terc*-butilo en forma de un sólido amarillo pálido (46,2 g, rendimiento: 14,6%).



A una solución de 3-[7-(2-hidroxifenil)-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il]-1-piperidincarboxilato de *terc*-butilo (45 mg, 0,11 mmol) en 1,4-dioxano (1,0 ml), se añadió HCl 4 N en 1,4-dioxano (2,0 ml). Se agitó la mezcla durante 1 hora a temperatura ambiente. Se recogió el sólido resultante por filtración, se lavó con 1,4-dioxano y se secó a presión reducida proporcionando clorhidrato de 7-(2-hidroxifenil)-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-2-ona en forma de un sólido blanco (22,8 mg, rendimiento: 60%).

Peso molecular: 361,83

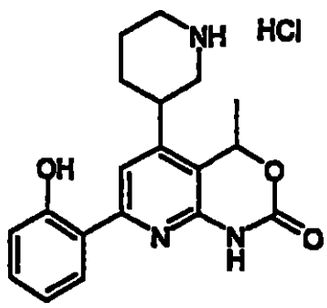
Espectrometría de masas: 326 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A/Jurkat-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,80 – 1,96 (5H, m), 2,86 – 2,93 (1H, m), 3,13 – 3,26 (3H, m), 5,46 – 5,55 (2H, m), 6,91 – 6,94 (2H, m), 7,30 – 7,33 (1H, m), 7,77 (1H, s), 8,03 – 8,04 (1H, m), 11,15 (1H, s), 12,46 (1H, s a).

Ejemplo 18-3



Utilizando 3-[2-amino-3-(1-hidroxietil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidin-carboxilato de *terc*-butilo, que se obtuvo en la etapa (2) del ejemplo 15-1, se preparó clorhidrato de 7-(2-hidroxifenil)-4-metil-5-piperidin-3-il-1,4-dihidrobenzo[d][1,3]-

oxazin-2-ona de manera similar a la del ejemplo 18-2.

Peso molecular: 375,86

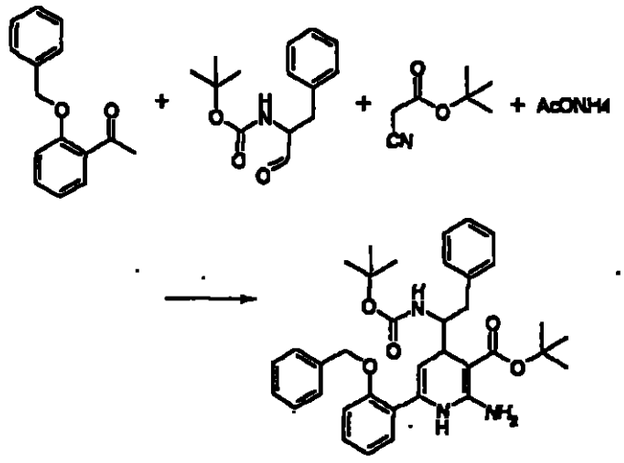
Espectrometría de masas: 340 $(M + H)^+$

Grado de actividad in vitro: B

Grado de actividad celular: (A549)-B

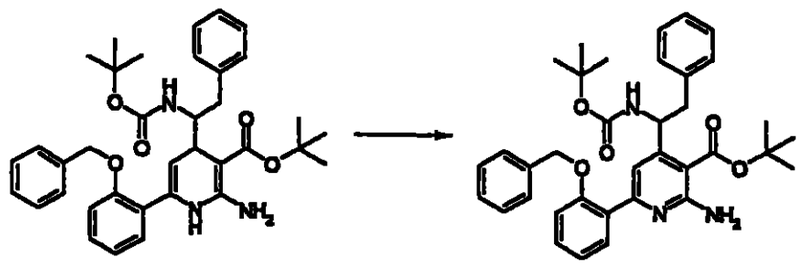
RMN de ^1H (500 MHz, DMSO-d_6): 1,52 – 1,53 (3H, m), 1,80 – 2,04 (5H, m), 2,91 – 2,95 (1H, m), 3,13 – 3,21 (3H, m), 5,83 – 5,85 (1H, m), 6,92 – 6,95 (3H, m), 7,32 (1H, dd, J=7,9, 7,3 Hz), 8,04 (1H, d, J=7,6 Hz), 11,2 (1H, s), 12,44 (1H, s a)

Ejemplo 18-4/18-5

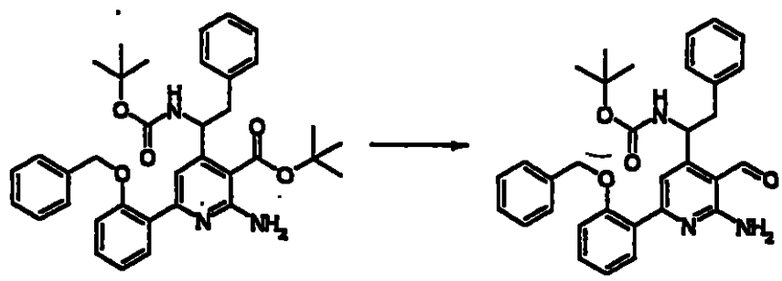


Se calentó a reflujo durante 6 horas una mezcla de material de partida 1A (3,000 g, 13,258 mmol), N-*terc*-butoxicarbonilfenilalaninal (3,305 g, 13,258 mmol), cianoacetato de *terc*-butilo (1,872 g, 13,258 mmol), acetato de amonio (3,066 g, 39,774 mmol) y 1,2-dimetoxietano (5,0 ml). Después de enfriar a temperatura ambiente se extrajo la mezcla con acetato de etilo y una solución saturada de $NaHCO_3$. Se lavó la fase orgánica separada con agua y salmuera sucesivamente, se secó sobre Na_2SO_4, se filtró y se

concentró a presión reducida. Se trituró el residuo con éter diisopropílico proporcionando 2-amino-6-[2-(benciloxi)fenil]-4-{1-[(*terc*-butoxicarbonil)amino]-2-feniletil}-1,4-dihidro-3-piridincarboxilato de *terc*-butilo en forma de un sólido amarillo (1,281 g, rendimiento: 16%).

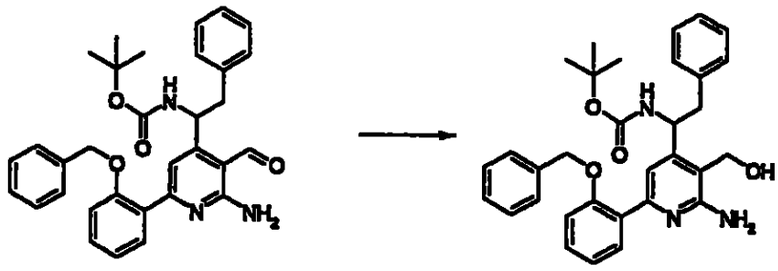


A una solución de 2-amino-6-[2-(benciloxi)fenil]-4-{1-[(*terc*-butoxicarbonil)amino]-2-feniletil}-1,4-dihidro-3-piridincarboxilato de *terc*-butilo (1,200 g, 2,007 mmol) en cloruro de metileno (20,0 ml) a temperatura ambiente, se añadió cloranilo (0,543 g, 2,208 mmol), y se continuó la agitación durante 1 hora. Se filtró la mezcla y se concentró el filtrado a presión reducida. Se extrajo el residuo con acetato de etilo y una solución acuosa al 10% de $NaHCO_3$. Se lavó la fase orgánica separada con agua y salmuera sucesivamente, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se cristalizó el producto bruto a partir de etanol proporcionando 2-amino-6-[2-(benciloxi)fenil]-4-{1-[(*terc*-butoxicarbonil)amino]-2-feniletil}nicotinato de *terc*-butilo en forma de un sólido amarillo pálido (0,972 g, rendimiento: 84%).

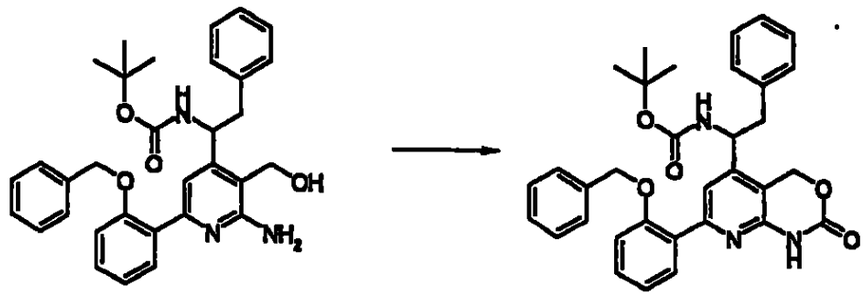


A una solución fría (0°C) de 2-amino-6-[2-(benciloxi)fenil]-4-{1-[(*terc*-

butoxicarbonil)amino]-2-feniletil}nicotinato de *terc*-butilo (0,100 g, 0,198 mmol) en THF (1,50 ml), se añadió gota a gota Vitride® (0,500 ml), y se continuó la agitación durante 2 horas. Se inactivó la mezcla a 0°C con una solución acuosa saturada de NH_4Cl y se extrajo con acetato de etilo. Se lavó la fase orgánica separada con agua y salmuera sucesivamente, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el producto bruto mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo, 1:1) proporcionando 1-{2-amino-6-[2-(benciloxi)fenil]-3-formil-4-piridinil}-2-feniletilcarbamato de *terc*-butilo en forma de un aceite incoloro (0,044 g, rendimiento: 51%).



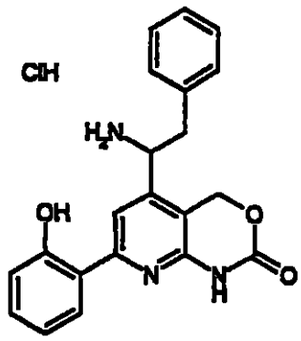
A una solución de 1-{2-amino-6-[2-(benciloxi)fenil]-3-formil-4-piridinil}-2-feniletilcarbamato de *terc*-butilo (0,040 g, 0,092 mmol) en etanol (1,0 ml), se añadió $NaBH_4$ (0,010 g, 0,26 mmol), y se continuó la agitación durante 3 horas. Se extrajo la mezcla con acetato de etilo y una solución acuosa saturada de cloruro de amonio. Se lavó la fase orgánica separada con agua y salmuera sucesivamente, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se cristalizó el producto bruto a partir de etanol, proporcionando 1-[2-amino-6-[2-(benciloxi)fenil]-3-(hidroximetil)-4-piridinil]-2-feniletilcarbamato de *terc*-butilo en forma de un sólido amarillo pálido (0,023 g, rendimiento; 57%).



A una solución fría (0°C) de 1-[2-amino-6-[2-(benciloxi)fenil]-3-(hidroximetil)-4-piridinil]-2-feniletilcarbamato de *terc*-butilo (0,210 g, 0,400 mmol) en THF (3,0 ml), que incluía trietilamina (0,167 ml, 1,199 mmol), se añadió gota a gota una solución de trifosgeno (0,059 g, 0,200 mmol) en THF (1,0 ml). Después de agitar a 0°C durante 45 minutos se dejó calentar la mezcla hasta temperatura ambiente, y se continuó la agitación durante 30 minutos. Se enfrió la mezcla de reacción hasta 0°C, y después se inactivó con una solución acuosa saturada de $NaHCO_3$. Se extrajo la mezcla resultante con acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el producto bruto mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo, 2:1), proporcionando 1-{7-[2-(benciloxi)fenil]-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il}-2-feniletil-carbamato de *terc*-butilo en forma de un aceite incoloro (0,170 g, rendimiento: 77%).

A continuación, de manera similar a la de la etapa (2) del ejemplo 1-1 y la etapa (3) del ejemplo 1-1, se trató 1-{7-[2-(benciloxi)fenil]-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il}-2-feniletilcarbamato de *terc*-butilo, proporcionando clorhidrato de 5-(1-amino-2-feniletil)-7-(2-hidroxifenil)-1,4-dihidropirido[2,3-d][1,3]oxazin-2-ona.

Ejemplo 18-4/18-5



Peso molecular: 397,86

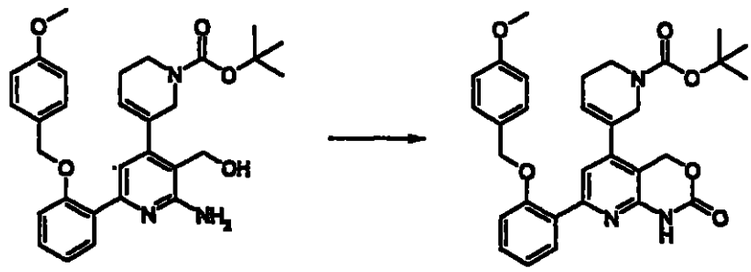
Espectrometría de masas: 362 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-B

RMN de ^1H (500 MHz, DMSO-d_6): 3,11 (1H, dd, J=10,1, 12,9 Hz), 3,44 (1H, dd, J=5,0, 12,9 Hz), 4,25 (1H, d, J=14,5 Hz), 4,71 – 4,74 (1H, m), 5,35 (1H, d, J=14,5 Hz), 6,93 – 6,99 (2H, m), 7,08 (2H, dd, J=1,9, 7,3 Hz), 7,23 – 7,28 (3H, m), 7,33 – 7,36 (1H, m), 8,13 (1H, dd, J=1,3, 7,9 Hz), 8,37 (1H, s), 8,98 (3H, a), 11,18 (1H, s), 12,32 (1H, a).

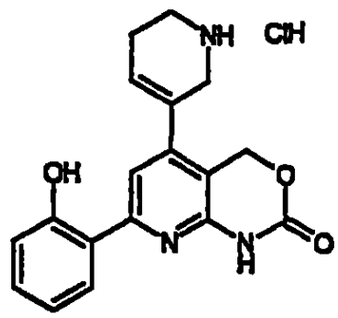
Ejemplo 18-6



A una solución enfriada (0°C) de 2'-amino-3'-(hidroximetil)-6'-{2-[(4-metoxibencil)oxi]fenil}-5,6-dihidro-3,4'-bipiridin-1(2H)carboxilato de *terc*-butilo (25,0 mg, 0,05 mmol), que se obtuvo en la etapa (2) del ejemplo 11-4, y trietilamina (0,02 ml, 0,14 mmol) en THF (3,0 ml), se añadió una solución de trifosgeno (5,7 mg, 0,02 mmol)

en THF (3,0 ml). y se continuó la agitación durante 30 minutos. Se dejó calentar la mezcla de reacción hasta temperatura ambiente. Se enfrió la reacción a 0°C y después se inactivó mediante la adición de una solución acuosa saturada de $NaHCO_3$ y se extrajo con acetato de etilo. Se lavó la fase orgánica separada con salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó. Se purificó el producto bruto mediante TLC preparativa con gel de sílice (acetona al 10% en cloroformo), proporcionando 5-(7-{2-[(4-metoxibencil)oxi]fenil}-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il)-3,6-dihidro-1(2H)-piridincarboxilato de *terc*-butilo en forma de un sólido blanco (21,7 mg, rendimiento: 83%).

A continuación se retiraron el *terc*-butilo y metoxibencilo de manera similar a la de la etapa (2) del ejemplo 1-1.



Peso molecular: 359,82

Espectrometría de masas: 324 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

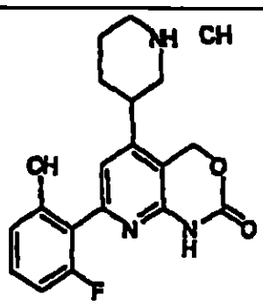
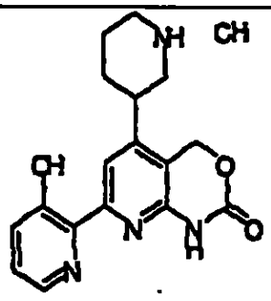
RMN de ^1H (500 MHz, MeOH-d4): 2,63 – 2,65 (2H, m), 3,44 – 3,49 (2H, m), 4,02 (2H, d a, J=1,9 Hz), 5,45 (2H, s), 6,04 (1H, s), 6,88 – 6,95 (2H, m), 7,29 – 7,32 (1H, m), 7,63 (1H, s), 7,90 (1H, dd, J=1,3, 7,9 Hz) .

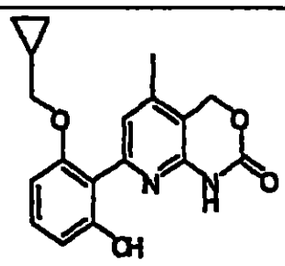
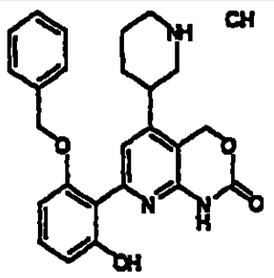
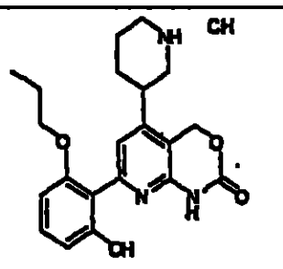
362
361

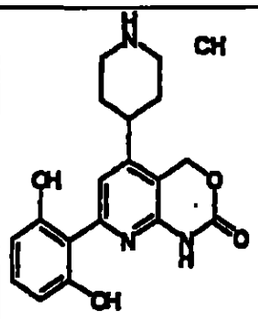
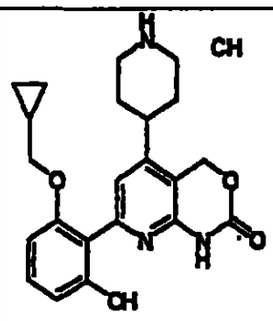
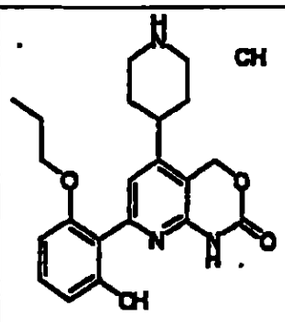
Ejemplos 18-7 a 18-16

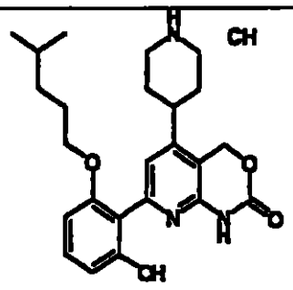
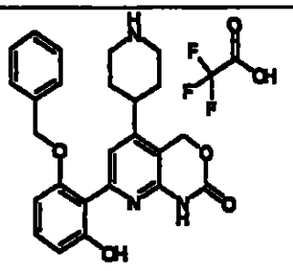
Se prepararon los compuestos mostrados en la tabla 5 según un procedimiento sintético similar al de los ejemplos 18-1 a 18-6.

Tabla 5

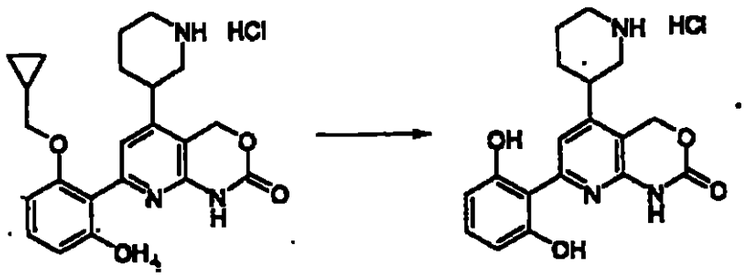
Ej. Nº	Estructura	Peso molecular	Masa	*In vitro*	A549	RMN
18-07		379,82	Sin pico	A	A	(500 MHz, DMSO-d_6): 1,82 (4H, m), 3,02 (3H, m), 3,29 (2H, d, J=21,5 Hz), 5,50 (2H, dd, J=23,9, 39,6 Hz), 6,73 (1H, d, J=23,9 Hz), 6,78 (1H, m), 7,28 (1H, dd, J=13,6, 24,8 Hz), 7,34 (1H, s), 8,58 (1H, m), 8,97 (1H, m), 10,95 (1H, s)
18-08		362,82	327	A	A	(500 MHz, DMSO-d_6): 1,88 - 1,94 (4H, m), 3,28 – 3,33 (2H, m), 3,57 – 3,59 (1H, m), 3,63 – 3,74 (2H, m), 5,51 (2H, d, J=14,2 Hz), 5,58 (1H, d, J=14,2 Hz), 7,39 – 7,40 (2H, m), 8,14 (1H, a), 8,22 (1H, t, J=2,8 Hz), 11,25 (1H, s)

18-09		326,36	327	C	A	(500 MHz, DMSO-d_6): 0,34 – 0,44 (2H, m), 0,61 – 0,72 (2H, m), 1,24 – 1,35 (1H, m), 2,33 (3H, s), 3,89 (2H, d, J=6,9 Hz), 5,39 (2H, s), 6,45 (1H, dd, J=1,0, 8,5 Hz), 6,65 (1H, dd, J=1,0, 8,5 Hz), 7,18 (1H, t, J=8,5 Hz), 7,54 (1H, s a), 8,10 (1H, s), 12,48 (1H, s a)
18-10		467,96	432	A	A	(500 MHz, DMSO-d_6): 1,25-1,32 (1H, m), 1,53–1,83 (3H, m), 2,58–2,80 (2H, m), 3,01–3,07 (1H, m), 3,13–3,18 (1H, m), 3,27–3,30 (1H, m), 5,07 (2H, dd, J=11,0, 18,2 Hz), 5,44 (2H, dd, J=14,2, 24,0 Hz), 6,58 (1H, d, J=8,2 Hz), 6,72 (1H, d, J=8,2 Hz), 7,22 (1H, t, J=8,2 Hz), 7,34–7,46 (6H, m), 8,77 (1H, a), 9,04 (1H, a), 10,92 (1H, a)
18-11		419,91	384	A	A	(300 MHz, DMSO-d_6): 0,90 (3H, t, J=7,2 Hz), 1,72 (2H, m), 1,84–1,88 (2H, m), 2,85–2,92 (2H, m), 3,18-3,34 (4H, m), 3,90-3,95 (2H, m), 5,48 (2H, d, J=5,6 Hz), 6,55 (2H, d, J=8,3, 8,5 Hz), 7,17 (1H, t, J=8,3 Hz), 7,54 (1H, s), 8,88 (1H, a), 9,13 (1H, a), 10,89 (1H, s)

18-12		377,83	342	B	C	(500 MHz, DMSO-d_6): 1,70-1,73 (2H, m), 1,78-1,89 (2H, m), 2,87–2,90 (2H, m), 3,00–3,05 (2H, m), 4,05 (1H, m), 5,49 (2H, s), 6,39 (1H, d, J=8,2 Hz), 6,42 (1H, d, J=8,2 Hz), 7,04 (1H, m), 7,92 (1H, m), 8,55 (1H, a), 8,77 (1H, a 10,95 (1H, s), 10,99 (1H, s)
18-13		431,92	396	A	A	(500 MHz, DMSO-d_6): 0,28-0.30 (2H, m), 0,55-0,58 (2H, m), 1,31 (1H, m), 1,88 (4H, m), 3,01-3,04 (3H, m), 3,35-3,38 (2H, m), 3,84 (2H, d, J=6,9 Hz), 5,50 (2H, s), 6,53 (2H, d, J=8,2 Hz), 7,17 (1H, t, J=8,2 Hz), 7,74 (1H, s), 8,92 (1H, a), 9,00 (1H, a), 10,95 (1H, s)
18-14		419,91	384	A	A	(500 MHz, DMSO-d_6): 0,90 (3H, t, J=7,5 Hz), 1,75 (2H, m), 1,85 (4H, m), 3,02 (3H, m), 3,36 (2H, m), 3,95 (2H, t, J=7,6 Hz), 5,49 (2H, s), 6,53 (1H, d, J=7,9 Hz), 6,57 (1H, d, J=8,2 Hz); 7,18 (1H, t, J=8,2 Hz), 7,50 (1H, s), 8,88 (1H, a), 8,99 (1H, a), 10,90 (1H, s)

18-15		461,99	426	A	A	(500 MHz, DMSO-d_6): 0,81 (6H, d, J=6,6 Hz), 1,14-1,19 (2H, m), 1,47–1,51 (1H, m), 1,67–1,71 (2H, m), 1,83-1,90 (4H, m), 2,96-3,06 (3H, m), 3,31-3,33 (2H, m), 3,95-3,97 (2H, m), 5,49 (2H, s), 6,53-6,58 (2H, m), 7,17 (1H, t, J=8,3 Hz), 7,42 (1H, s), 9,05-9,11 (1H, m), 10,88 (1H, a)
18-16		545,52		A	B	(500 MHz, DMSO-d_6): 1,56-1,64 (4H, m), 2,95 (4H, s a), 5,09 (2H, s), 5,45 (2H, s), 6,55-6,59 (1H, m), 6,70 (1H, d, J=8,3 Hz), 7,20 (1H, t, J=8,1 Hz), 7,33-7,38 (6H, m), 8,26 (1H, s a), 8,57 (1H, s a), 10,85 (1H, s a), 11,11 (1H, s a)

Ejemplo 19-1



Se agitó a 80°C durante la noche una mezcla de clorhidrato de 7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-2-ona (0,070 g, 0,160 mmol), que se obtuvo en el ejemplo 18-1, y HCl 2,5 N en 1,4-dioxano (4 ml). Después de enfriar hasta temperatura ambiente se concentró la mezcla a presión reducida. Se diluyó el residuo resultante con diclorometano (3 ml) y se añadió

trietilamina (0,064 g, 0,497 mmol). Se añadió a la mezcla enfriada (0°C) dicarbonato de di-*terc*-butilo (0,047 g, 0,218 mmol) en atmósfera de argón. Se continuó la agitación a temperatura ambiente durante la noche. Después de inactivar con agua, se extrajo la mezcla con acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. Se purificó el residuo mediante TLC preparativa (hexano/acetato de etilo= 1/1), proporcionando 3-[7-(2,6-dihidroxifenil)-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il]-1-piperidincarboxilato de *terc*-butilo (0,019 g, 19%). A una solución de 3-[7-(2,6-dihidroxifenil)-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il]-1-piperidincarboxilato de *terc*-butilo en dioxano (1 ml), se añadió HCl 4 N en dioxano (1 ml) a temperatura ambiente. Se continuó la agitación durante 3 horas. Después de retirar el disolvente por evaporación, se lavó el residuo resultante con acetonitrilo y se secó a presión reducida proporcionando clorhidrato de 7-(2,6-dihidroxifenil)-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]-oxazin-2-ona en forma de un sólido marrón (0,007 g, 46%).

Peso molecular: 377,83

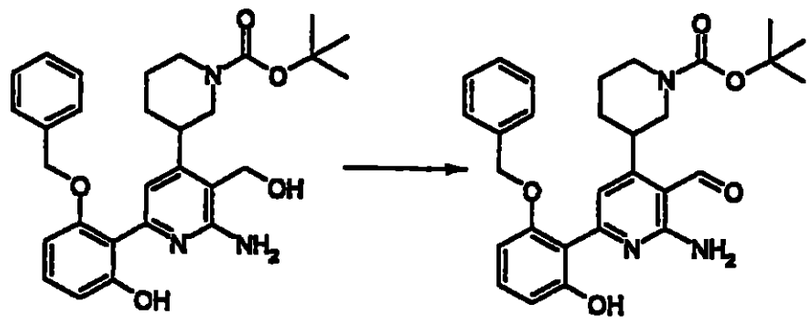
Espectrometría de masas: 342 $(M + H)^+$

Grado de actividad in vitro:

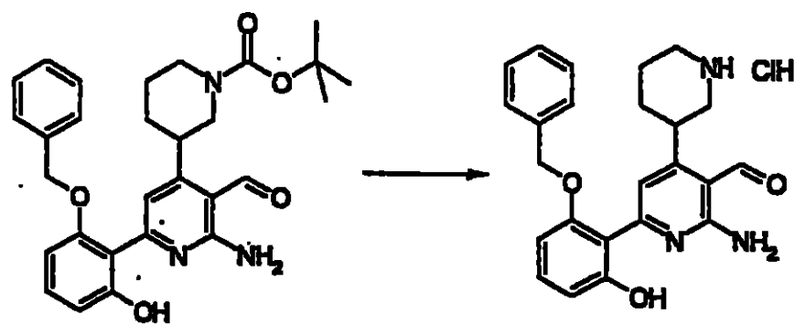
Grado de actividad celular: (A549)-

RMN de ^1H (500 MHz, DMSO-d_6): 1,73 – 1,89 (4H, m), 2,89-2,94 (2H, m), 3,19 (1H, m), 3,25 – 3,32 (2H, m), 5,46 (1H, d, J=14,2 Hz), 5,51 (1H, d, J=14,2 Hz), 6,41 (2H, d, J=8,2 Hz), 7,03 (1H, t, J=8,2 Hz), 7,88 (1H, s), 8,90 (1H, a), 9,14 (1H, a), 11,01 (1H, s).

Ejemplo 20-1

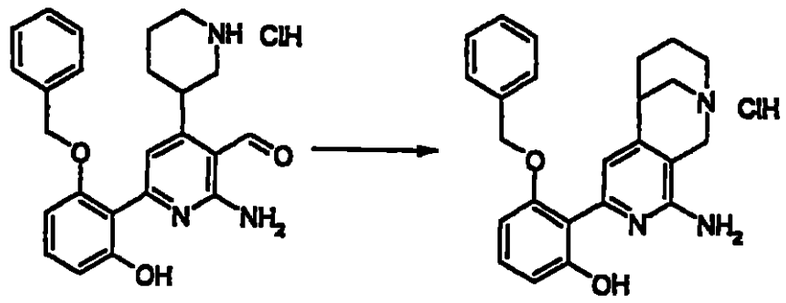


A una solución agitada de 3-[2-amino-6-[2-(benciloxi)-6-hidroxifenil]-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,100 g, 0,198 mmol), que se obtuvo en un procedimiento similar al del ejemplo 13-1, en diclorometano (3 ml), se añadió MnO_2 (0,340 g, 3,956 mmol). Se agitó la mezcla a temperatura ambiente durante 2 horas. Se filtró la mezcla a través de celite® y se concentró a presión reducida. Se recristalizó el residuo en alcohol etílico proporcionando 3-{2-amino-6-[2-(benciloxi)-6-hidroxifenil]-3-formil-4-piridinil}-1-piperidincarboxilato de *terc*-butilo en forma de un sólido amarillo (0,092 g, rendimiento: 93%).



A una solución agitada de 3-{2-amino-6-[2-(benciloxi)-6-hidroxifenil]-3-formil-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,090 g, 0,183 mmol) en 1,4-dioxano (2 ml), se añadió HCl 4 N en dioxano (2 ml). Se agitó la mezcla a temperatura ambiente durante 2 horas. Se recogió el precipitado resultante por filtración, se lavó con

acetonitrilo y se secó a presión reducida, proporcionando clorhidrato de 2-amino-6-[2-(benciloxi)-6-hidroxifenil]-4-(3-piperidinil)nicotinaldehído (0,103 g, rendimiento: cuantitativo).



A una solución fría (0°C) de clorhidrato de 2-amino-6-[2-(benciloxi)-6-hidroxifenil]-4-(3-piperidinil)nicotinaldehído (0,100 g, 0,227 mmol) en metanol, se añadió $NaBH_3CN$ (0,040 ml, 0,682 mmol) en atmósfera de argón. Se agitó la mezcla a temperatura ambiente durante 12 horas y se concentró a presión reducida. Se extrajo el residuo con acetato de etilo y agua. Se lavó la fase orgánica separada con una solución acuosa saturada de $NaHCO_3$ y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el residuo resultante mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo= 2/1), proporcionando 2-(6-amino-5,9-diazatriciclo[7.3.1.$0^{2,7}$]trideca-2,4,6-trien-4-il)-3-(benciloxi)fenol en forma de un sólido blanco.

A una solución agitada de 2-(6-amino-5,9-diazatriciclo[7.3.1.$0^{2,7}$]trideca-2,4,6-trien-4-il)-3-(benciloxi)fenol en 1,4-dioxano (2 ml), se añadió HCl 4 N en dioxano (2 ml). Se agitó la mezcla a temperatura ambiente durante 2 horas. Se recogió el precipitado resultante por filtración, se lavó con acetonitrilo y se secó a presión reducida, proporcionando clorhidrato de 2-(6-amino-5,9-diazatriciclo[7.3.1.$0^{2,7}$]trideca-2,4,6-

trien-4-il)-3-(benciloxi)fenol (0,018 g, rendimiento: 19%).

Peso molecular: 423,95

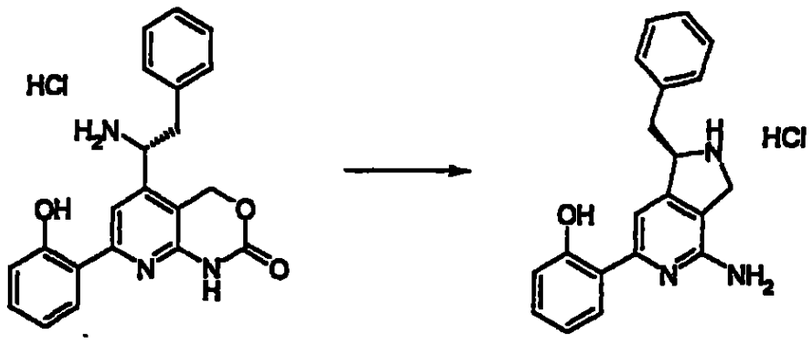
Espectrometría de masas: 388 $(M + H)^+$

Grado de actividad in vitro: B

Grado de actividad celular: (A549)-C

RMN de ^1H (500 MHz, DMSO-d_6): 1,10 – 1,23 (2H, m), 1,41 (1H, d, J=12,3 Hz), 1,71 – 1,80 (1H, m), 2,79 (1H, d, J=12,9 Hz), 2,89 – 2,91 (2H, m), 2,97 (1H, d, J=12,9 Hz), 3,44 (2H, d, J=18,3 Hz), 3,81 (1H, d, J=18,0 Hz), 5,09 – 5,17 (2H, m), 6,01 (1H, s), 6,64 (1H, d, J=8,5 Hz), 7,13 (1H, t, J=8,2 Hz), 7,33 – 7,41 (4H, m), 7,49 (2H, d, J=1,6 Hz).

Ejemplo 20-2



Se calentó a reflujo durante 2 horas una mezcla de clorhidrato de 5-[(1R)-1-amino-2-feniletil]-7-(2-hidroxifenil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-2-ona (0,014 g, 0,035 mmol), que se obtuvo en el ejemplo 18-4, en acetonitrilo (3,0 ml). Se concentró la mezcla resultante a presión reducida. Se disolvió el residuo en 1,4-dioxano (1,0 ml), se trató con una solución de HCl 4 N en 1,4-dioxano (0,5 ml) y se concentró a presión reducida. Se trituró el residuo con acetonitrilo y se secó a presión reducida,

proporcionando clorhidrato de 2-[(1R)-4-amino-1-bencil-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-il]fenol en forma de un sólido blanco (0,010 g, rendimiento: 80%).

Peso molecular: 353,85

Espectrometría de masas: 318 $(M + H)^+$

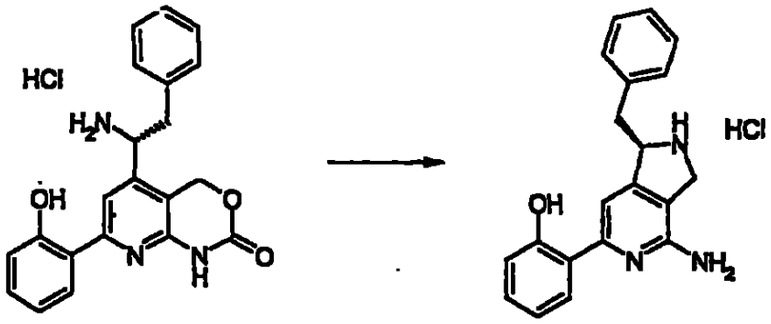
Grado de actividad in vitro: A

Grado de actividad celular: (A549)-B

RMN de ^1H (500 MHz, DMSO-d_6): 3,30 (1H, dd, J=9,1, 14,1 Hz), 3,54 (1H, dd, J=5,0, 14,1 Hz), 4,26 – 4,42 (2H, m a), 5,20 (1H, a), 6,91 (1H, t, J=7,9 Hz), 6,97 (1H, d, J=8,2 Hz), 7,29 – 7,39 (2H, m), 7,41 (1H, t, J=7,9 Hz), 7,62 (1H, d, J=7,3 Hz), 10,14 (1H, a), 10,31 (1H, a), 13,90 (1H, a).

Ejemplo 20-3

De manera similar a la descrita en los ejemplos 20-1 y 20-2, se preparó clorhidrato de 2-[(1S)-4-amino-1-bencil-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-il]fenol.



Peso molecular: 353,85

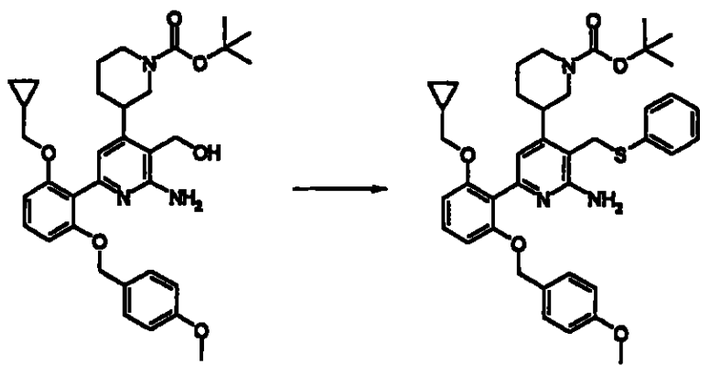
Espectrometría de masas: 318 $(M + H)^+$

Grado de actividad in vitro: A

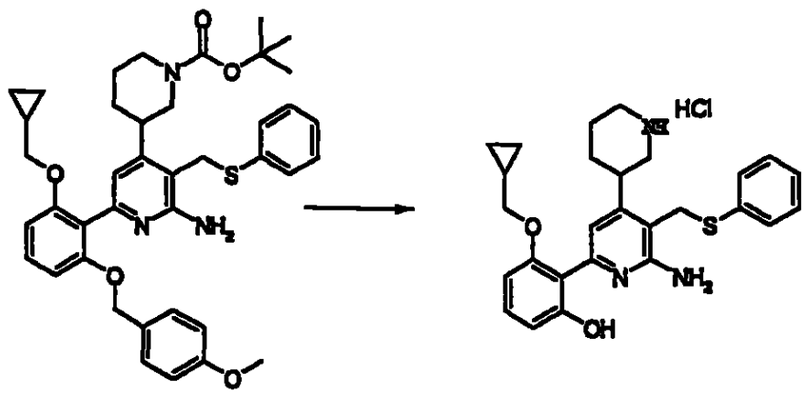
Grado de actividad celular: (A549)-B

RMN de ^{1}H (500 MHz, DMSO-d_6): 3,30 (1H, dd, J=9,1, 14,1 Hz), 3,54 (1H, dd, J=5,0, 14,1 Hz), 4,26 – 4,42 (2H, m a), 5,20 (1H, a), 6,91 (1H, t, J=7,9 Hz), 6,97 (1H, d, J=8,2 Hz), 7,29 – 7,39 (2H, m), 7,41 (1H, t, J=7,9 Hz), 7,62 (1H, d, J=7,3 Hz), 10,14 (1H, a), 10,31 (1H, a), 13,90 (1H, a).

Ejemplo 21-1



(1) A una solución agitada de 3-[2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,050 g, 0,085 mmol), que se obtuvo en la etapa (2) del ejemplo 17-1, y disulfuro de fenilo (0,055 g, 0,254 mmol) en tetrahidrofurano (3 ml), se añadió tributilfosfina (0,060 ml, 0,254 mmol). Se agitó la mezcla a temperatura ambiente durante 24 horas. Se extrajo la mezcla con acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el residuo resultante (líquido) mediante cromatografía en columna sobre gel de sílice (hexano/acetato de etilo: 3/1 – 1/1), proporcionando 3-{2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-[(fenil-sulfanil)metil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,021 g, rendimiento: 37%) en forma de una espuma.



(2) A una solución agitada de 3-{2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-[(fenilsulfanil)metil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo en 1,4-dioxano (2 ml), se añadió HCl 4 N en dioxano (2 ml). Se agitó la mezcla a temperatura ambiente durante la noche y se diluyó con acetato de etilo. Se recogió el precipitado resultante por filtración, se lavó con etanol y se secó a presión reducida, proporcionando clorhidrato de 2-[6-amino-5-[(fenilsulfanil)metil]-4-(3-piperidinil)-2-piridinil]-3-(ciclopropilmetoxi)fenol.

Peso molecular: 498,09

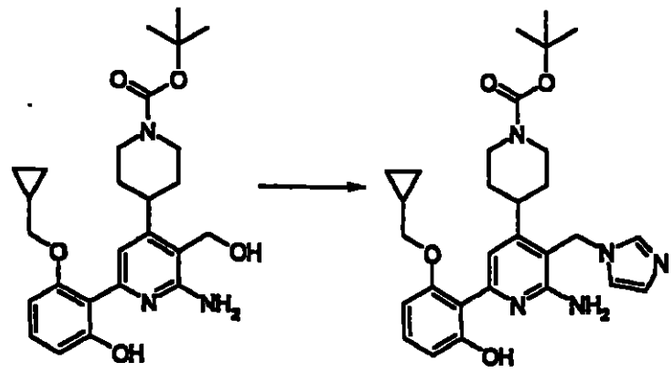
Espectrometría de masas: 462 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-B

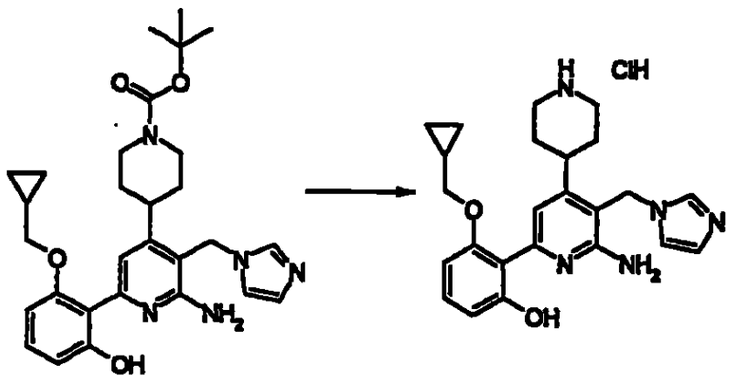
RMN de ^1H (500 MHz, DMSO-d_6): 0,30 (2H, s a), 0,51 (2H, s a), 1,67 (2H, m), 1,80 (1H, a), 4,26 (1H, d, J=12,6 Hz), 4,37 (1H, a), 6,59 (2H, a), 7,36 (2H, t, J=7,6 Hz), 7,46 (2H, d, J=7,6 Hz), 7,72 (1H, a), 8,61 – 8,98 (2H, a), 10,36 (1H, a), 13,58 (1H, a).

Ejemplo 21-2



(1) Utilizando el compuesto de partida 1G, éster *terc*-butílico del ácido 4-formilpiperidin-1-carboxílico, preparado de manera similar a la del compuesto de partida 2B y otros materiales se preparó 4-[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo de manera similar a la de la etapa (1) del ejemplo 11-1.

(2) A una solución agitada de 4-[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,250 g, 0,528 mmol) en acetonitrilo (10 ml), se añadió 1,1'-carbonildiimidazol (0,170 g, 1,056 mmol) a temperatura ambiente. Después de agitar durante 2 horas, se extrajo la mezcla de reacción con acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se recogió el sólido resultante por filtración, se lavó con hexano y se secó a presión reducida, proporcionando 4-[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-(1H-imidazol-1-ilmetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,242 g, rendimiento: 88%).



(3) A una solución agitada de 4-[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-(1H-imidazol-1-ilmetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,260 g, 0,500 mmol) en 1,4-dioxano (10 ml), se añadió HCl 4 N en dioxano (10 ml). Se agitó la mezcla a temperatura ambiente durante 2 horas. Se recogió el precipitado resultante por filtración, se lavó con acetonitrilo y se secó a presión reducida, proporcionando clorhidrato de 2-[6-amino-5-(1H-imidazol-1-ilmetil)-4-(4-piperidinil)-2-piridinil]-3-(ciclopropilmetoxi)fenol (0,248 g, rendimiento: cuantitativo).

Peso molecular: 455,99

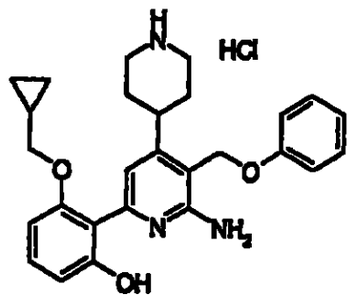
Espectrometría de masas: 420 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,32 (2H, d, J=4,7 Hz), 0,52 (2H, d, J=4,7 Hz), 1,27 (1H, s a), 1,71 (2H, d, J=13,6 Hz), 1,91 – 1,98 (2H, m), 3,00 – 3,31 (2H, m), 3,32 – 3,35 (3H, m), 3,86 (2H, d, J=6,9 Hz), 5,62 (2H, s), 6,58 (1H, d, J=8,5 Hz), 6,64 (1H, d, J=6,9 Hz), 7,26 (1H, dd, J=8,5, 7,9 Hz), 7,66 (1H, s), 7,71 (1H, s), 9,31 (1H, s).

Ejemplo 21-3



Utilizando carbonato de difenilo en lugar de clorhidrato de 1,1'-carbonildiimidazol, se preparó clorhidrato de 2-[6-amino-5-(fenoximetil)-4-(4-piperidinil)-2-piridinil]-3-(ciclopropilmetoxi)fenol de manera similar a la del ejemplo 21-2.

Peso molecular: 482,03

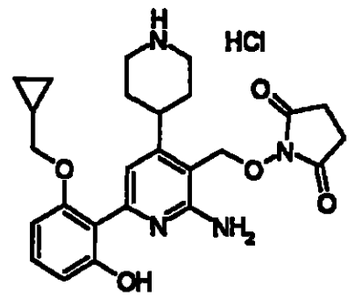
Espectrometría de masas: 446 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,31 (2H, d, J=4,7 Hz), 0,50 (2H, d, J=6,9 Hz), 1,16 – 1,19 (1H, m), 1,84 (2H, d, J=13,2 Hz), 1,91 – 1,99 (2H, m), 2,96 (2H, m), 3,57 (1H, s), 3,76 (2H, d, J=6,6 Hz), 5,20 (2H, s), 6,61 (1H, d, J=8,2 Hz), 6,66 (1H, d, J=6,0 Hz), 6,75 (1, d, J=8,5 Hz), 7,20 (1H, t, J=7,3 Hz), 7,08 (2H, d, J=7,9 Hz), 7,15 (1H, t, J=7,9 Hz), 7,36 (2H, t, J=7,9 Hz).

Ejemplo 21-4



Utilizando carbonato de N,N'-disuccinimidilo en lugar de clorhidrato de 1,1'-carbonildiimidazol, se preparó 1-{[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(4-piperidinil)-3-piridinil]metoxi}-2,5-pirrolidindiona de manera similar a la del ejemplo 21-2.

Peso molecular: 503,00

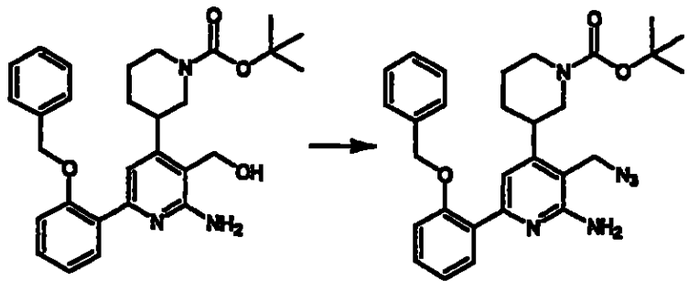
Espectrometría de masas: 467 $(M + H)^+$

Grado de actividad in vitro: A

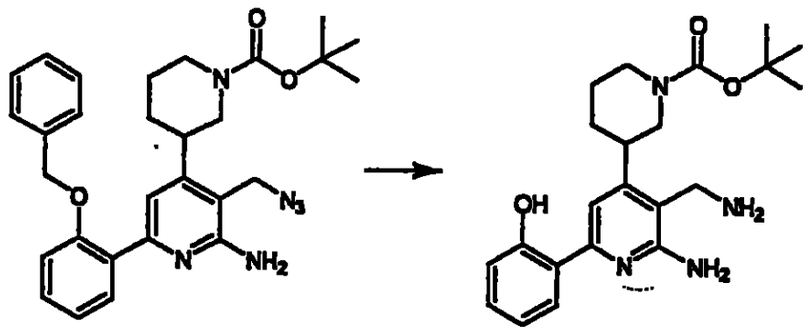
Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,19 (2H, d, J=5,0 Hz), 0,52 (2H, d, J=7,3 Hz), 1,21 (1H, s a), 1,91 – 1,96 (4H, m), 2,71 (4H, s), 3,03 (2H, d, J=8,2 Hz), 3,85 (2H, d, J=6,9 Hz), 5,18 (2H, s), 6,59 (1H, d, J=8,5 Hz), 6,64 (1H, d, J=7,6 Hz), 7,05 (1H, s a), 7,27 (1H, t, J=7,9 Hz), 7,60 (1H, s a), 8,82 (1H, s a), 8,92 (1H, d, J=9,1 Hz).

Ejemplo 22-1

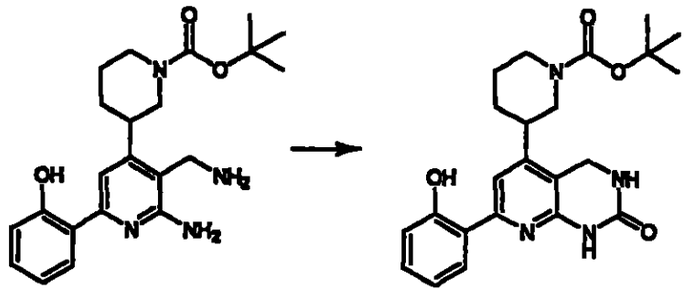


(1) A una solución fría (0°C) de 3-[2-amino-6-[2-(benciloxi)fenil]-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,050 g, 0,102 mmol), obtenido en la etapa (1) del ejemplo 13-1, en tolueno (1,0 ml), se añadió difenilfosforilazida (0,024 ml, 0,112 mmol) seguida de 1,8-diazabiciclo[5.4.0]undec-7-eno (0,017 ml, 0,112 mmol). Después de 30 minutos, se dejó calentar la mezcla hasta temperatura ambiente y se continuó la agitación durante 2 horas. Se concentró la mezcla a presión reducida y se repartió el residuo entre acetato de etilo y agua. Se lavó la fase orgánica separada con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el residuo mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo, 2:1), proporcionando 3-{2-amino-3-(azidometil)-6-[2-(benciloxi)fenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,038 g, rendimiento: 72%).

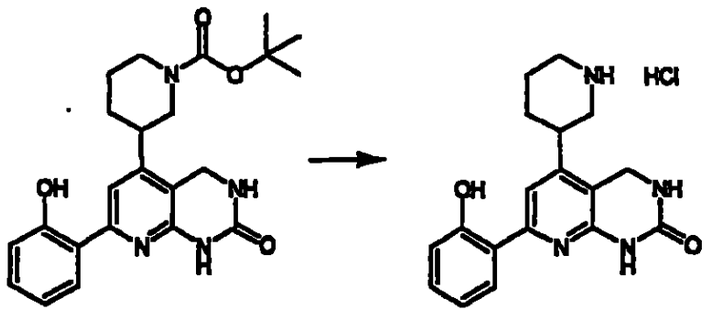


(2) Se sometió a hidrogenación a 1 atm en presencia de paladio sobre carbón (10%, 0,015 g) durante la noche una solución de 3-{2-amino-3-(azidometil)-6-[2-

(benciloxi)fenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,030 g, 0,058 mmol) en acetato de etilo (1,0 ml). Se filtró la mezcla resultante y se lavó con acetato de etilo. Se concentró el filtrado reunido a presión reducida, proporcionando 3-[2-amino-3-(aminometil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo, que se utilizó para la siguiente etapa sin purificación adicional.



(3) A una solución fría (0°C) de 3-[2-amino-3-(aminometil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,020 g, 0,050 mmol) en THF (2,0 ml) en atmósfera de argón, se añadió 1,1'-carbonildiimidazol (0,009 g, 0,055 mmol). Después de agitar durante 15 minutos, se inactivó la mezcla con una solución saturada de bicarbonato de sodio. Se repartió la mezcla resultante entre acetato de etilo y una solución saturada de cloruro de amonio. Se lavó la fase orgánica separada con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se disolvió el residuo en acetato de etilo (2,0 ml). Se calentó la mezcla a 60°C durante 1 hora y se dejó enfriar hasta temperatura ambiente. Se recogieron los precipitados resultantes por filtración, se lavarón con acetato de etilo y se secaron a presión reducida, proporcionando 3-[7-(2-hidroxifenil)-2-oxo-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-5-il]-1-piperidincarboxilato de *terc*-butilo (0,007 g, rendimiento: 33%).



(4) Se trató 3-[7-(2-hidroxifenil)-2-oxo-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-5-il]-1-piperidincarboxilato de *terc*-butilo (0,006 g, 0,014 mmol) en condiciones ácidas de manera similar a la descrita en la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de 7-(2-hidroxifenil)-5-(3-piperidinil)-3,4-dihidropirido[2,3-d]pirimidin-2(1H)-ona (0,005 g, rendimiento: 98%).

Peso molecular: 360,85

Espectrometría de masas: 325 $(M + H)^+$

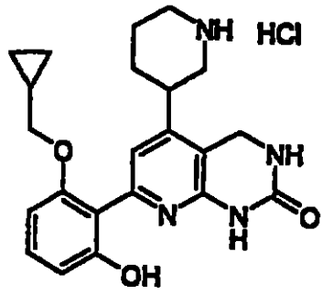
Grado de actividad in vitro: A

Grado de actividad celular: B

RMN de ^1H (500 MHz, DMSO-d_6): 1,76 – 1,93 (4H, m), 2,88 – 3,37 (5H, m), 4,47 (2H, dd, J=15,4, 24,3 Hz), 6,87 – 6,92 (2H, m), 7,26 – 7,30 (2H, m), 7,63 (1H, s), 8,00 (1H, d, J=8,2 Hz), 8,57 (1H, a), 9,01 (1H, a), 10,08 (1H, s), 12,78 (1H, a).

Ejemplo 22-2

380
379



Utilizando el compuesto de partida 1G, 2B y otros materiales, se preparó clorhidrato de 7-(2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-3,4-dihidro-1H-pirido-[2,3-d]pirimidin-2-ona de manera similar a la del ejemplo 22-1.

Peso molecular: 430,94

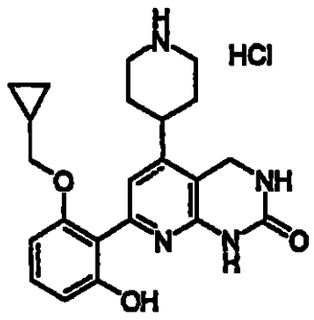
Espectrometría de masas: 395 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,34 (2H, m), 0,57 (2H, m), 1,27 (1H, m), 1,73 – 1,87 (4H, m), 2,82 – 2,90 (2H, m), 3,14 (1H, m), 3,29 – 3,33 (2H, m), 3,80 – 3,88 (2H, m), 4,49 (2H, s), 6,52 (2H, d, J=8,2 Hz), 7,16 (1H, t, J=8,2 Hz), 7,75 (1H, s), 9,11 (1H, a), 9,26 (1H, a), 9,92 (1H, s).

Ejemplo 22-3



Utilizando el compuesto de partida 1G y ácido 4-formilpiperidin-1-carboxílico y otros materiales, se preparó clorhidrato de 7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(4-piperidinil)-3,4-dihidro-1H-pirido[2,3-d]pirimidin-2-ona de manera similar a la del ejemplo 22-1.

Peso molecular: 430,94

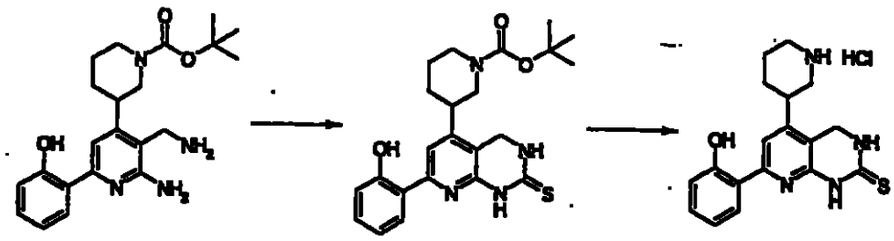
Espectrometría de masas: 395 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,32 (2H, d, J=4,5 Hz), 0,57 (2H, d, J=1,7 Hz), 1,33 – 1,38 (1H, m), 1,80 – 1,91 (4H, m), 2,96 – 3,05 (3H, m), 3,34 – 3,39 (3H, m), 4,47 (2H, s), 6,51 (2H, dd, J=3,8, 8,3 Hz), 7,15 (1H, t, J=7,9 Hz), 7,24 (1H, s), 7,74 (1H, s), 9,86 (1H, s).

Ejemplo 22-4



Utilizando 3-[2-amino-3-(aminometil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo obtenido en la etapa (2) del ejemplo 22-1, se preparó clorhidrato de 7-(2-hidroxifenil)-5-(3-piperidinil)-3,4-dihidro-1H-pirido[2,3-d]pirimidin-2-tiona de manera similar a la del ejemplo 22-1 ó 22-2.

Peso molecular: 447,00

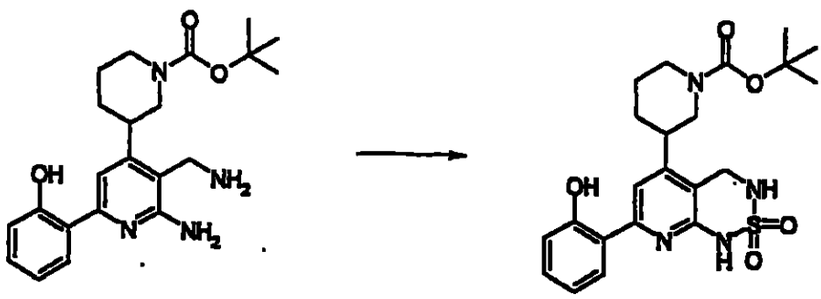
Espectrometría de masas: 411 $(M + H)^+$

Grado de actividad in vitro:

Grado de actividad celular: (A549)-

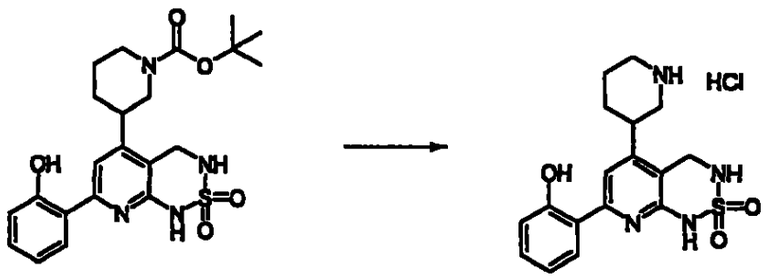
RMN de ^1H (500 MHz, DMSO-d_6): 0,33 – 0,36 (2H, m), 0,57 – 0,59 (2H, m), 1,28 (1H, m), 1,72 – 1,81 (2H, m), 1,89 – 1,90 (2H, m), 2,82 – 2,89 (2H, m), 3,00 (1H, m), 3,27 – 3,34 (2H, m), 3,82 – 3,85 (2H, m), 4,54 – 4,56 (2H, m), 6,52 (2H, d, J=8,2 Hz), 7,16 (1H, t, J=8,2 Hz), 7,83 (1H, s), 8,73 (1H, a), 9,08 (2H, a), 11,13 (1H, s).

Ejemplo 22-5



Se agitó a reflujo durante la noche una mezcla de 3-[2-amino-3-(aminometil)-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,060 g, 0,151 mmol), que se obtuvo en la etapa (2) del ejemplo 22-1, sulfamina (0,022 g, 0,226 mmol) y piridina (2,0 ml). Después de enfriar hasta temperatura ambiente, se repartió la mezcla entre acetato de etilo y agua. Se lavó la fase orgánica separada con una solución 0,5 N

de HCl, agua y salmuera sucesivamente, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó el producto bruto mediante cromatografía en columna sobre gel de sílice (hexano:acetato de etilo, 1:1), proporcionando 3-[7-(2-hidroxifenil)-2,2-dióxido-3,4-dihidro-1H-pirido[2,3-c][1,2,6]tiadiazin-5-il]-1-piperidincarboxilato de *terc*-butilo en forma de una espuma amarillo pálido (0,059 g, rendimiento: 85%).



A continuación, se trató el carbamato de *terc*-butilo de manera similar a la de la etapa (3) del ejemplo 1-1, proporcionando clorhidrato de 2-[2,2-dióxido-5-(3-piperidinil)-3,4-dihidro-1H-pirido[2,3-c][1,2,6]tiadiazin-7-il]fenol.

Peso molecular: 396,90

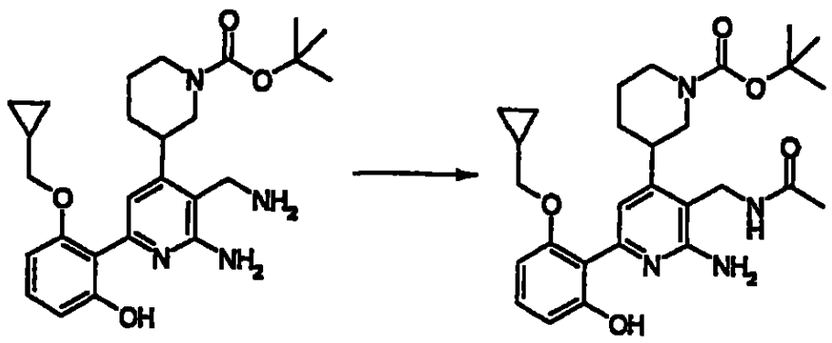
Espectrometría de masas: 361 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-B

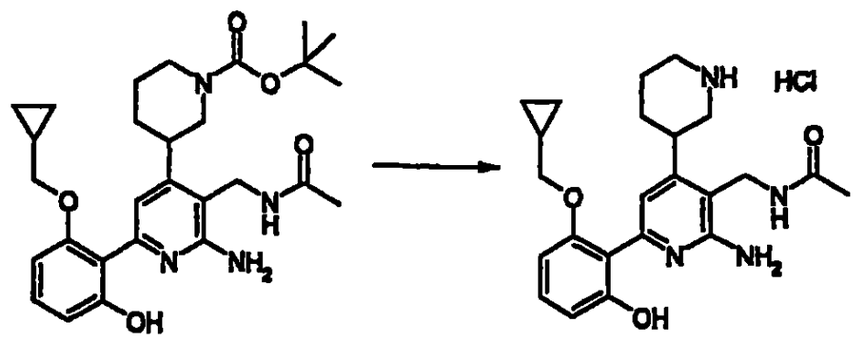
RMN de ^1H (500 MHz, DMSO-d_6): 1,82 – 1,91 (4H, m), 2,86 – 2,93 (1H, m), 3,18 – 3,36 (4H, m), 4,52 (2H, s), 6,90 – 6,93 (2H, m), 7,30 (1H, dt, J=1,6, 8,5 Hz), 7,65 (1H, s a), 8,00 (1H, d, J=7,6 Hz), 8,97 (1H, a), 9,32 (1H, a).

Ejemplo 23-1



(1) Utilizando los compuestos de partida 1G, 2B y mediante un proceso similar al de las etapas (1) y (2) del Ejemplo 22-1, se preparó una solución de 3-{2-amino-3-(aminometil)-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo.

(2) A una solución fría (0°C) de 3-{2-amino-3-(aminometil)-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (1,9 g, 4,055 mmol) y trietilamina (1,13 ml, 8,109 mmol) en tetrahidrofurano (40 ml) se añadió anhídrido acético (0,457 ml, 4,865 mmol). Se agitó la mezcla a 0°C durante 4 horas. Una vez enfriada con agua, la mezcla se extrajo con acetato de etilo y agua. La fase orgánica separada se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El producto resultante (sólido amarillo) se purificó mediante recristalización en acetato de etilo/éter diisopropílico proporcionando 3-{3-acetilamino-metil)-2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (1,13 g, rendimiento; 55%)



(3) Se trató el carbamato de *terc*-butilo de forma similar a la de la etapa (3) del Ejemplo 1-1 proporcionando clorhidrato de N-{[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil}-3-piridinil] metil}acetamida.

Peso molecular: 446,98

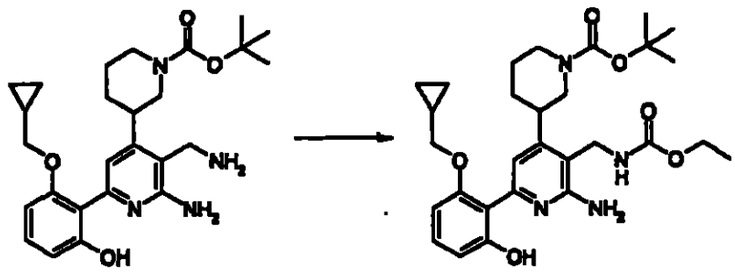
Espectrometría de masas: 411 $(M + H)^+$

Grado de actividad in vitro: A

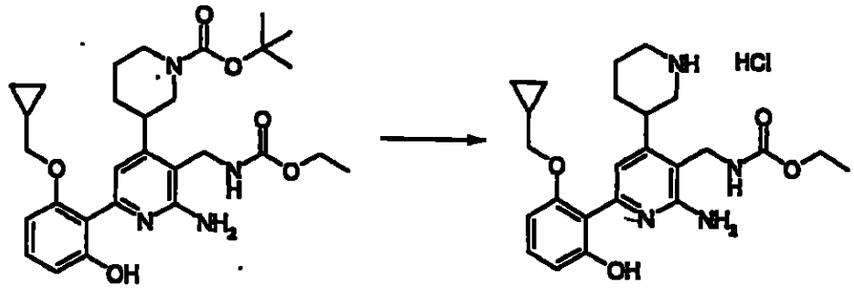
Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,28 – 0,30 (2H, m), 0,47 – 0,50 (2H, m), 1,13 (1H, m), 1,85 – 1,90 (4H, m), 1,93 (3H, s), 2,88 (1H, m), 3,06 (1H, m), 3,23 (1H, m), 3,33 (1H, m), 3,73 (1H, m), 3,80 (2H, m), 4,32 – 4,39 (2H, dd, J=5,6, 15,5 Hz), 6,58 (1H, d, J=8,5 Hz), 6,65 (1H, d, J=8,2 Hz), 7,09 (1H, s), 7,27 (1H, t, J=8,2 Hz), 7,80 (1H, a), 8,98 (2H, a), 9,29 (1H, a), 13,63 (1H, a).

Ejemplo 23-2



(1) A una solución fría (0°C) de 3-{[2-amino-3-(2-aminometil)-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,300 g, 0,640 mmol), que se obtuvo en la etapa (1) del Ejemplo 23-1, y trietilamina (0,067 ml, 0,704 mmol) en tetrahidrofurano (30 ml) se añadió cloroformiato de etilo (0,134 ml, 0,960 mmol) en una atmósfera de argón. Se dejó que la mezcla se calentara hasta temperatura ambiente, y se siguió agitando durante 4 horas. Después de enfriarse con agua, la mezcla se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, a continuación se concentró a presión reducida. El producto resultante se purificó por cromatografía en columna sobre gel de sílice (hexano / acetato de etilo = 1/1) proporcionando 3-(2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-{[(etoxicarbonil)amino]metil}-4-(piridinil)-1-piperidincarboxilato de *terc*-butilo como una espuma amarillo pálido (0,246 g, rendimiento; 71%).



(2) A continuación el carbamato de *terc*-butilo se trató de manera similar a la de la etapa (3) del Ejemplo 1-1 proporcionando clorhidrato de [2-amino-6-[-2-(ciclopropilmetoxi)-

6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]metilcarbamato de etilo.

Peso molecular: 477,01

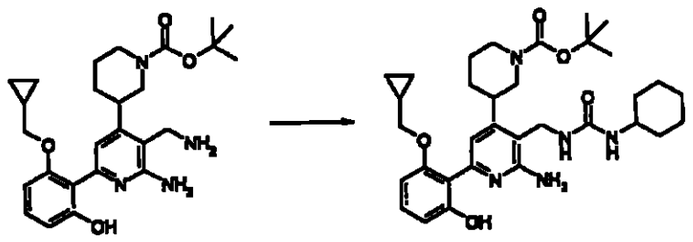
Espectrometría de masas: 441 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

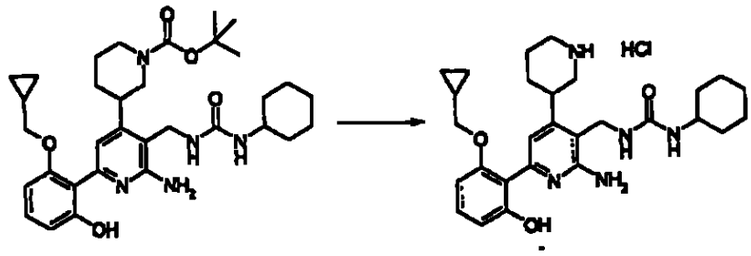
RMN de ^1H (500 MHz, DMSO-d_6): 0,28 – 0,30 (2H, m), 0,48 – 0,51 (2H, m), 1,17 (3H, t, J=7,1 Hz), 1,22 (1H, m), 1,82 – 1,89 (5H, m), 2,88 (1H, m), 3,03 (1H, m), 3,25 (1H, m), 3,69 (1H, m), 3,84 (2H, m), 4,03 (2H, q, J=6,9 Hz), 4,28 (2H, dd, J=5,4, 15,1 Hz), 6,59 (1H, d, J=8,2 Hz), 6,65 (1H, d, J=8,2 Hz), 7,11 (1H, a), 7,27 (1H, t, J=8,2 Hz), 7,64 (1H, s), 7,86 (1H, s), 8,80 (1H, s), 9,27 (1H, s).

Ejemplo 23-3



(1) A una solución de 3-{2-amino-3-aminometil}-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,150 g, 0,320 mmol), que se obtuvo en la etapa (1) del Ejemplo 23-1, en tetrahidrofurano (10,0 ml) se le añadió isocianato de ciclohexilo (0,044 g, 0,352 mmol). La mezcla se agitó a temperatura ambiente durante 1,5 horas y se concentró a presión reducida. El producto resultante se purificó mediante un TLC preparativa (acetato de etilo) proporcionando 3-[2-amino-3-[(3-cicloexil-ureido)-metil]-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo como una espuma amarilla (0,113 g,

rendimiento; 60%).



(2) A continuación el carbamato de *terc*-butilo se trató de manera similar a la de la etapa (3) del ejemplo 1-1 proporcionando clorhidrato de N-{[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil}-3-piridinil]metil}-N'-ciclohexilurea.

Peso molecular: 530,12

Espectrometría de masas: 494 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

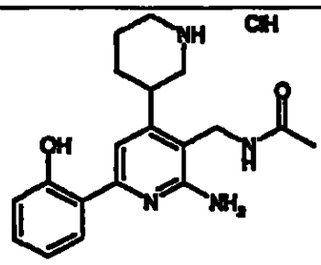
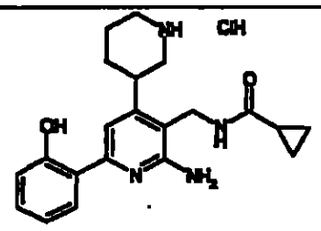
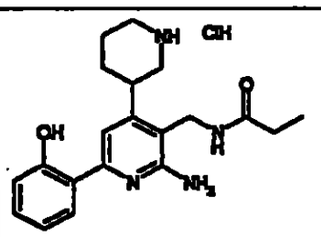
RMN de ^1H (500 MHz, DMSO-d_6): 0,27 – 0,28 (2H, m), 0,47 – 0,49 (2H, m), 1,10 – 1,14 (4H, m), 1,22 – 1,27 (3H, m), 1,51 (1H, m), 1,61 – 1,65 (2H, m), 1,73 – 1,74 (3H, m), 1,83 – 1,89 (5H, m), 2,88 (1H, m), 3,01 (1H, m), 3,72 (1H, m), 3,78 – 3,85 (2H, m), 4,29 – 4,32 (2H, m), 6,59 (1H, d, J=8,5 Hz), 6,66 (1H, d, J=8,2 Hz), 7,05 (1H, s), 7,27 (1H, t, J=8,2 Hz), 8,98 (1H, s), 9,25 (1H, s), 10,3 (1H, s), 13,5 (1H, s).

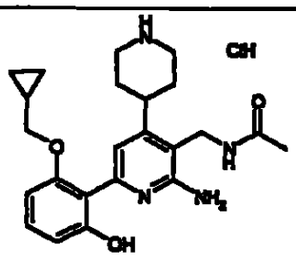
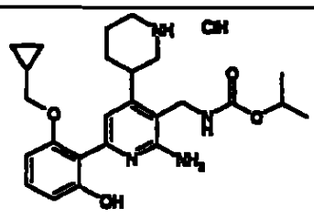
Ejemplos 23-4 a 23-15.

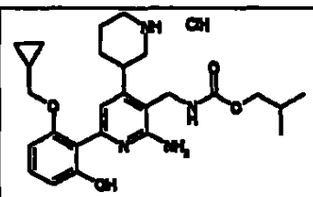
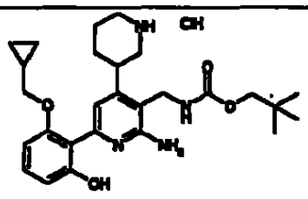
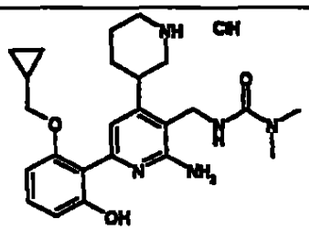
Los compuestos de la tabla 6 se prepararon de acuerdo con el procedimiento sintético similar al de los Ejemplos 23-1 a 23-3.

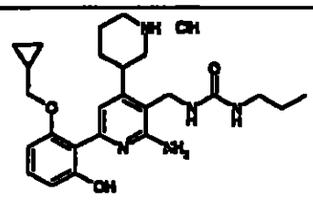
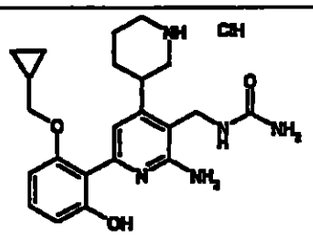
~~384~~
388

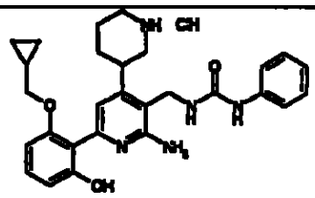
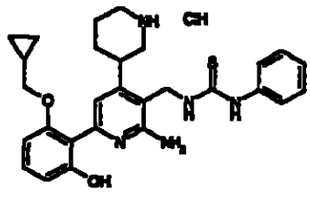
Tabla 6

Ej. Nº	Estructura	Peso molecular	Masa	In vitro	A549	RMN
23-04		376,89	341	A	A	(500 MHz, DMSO-d_6): 1,80–1,95 (4H, m), 2,90-2,95 (1H, m), 3,13-3,34 (2H, m), 4,26 (1H, dd, J=5,8, 15,2 Hz), 4,34 (1H, dd, J=5,8, 15,2 Hz)), 6,95 (1H, t, J=7,3 Hz), 6,98 (1H, d, J=8,2 Hz), 7,22 (1H, s), 7,35 (1H, t, J=8,2 Hz), 7,67 (1H, s a), 8,81 (1H, a), 8,93 (1H, a), 9,26 (1H, a), 13,66 (1H, a)
23-05		402,93	367	A	A	(500 MHz, DMSO-d_6): 0,78 (4H, m), 1,68 (1H, m), 1,88 (4H, m), 1,99 (1H, m), 3,05 (2H, dd, J=11,4, 23,9 Hz)), 3,38 (2H, m), 3,49 (1H, m), 4,34 (2H, ddd, J=6,0, 13,5, 44,4 Hz), 6,94 (1H, t, J=7,6 Hz), 7,00 (1H, d, J=8,2 Hz), 7,23 (1h, A), 7,35 (1H, t, J=8,2 Hz), 7,70 (1H, a), 8,90 (1H, a), 9,02 (1H, a), 9,21 (1H, a), 13,7 (1H, a)
23-06		390,92	355	B	B	(500 MHz, DMSO-d_6): 1,03 (3H, t, J=7,6 Hz), 1,85 (2H, d, J=13,3 Hz), 1,99 (1H, m), 2,18 (2H, q, J=7,6 Hz), 3,05 (2H, dd, J=11,4, 23,9 Hz), 3,38 (2H, m), 3,49 (1H,

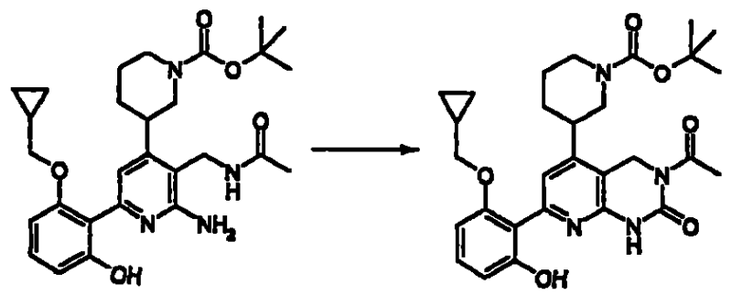
						m), 4,33 (2H, d, J=6,0 Hz), 6,97 (2H, t, J=7,9 Hz), 7,07 (1H, m), 7,37 (1H, t, J=7,9 Hz), 7,56 (1H, s a), 7,88 (1H, a), 8,75 (1H, a), 8,96 (1H, m), 13,6 (1H, a)
23-07		446,98	411	A	A	(500 MHz, DMSO-d_6): 0,28-0,31 (2H, m), 0,47-0,50 (2H, m), 1,18 (1H, m), 1,85-1,91 (3H, m), 1,92 (3H, s), 1,94-2,00 (2H, m), 3,04-3,09 (2H, m), 3,49-3,57 (2H, m), 3,83 (2H, d, J=6,9 Hz), 4,35 (2H, d, J=5,7 Hz), 6,60 (1H, d, J=8,5 Hz), 6,68 (1H, d, J=8,2 Hz), 6,83 (1H, m), 7,27 (1H, dd, J=8,2, 8,5 Hz), 7,84 (1H, s a), 8,96 (3H, m), 10,4 (1H, s a), 13,6 (1H, s a)
23-08		491,04	455	A	A	(500 MHz, DMSO-d_6): 0,23-0,35 (2H, m), 0,41-0,57 (2H, m), 1,19 (6H, d, J=6,4 Hz), 1,06-1,28 (1H, m), 1,70-1,98 (4H, m), 2,76-3,15 (2H, m), 3,15-3,60 (2H, m), 3,60-3,75 (1H, m), 3,75-3,90 (2H, m), 4,70-4,90 (1H, m), 6,59 (1H, d, J=8,3 Hz), 6,66 (1H, d, J=8,3 Hz), 7,11 (1H, s a), 7,27 (1H, t, J=8,3 Hz), 7,61 (1H, a), 7,80 (1H, s a), 8,65-8,95 (1H, m), 9,15-9,40 (1H, m), 10,38 (1H, a), 13,64 (1H, a)

23-09		505,06	469	A	A	(500 MHz, DMSO-d_6): 0,22–0,35 (2H, m), 0,41-0,56 (2H, m), 0.88 (6H. d, J=6,8 Hz), 1,02-1.25 (1H. m). 1,70-2,00 (5H, m), 2,75-3.15 (2H, m), 3,15-3,65 (2H, m), 3,65-3,97 (5H, m), 4,15-4,44 (2H, m), 6,59 (1H, d, J=8,3 Hz), 6,67 (1H, d, J=8,3 Hz), 7,10 (1H, s a), 7,27 (1H, t, J=8,3 Hz), 7,69 (1H, a), 7,92 (1H, s a), 8,94 (1H, a), 9,41 (1H, a), 10,41 (1H, a), 13,68 (1H, a)
23-10		519,09	483	A	A	(500 MHz, DMSO-d_6): 0,24–0,35 (2H, m), 0,40-0,57 (2H, m), 0,89 (9H, s), 1,06-1,25 (1H, m), 1,70-2,00 (4H, m)), 2,75-3,15 (2H, m), 3,15-3,50 (2H, m), 3,72 (2H, s), 3,67-3,90 (3H, m), 4,24 (1H, dd, J=5,7, 15,5 Hz), 4,37 (1H, dd, J=5,7, 15,5 Hz), 6,58 (1H, d, J=8,3 Hz), 6,67 (1H, d, J=8,3 Hz), 7,11 (1H, s a), 7,26 (1H, t, J=8,3 Hz), 7,67 (1H, a), 7,91 (1H, s a), 8,95 (1H, a), 9,39 (1H, a), 10,39 (1H, a), 13,68 (1H, a)
23-11		476,02	440	A	A	(500 MHz, DMSO-d_6): 0,28–0,29 (2H, m), 0,47-0,49 (2H, m), 1,13 (1H, m), 1,85-1,90 (5H, m), 2,86 (6H, s), 3,01 (1H, m), 3,25-3,27 (2H, m), 3,78-3,84 (2H, m), 3,96

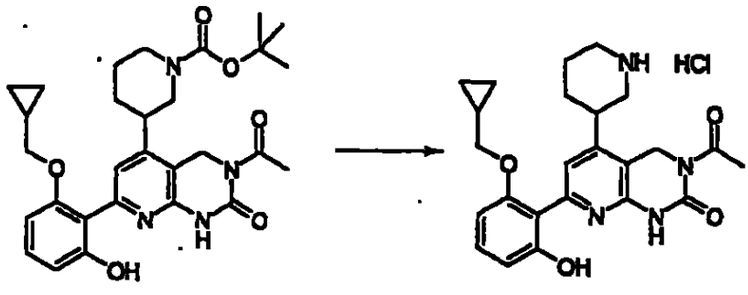
						(1H, m), 4,31 (2H, d, J=5,0), 6,59 (1H, d, J=7,9 Hz), 6,64 (1H, d, J=7,0 Hz), 7,04 (1H, s), 7,27 (1H, t, J=7,5 Hz), 8,00 (1H, s), 9,09 (2H, s), 10,35 (1H, s)
23-12		490,05	454	A	A	(500 MHz, DMSO-d_6): 0,28–0,29 (2H, m), 0,47-0,49 (2H, m), 0,82 (3H, t, J=7,4 Hz), 1,13 (1H, m), 1,37-1,42 (2H, m), 1,84-1,89 (4H, m), 2,90 (1H, m), 3,00-3,01 (3H, m), 3,02-3,05 (2H, m), 3,78-3,85 (3H, m), 4,30-4,36 (2H, m), 6,58 (1H, d, J=8,5 Hz), 6,67 (1H, d, J=8,2 Hz), 7,04 (1H, a), 7,18 (1H, s), 7,26 (1H, t, J=8,2 Hz), 8,06 (2H, s), 9,05 (1H, a), 9,39 (1H, s), 10,39 (1H, s), 13,60 (1H, s)
23-13		417,97	412	A	A	(500 MHz, DMSO-d_6): 0,28–0,29 (2H, q), 0,47-0,49 (2H, q), 1,14 (1H, s a), 1,85-1,89 (4H, m), 2,88 (1H, m), 3,02 (1H, m), 3,25-3,33 (2H, m), 3,71 (1H, m), 3,78-3,86 (2H, m), 4,28-4,34 (2H, m), 5,95 (1H, a), 6,58 (1H, d, J=8,2 Hz), 6,67 (1H, d, J=8,2 Hz), 7,04 (1H, s), 7,26 (1H, t, J=8,2 Hz), 8,09 (2H; s), 9,04 (1H, a), 9,40 (1H, a), 10,40 (1H, a), 13,35 (1H, a)

23-14		524,07	488	A	A	(500 MHz, DMSO-d_6): 0,27–0,28 (2H, m), 0,47-0,48 (2H, m), 1,12 (1H, m), 1,88-1,90 (4H, m), 2,89-3,09 (2H, m), 3,35-3,38 (3H, m), 3,70-3,85 (2H, m), 4,38-4,45 (2H, m), 6,58 (1H, d, J=8,8 Hz), 6,66 (1H, d, J=8,2 Hz), 6,91-7,00 (1H, m), 7,10 (1H, s), 7,25 (3H, t, J=7,6 Hz), 7,40 (2H, d, J=7,6 Hz), 7,82 (1H, s), 8,85 (1H, s), 9,28 (2H, s), 10,37 (1H, s)
23-15		540,13	504	A	A	(500 MHz, DMSO-d_6): 0,29–0,31 (2H, m), 0,48-0,50 (2H, m), 1,14 (1H, m), 1,81-1,92 (4H, m), 2,89 (1H, m), 3,08 (1H, m), 3,59-3,60 (2H, m), 3,61 (1H, m), 3,82 (2H, dd, J=6,2, 10,1 Hz), 4,85 (2H, dd, J=5,4, 15,6 Hz), 6,59 (1H, d, J=8,5 Hz), 6,65 (1H, d, J=8,2 Hz), 7,12 (1H, t, J=7,5 Hz), 7,14 (1H, s), 7,27 (1H, t, J=8,5 Hz), 7,32 (2H, t, J=7,6 Hz), 7,49 (2H, d, J=7,8 Hz), 7,70 (1H, a), 8,71 (2H, a), 9,25 (1H, a), 10,23 (1H, a)

Ejemplo 24-1



A una solución fría (0°C) de 3-{3-[(acetilamina)metil]-2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (1,134 g, 2,220 mmol) que se obtuvo en la etapa (1) del Ejemplo 23-1, y trietilamina (1,871 ml, 13,320 mmol) en tetrahidrofurano (150 ml) se añadió gota a gota una solución de trifosgeno (0,652 g, 2,220 mmol) en tetrahidrofurano (150 ml) en atmósfera de argón. Después de agitar durante la noche, la mezcla se enfrió con agua. Se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El producto resultante (sólido amarillo) se purificó mediante cromatografía en columna sobre gel de sílice (Hexano / Acetato de etilo = 1/1) proporcionando 3-{3-acetil-7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2- oxi 1,2,3,4-tetrahidropirido[2,3-d]pirimidin-5-il}-1-piperidincarboxilato de *terc*-butilo como una espuma blanca (0,569 g, rendimiento; 48%).



A continuación el carbamato de *terc*-butilo se trató de manera similar a la de la etapa (3)

del Ejemplo 1-1 proporcionando clorhidrato de 3-acetil-7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(piperidinil)-3,4-dihidropirido[2,3-d]pirimidin-2(1H)-ona.

Peso molecular: 472,98

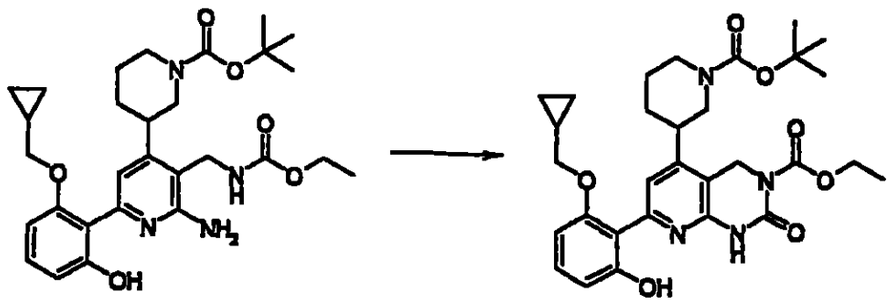
Espectrometría de masas: 437 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A594)-A

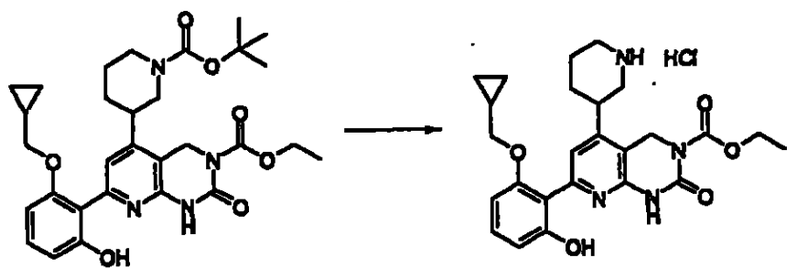
RMN de ^1H (500 MHz, DMSO-d_6): 0,31-0,34 (2H, m), 0,56-0,59 (2H, m), 1,26 (1H, m), 1,74-1,79 (2H, m), 1,81-1,93 (2H, m), 2,47 (H, s), 2,85-2,98 (2H, m), 3,21-3,34 (3H, m), 3,81-3,86 (2H, m), 4,93 (2H, s), 6,52 (2H, d, J= 8,2 Hz), 7,16 (1H, t, J= 8,2 Hz), 7,78 (1H, s), 8,79 (1H, a), 9,30 (1H, a), 10,95 (1H, s).

Ejemplo 24-2



A una solución fría (0°C) de 3-(2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-{[(etoxicarbonil)amino]metil}-4-piridinil)1-piperidincarboxilato de *terc*-butilo (0,145 g, 0,268 mmol), que se obtuvo en la etapa (1) del Ejemplo 23-2, y trietilamina (0,226 ml, 1069 mmol) en tetrahidrofurano (30 ml) se añadió trifosgeno (0,079 g, 0,268 mmol) en tetrahidrofurano (10 ml) en atmósfera de argón. Se dejó calentar la mezcla hasta temperatura ambiente y se agitó continuamente durante 3 horas. Después de inactivar con agua, se extrajo la mezcla con acetato de etilo. La fase orgánica separada se lavó

con agua y salmuera sucesivamente, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El producto resultante se purificó mediante TLC preparativa (hexano / acetato de etilo = 1/1) proporcionando 5-[1-(*terc*-butoxicarbonil)-3-piperidinil]-7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-1,4-dihidropirido[2,3-d]pirimidin-3(2H)-carboxilato de etilo como un sólido blanco (0,904 g, rendimiento; 60%).



A continuación el éster *terc*-butílico se trató de manera similar a la de la etapa (3) del Ejemplo 1-1 proporcionando clorhidrato de 7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido [2,3-d]piridimidin-3(2H)-carboxilato de etilo.

Peso molecular: 503,00

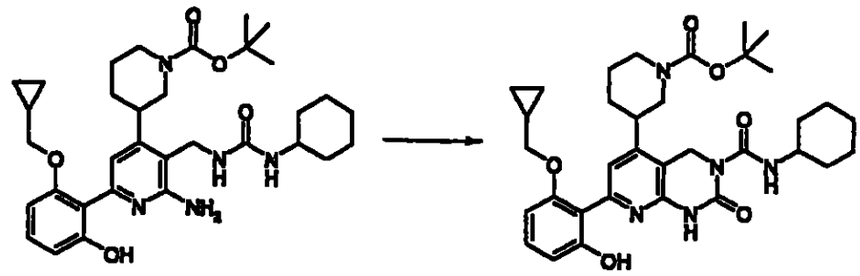
Espectrometría de masas: 467 $(M + H)^+$

Grado de actividad in vitro: A

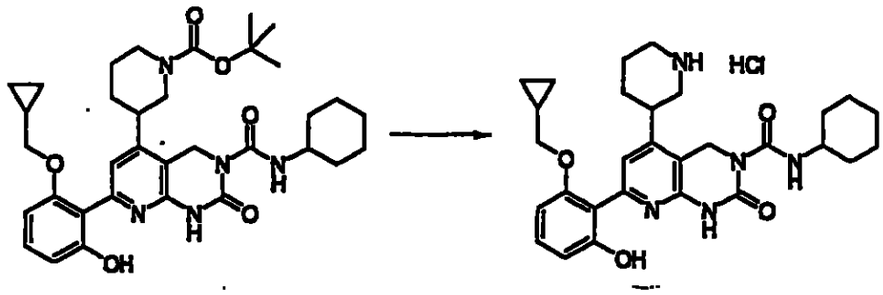
Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,31-0,34 (2H, m), 0,55-0,59 (2H, m), 1,26-1,28 (1H, s a), 1,27 (3H, t, J= 7,3 Hz), 1,74-1,85 (3H, m), 2,85-2,95 (2H, m), 3,22-3,25 (1H, m), 3,30-3,32 (2H, m), 3,79-3,87 (1H, m), 4,22-4,25 (2H, m), 4,91 (2H, s), 6,52 (2H, d, J= 8,2 Hz), 7,16 (1H, t, J= 8,2 Hz), 7,78 (1H, s), 8,91 (1H, s a), 9,29 (1H, a), 10,86 (1H, s).

Ejemplo 24-3



A una solución fría (0°C) de 3-{2-amino-3-({[(ciclohexilamino)-carbonil]amino}-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,039 g,0,065 mmol) que se obtuvo en la etapa (1) del Ejemplo 23-3 y trietilamina (15,0 ml, 0,389 mmol) en tetrahidrofurano (10,0 ml) se añadió gota a gota una solución de trifosgeno (0,019 g,0,065 mmol) en tetrahidrofurano (5,0 ml) en atmósfera de argón. La mezcla se agitó a 0°C durante 2 horas. Después de inactivar con agua, la mezcla se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre Mg SO_4, se filtró y se concentró a presión reducida. El producto resultante (sólido blanco) se trituró con éter diisopropílico y se secó a presión reducida proporcionando 3-{3-{[(ciclohexilamino)carbonil)]-7-[carbonil]amino}-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-1,2,3,4-tetrahidropirido[2,3-d]piridin-5-il}-1-piperidincarboxilato de *terc*-butilo (0,021 g, rendimiento; 52%).



A continuación el carbamato de *terc*-butílico se trató de manera similar a la de la etapa (3) del Ejemplo 1-1 proporcionando clorhidrato de N-ciclohexil-7[2-ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido[2,3-d]pirimidin-3(2H)-

carboxamida.

Peso molecular: 556,11

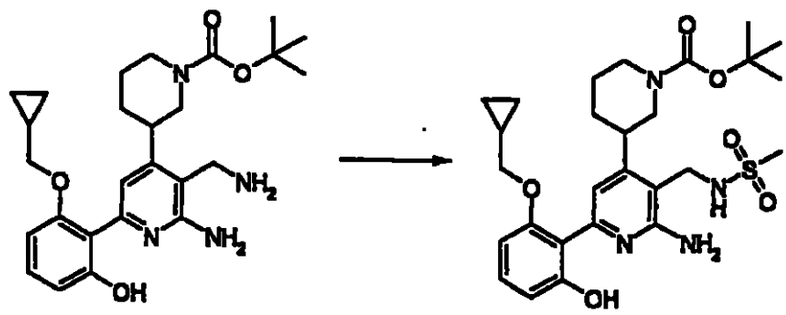
Espectrometría de masas: 520 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

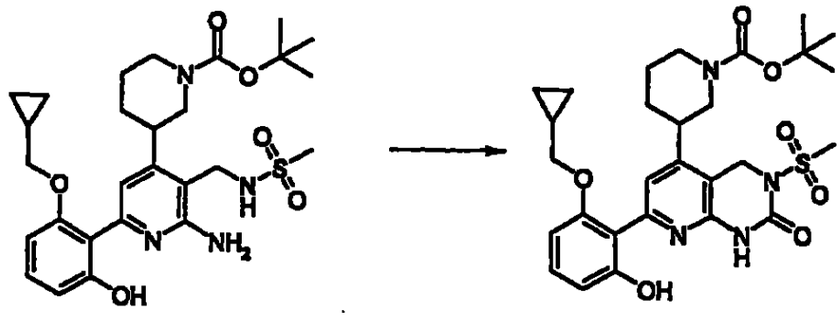
RMN de ^1H (500 MHz, DMSO-d_6): 0,32-0,34 (2H, m), 0,55-0,59 (2H, m), 1,24-1,35 (8H, m), 1,64 (1H, m), 1,75-1,78 (2H, m), 1,82-1,84 (4H, m), 1,91-1,93 (2H, m), 2,86 (1H, m), 2,96 (1H, m), 3,16 (1H, m), 3,62 (1H, m), 3,63-3,88 (2H, dd, J= 6,9, 9,8 Hz), 4,98 (2H, s), 6,52 (2H, d, J= 8,2 Hz), 7,16 (1H, t, J= 8,5 Hz), 7,77 (1H, s), 9,00 (1H, s), 10,82 (1H, s), 11,73 (1H, s).

Ejemplo 24-4

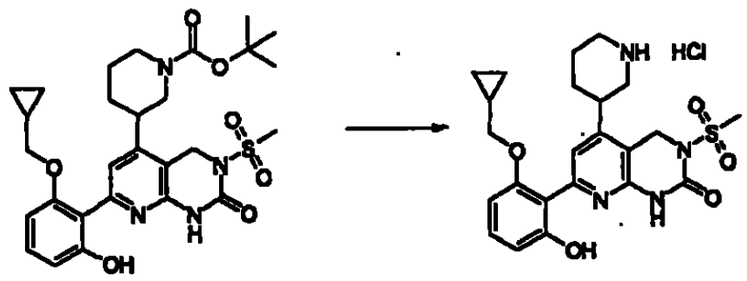


A una solución fría (0°C) de 3-{2-amino-3-(aminometil)-6-[2-(ciclopropilmetoxi)-6-hidroxifenilcarbonil]amino}-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-piridinil}-1-piperidincarboxilato de *terc*-butilo (0,150 g, 0,320 mmol) que se obtuvo en la etapa (1) del Ejemplo 23-1, y trietilamina (0,067 g, 0,480 mmol) en tetrahidrofurano (9 ml) se añadió cloruro de metanosulfonilo (0,027 ml, 0,352 mmol) en atmósfera de argón. Se agitó a 0°C continuamente durante 1 hora. Después de inactivar con agua, la mezcla se

extrajo con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El producto resultante amarillo se purificó por recristalización en éter diisopropílico / diclorometano proporcionando 3-{2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-{[((metilsulfonil)amino]metil}-4-piridinil)-1-piperidincarboxilato de *terc*-butilo como un sólido amarillo (0,097 g, rendimiento; 56%).



A una solución fría (0°C) de 3-{2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-{[(2-metilsulfonil)amino]metil}-4-piridinil)-1-piperidincarboxilato de *terc*-butilo (0,050 g, 0,91 mmol y trietilamina (0,077 ml, 0,549 mmol) en tetrahidrofurano (15 ml) se añadió una solución de trifosgeno (0,027 g, 0,091 mmol) en tetrahidrofurano (5 ml) en atmósfera de argón. Se dejó calentar la mezcla hasta temperatura ambiente, y se continuó agitando durante 3 horas en atmósfera de argón. Después de inactivar con agua, la mezcla se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El sólido resultante amarillo se trituró con éter diisopropílico y se recogió por filtración proporcionando 3-[7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-(metilsulfonil)-2-oxo-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-5-il]-1-piperidincarboxilato de *terc*-butilo como un sólido amarillo (0,028 g, rendimiento, 55%).



A continuación el carbamato de *terc*-butilo se trató de manera similar a la de la etapa (3) del Ejemplo 1-1 proporcionando clorhidrato de 7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-(metil-sulfonil)-5-(3-piperidinil)-3,4-dihidropirido[2,3-d]pirimidin-2(1H)-ona

Peso molecular: 509,03

Espectrometría de masas: 473 $(M + H)^+$

Grado de actividad in vitro: A

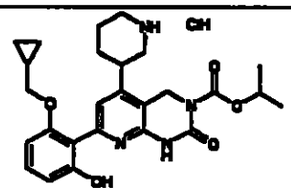
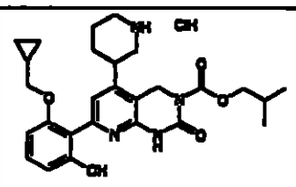
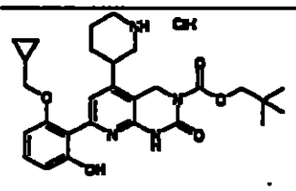
Grado de actividad celular: (A549)-A

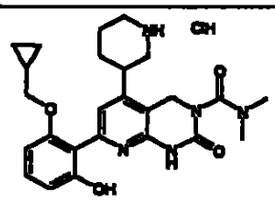
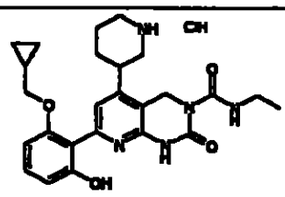
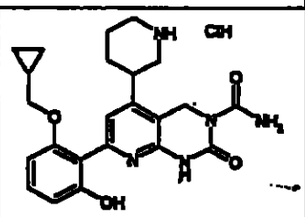
RMN de ^1H (500 MHz, DMSO-d_6): 0,30-0,33 (2H, m), 0,54-0,58 (2H, m), 1,26 (1H, m), 1,73-1,78 (2H, m), 1,88-1,93 (2H, m), 2,88 (1H, m), 2,99 (1H, m), 3,13 (1H, m), 3,30-3,35 (2H, m), 3,50 (3H, s), 3,83 (2H, dd, J= 6,9, 7,2 Hz), 4,97 (2H, s), 6,53 (2H, d, J= 8,2 Hz), 7,17 (1H, t, J= 8,5 Hz), 7,75 (1H, s), 8,67 (1H, s), 9,11 (1H, s), 11,02 (1H, s).

Ejemplos 24-5 a 24-10

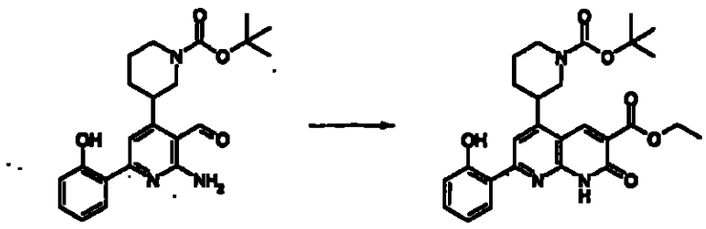
Los compuestos de la tabla 7 fueron preparados de acuerdo con un procedimiento sintético similar al de los ejemplos 24-1 a 24-4

Tabla 7

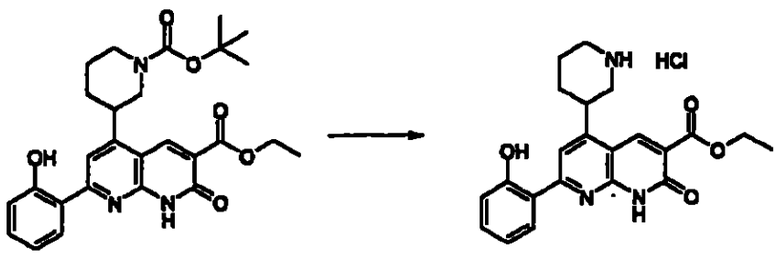
Ej. nº	Estructura	Peso molec.	Masa	*In vitro*	A549	RMN
24-05		517,03	481	A	A	(300 MHz, DMSO-d_6): 0,25-0,38 (2H, m), 0,50-0,64 (2H, m), 1,29 (6H, d, J= 6,0 Hz), 1,20-1,32 (1H, m), 1,60-2,00 (4H, m), 2,75-3,05 (2H, m), 3,15-3,40 (3H, m), 3,75-3,92 (2H, m), 4,89 (2H, s), 4,90-5,04 (1H, m), 6,53 (2H, d, J= 8,3 Hz), 7,17 (1H, t, J= 8,3 Hz),7,78 (1H, s), 8,92 (1H, a), 9,25 (1H, a), 10,82 (1H, s)
24-06		531,06	495	A	A	(300 MHz, DMSO-d_6): 0,25-0,38 (2H, m), 0,51-0,64 (2H, m), 0,95 (6H, d, J= 6,4 Hz), 1,17-1,35 (1H, m), 1,63-2,05 (5H, m), 2,75-3,10 (2H, m), 3,10-3,45 (3H, m), 3,75-3,92 (2H, m), 3,99 (2H, d, J= 8,3 Hz), 4,89 (1H, d, J= 15,8 Hz), 4,95 (1H, d, J= 15,8 Hz), 6,53 (2H, d, J= 8,3 Hz), 7,17 (1H, t, J= 8,3 Hz), 7,78 (1H, a), 8,65-9,20 (1H, m), 9,20-9,75 (1H, m), 10,84 (1H, s)
24-07		545,08	509	A	A	(300 MHz, DMSO-d_6): 0,25-0,37 (2H, m), 0,52-0,63 (2H, m), 0,97 (9H, s), 1,17-1,35 (1H, m), 1,60-2,00 (4H, m), 2,75-3,10 (2H, m), 3,10-3,40 (2H, m), 3,76-3,92 (3H, m), 3,90 (2H, s), 4,89 (1H, d, J= 15,8 Hz), 4,96 (1H, d, J= 15,8 Hz), 6,53 (2H, d, J= 8,3 Hz),

						7,17 (1H, t, J= 8,3 Hz), 7,77 (1H, s), 8,65-9,05 (1H, m). 9,25-9,80 (1H, m), 10,83 (1H, s).
24-08		502,02	466	A	A	(500 MHz, DMSO-d_6): 0,33-0,35 (2H, m), 0,56-0,58 (2H, m), 1,26 (1H, m), 1,76-1,80 (2H, m), 1,90-1,92 (2H, m), 2,84-2,91 (10H, m), 3,14 (1H, m), 3,83-3,85 (2H, m), 4,64-4,70 (2H, m), 6,51-6,54 (2H, m), 7,16 (1H, t, J= 8,2 Hz), 7,80 (1H, s), 8,47 (1H, s), 8,97 (1H,. s), 10,68 (1H, s).
24-09		502,02	466			(500 MHz, DMSO-d_6): 0,32-0,33 (2H, m), 0,56-0,58 (2H, m), 1,10 (3H, t, J= 7,3 Hz), 1,27 (1H, m), 1,72-1,91 (4H, m). 2,85-2,95 (2H, m), 3,16 (1H, m), 3,22-3,27 (2H, m), 3,31-3,33 (2H, m), 3,82-3,86 (2H, m), 4,99 (2H, s), 6,52 (2H, d, J= 8,2 Hz), 7,17 (1H, t, J= 8,2 Hz), 7,78 (1H, s), 8,96 (1H,. a), 9,17 (1H, a), 10,84 (1H, s).
24-10		473,96	438	A	A	(300 MHz, DMSO-d_6): 0,32-0,33 (2H, m), 0,56-0,58 (2H, m), 1,26 (1H, m), 1,73-1,95 (3H, m), 2,85-2,97 (3H, m), 3,19-3,34 (4H, m), 3,78-3,86 (2H, m), 4,98 (2H, a), 6,53 (2H, d, J= 7,9 Hz), 7,16 (1H, t, J= 8,3 Hz), 7,46 (1H, a), 7,78 (1H, s), 8,33 (1H, a), 8,67 (1H, a), 9,12 (1H, a), 10,80 (1H, s)

Ejemplo 25-1



A una suspensión de 3-[2-amino-3-formil-6-(2-hidroxifenil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (0,86 g, 2,16 mmol) en etanol (25 ml) se añadió malonato dietílico (6,93 g, 43,27 mmol) y piperidina (2,4 ml, 21,64 mmol) y se calentó la mezcla en reflujo durante la noche. Se dejó enfriar la mezcla hasta temperatura ambiente y, a continuación, se diluyó con etanol. El precipitado resultante se recogió por filtración, se lavó con etanol y se secó a presión reducida proporcionando 5-[1-(terc-butoxicarbonil)-3-piperidinil]-7-(2-hidroxifenil)-2-oxo-1,2-dihidro-1,8-naftiridin-3-carboxilato de etilo en forma de sólido amarillo (0,752 g, rendimiento; 71%).



A continuación, el carbamato de *terc*-butilo se trató de manera similar a la de la etapa (3) del Ejemplo 1-1 proporcionando clorhidrato de 7-(2-hidroxifenil)-2-oxo-5-(3-piperidinil)-1,2-dihidro-1,8-naftiridin-3-carboxilato de etilo.

Peso molecular: 429,91

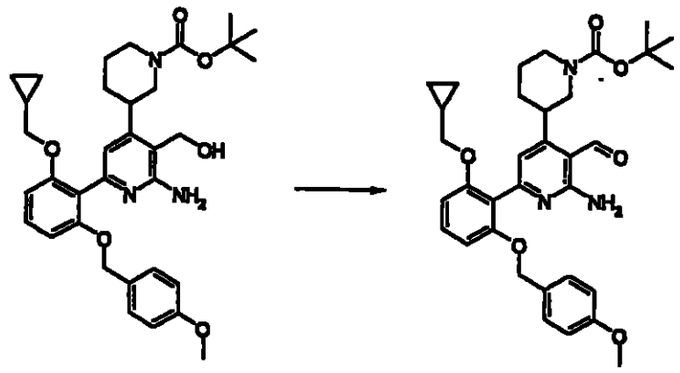
Espectrometría de masas: 394 $(M + H)^+$

Grado de actividad in vitro: A

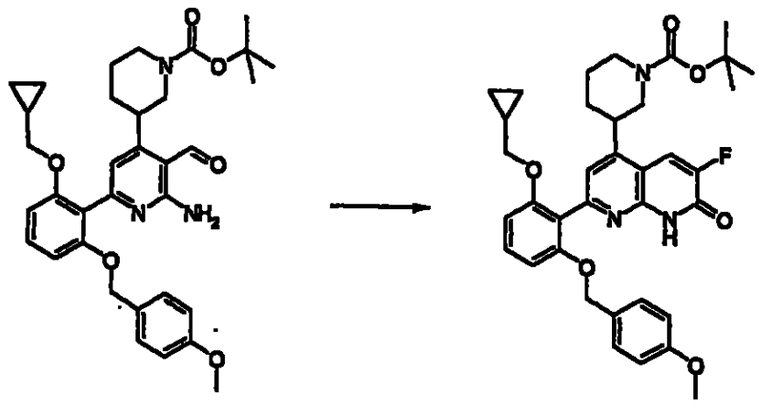
Grado de actividad celular: (A549)-B

RMN-H^1 (500 MHz, DMSO-d_6): 1,34 (3H, t, J= 7,1 Hz), 1,89-2,07 (4H, m), 2,92-3,00 (1H, m), 3,40-3,44 (1H, m), 3,77 (1H, a), 4,32 (2H, q, J= 7,1 Hz), 6,97-7,01 (2H, m), 7,41 (1H, t, J= 7,25 Hz), 8,01 (1H, s), 8,21 (1H, d, J= 7,25 Hz), 8,62 (1H, s), 8,83 (1H, a), 9,18 (1H, a), 12,69 (1H, s), 12,96 (1H, s a).

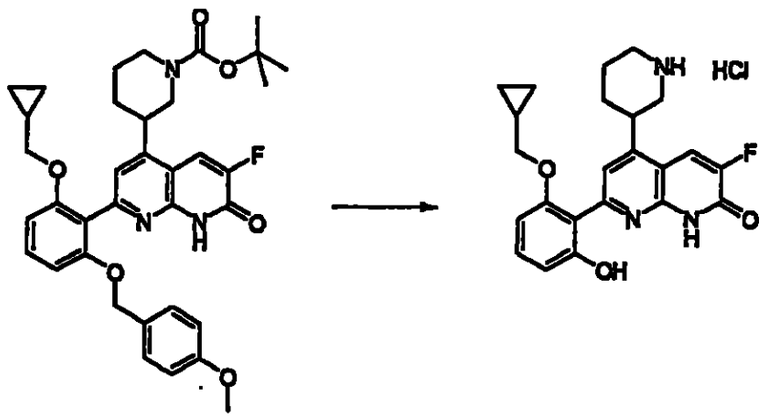
Ejemplo 25-2



(1) A una suspensión agitada de 3-[2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-(hidroximetil)-4-piridinil]-1-piperidincarboxilato de *terc*-butilo (1,100 g, 1,863 mmol), que se obtuvo en la etapa (2) del Ejemplo 17-1 en diclorometano (50 ml) se añadió dióxido de manganeso (3,240 g, 37,261 mmol). La mezcla se agitó a temperatura ambiente durante 3 horas y se filtró a través de celite®. El filtrado se concentró a presión reducida proporcionando 3-(2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-formil-4-piridinil)-1-piperidincarboxilato de *terc*-butilo (0,978 g, rendimiento; 89%).



(2) A una solución agitada de 3-(2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-formil-4-piridinil)-1-piperidincarboxilato de *terc*-butilo (0,500 g, 0,851 mmol), y 2-fluoro-2-fosfoacetato de trietilo (0,350 ml, 1,701 mmol) y cloruro de litio anhidro (0,072 g, 1,701 mmol) en acetonitrilo (20 ml) se añadió 1,8-diazabiciclo[5,4,0]undec-7-eno (0,250 ml, 1,701 mmol). La mezcla se agitó a temperatura ambiente durante 30 minutos y se concentró a presión reducida. Se extrajo el producto con acetato de etilo y agua. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El producto resultante (líquido) se purificó por cromatografía en columna sobre gel de sílice (hexano / acetato de etilo = 1/1 proporcionando 3-(2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-6-fluor-7-oxi-7,8-dihidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo como una espuma (0,261 g, 49%).



A continuación, el carbamato de *terc*-butilo se trató de una manera similar a la de la etapa (2) del Ejemplo 21-1 proporcionando un clorhidrato de 7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-fluoro-5-(3-piperidinil)-1,8-naftiridin-2(1H)-ona.

Peso molecular: 445,93

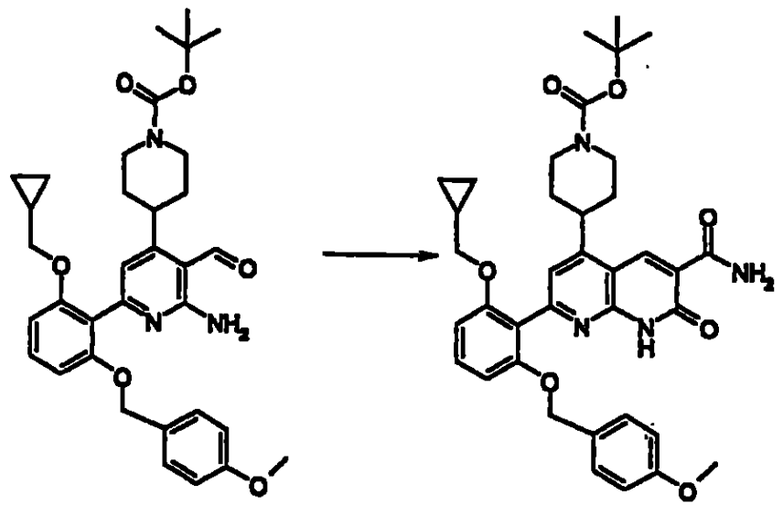
Espectrometría de masas: 410 $(M + H)^+$

Grado de actividad in vitro: A

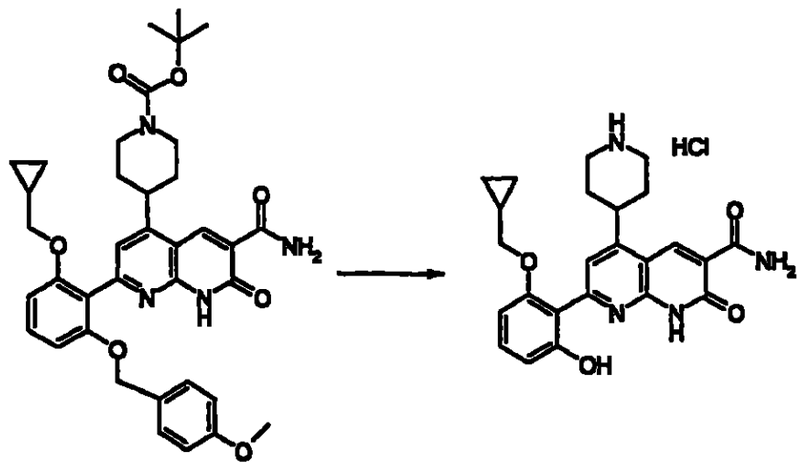
Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,32 (2H, m), 0,55 (2H, m), 1,25 (1H, m), 1,94 (4H, m), 2,95 (2H, m), 3,65 (1H, a), 6,58 (2H, d, J= 8,2 Hz), 7,23 (1H, t, J= 8,2 Hz), 7,97 (1H, s), 8,15 (1H, d, J= 11,4 Hz), 8,64 (1H, a), 9,01 (1H, a), 11,66 (1H, a), 13,02 (1H, d, J= 5,4 Hz).

Ejemplo 25-3



(1) Utilizando el compuesto de partida 1G y ácido *terc*-butil-4-formilpiperidin-1-carboxílico, se preparó 4-(2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-formil-4-piridinil)-1-piperidincarboxilato de *terc*-butilo de manera similar a la de la etapa (1) del Ejemplo 25-2. A una solución de 4-(2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-formil-4-piridinil)-1-piperidincarboxilato de *terc*-butilo (0,400 g, 0,681 mmol) en alcohol etílico (5,0 ml), se añadió monoamina malonato de etilo (1,780 g, 13,612 mmol y piperidina (0,580 g, 6,806 mmol). La mezcla se calentó a reflujo durante 12 horas. La mezcla resultante de la reacción se extrajo con acetato de etilo y agua. La fase orgánica se lavó con Na HCO_3 y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El producto resultante (líquido) se purificó mediante cromatografía en columna sobre gel de sílice (hexano / acetato de etilo = 1/1 y acetato de etilo 100%) proporcionando 4-(6-(aminocarbonil)-2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-7-oxo-7,8-dihidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo como una espuma amarilla (0,455 g, rendimiento; cuantitativo).



(2) A continuación el carbamato de *terc*-butilo se trató de manera similar a la de la etapa (2) del Ejemplo 21-1 proporcionando clorhidrato de 7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(4-piperidinil)-1,2-dihidro-1,8-naftiridin-3-carboxamida.

Peso molecular: 470,96

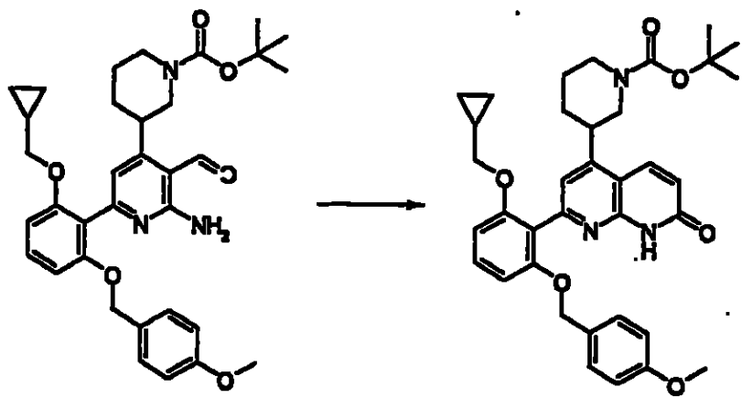
Espectrometría de masas: 435 $(M + H)^+$

Grado de actividad in vitro: A

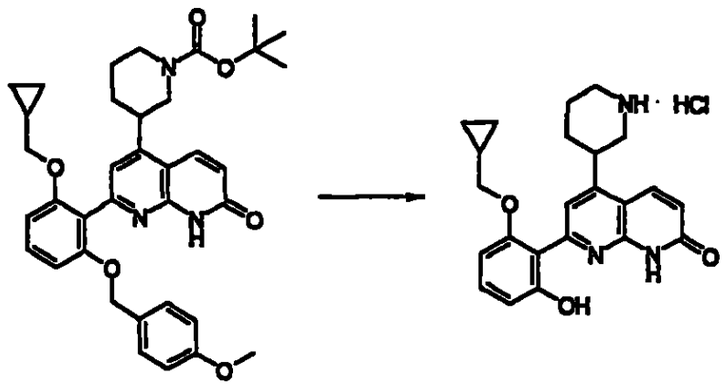
Grado de actividad celular (A549)-B

RMN de ^1H (500 MHz, DMSO-d_6): 0,32 (2H, d, J= 4,7 Hz), 0,57 (2H, d, J= 7,9 Hz), 1,32-1,35 (1H, m), 1,91-2,01 (5H, m), 3,23-3,26 (3H, m), 3,70-3,80 (2H, m), 3,90 (2H, d, J= 6,9 Hz), 6,59 (2H, dd, J= 1,7, 8,3 Hz), 7,26 (1H, t, J= 8,2 Hz), 7,87 (1H, d, J= 3,5 Hz), 8,01 (1H, s), 8,70 (1H, d, J= 12,3 Hz), 8,87 (1H, d, J= 10,7 Hz), 8,99 (1H, d, J= 3,4 Hz), 9,06 (1H, s), 13,05 (1H, s).

Ejemplo 25-4



(1) A una solución de (difenoxifosforil)acetato de etilo (1,090 g, 3,403 mmol) en THF (15 ml) se añadió 1,8-diazabiciclo[5,4,0]]undec-7-eno (0,520 g, 3,403 mmol) y NaI (0,510 g, 3,403 mmol) y después se añadió una solución de 3-(2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]-fenil}-3-formil-4-piridinil)-1-piperidincarboxilato de *terc*-butilo (1,000 g, 1,701 mmol), obtenido en la etapa (1) del Ejemplo 25-2, en THF (5 ml). La mezcla se agitó a 0°C durante 1,5 horas y se enfrió con una solución saturada de $NaHCO_3$ en agua. La mezcla se extrajo con acetato de etilo, y el extractose lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El producto se purificó mediante cromatografía en columna sobre gel de sílice (hexano / acetato de etilo = 3/2 a 1/2) proporcionando 3-(2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-7-oxo-7,8-dihidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo en forma de sólido amorfo (0,276 g, 27%).



(2) A una solución agitada de 3-(2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-7-oxo-7,8-dihidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo (0,260 g, 0,425 mmol) en 1,4-dioxano (2 ml) se añadió HCl 4 N en dioxano (2 ml). Se agitó la mezcla a temperatura ambiente durante la noche, y se diluyó con acetato de etilo. El precipitado resultante se recogió por filtración, se lavó con etanol, y se secó a presión reducida proporcionando clorhidrato de 7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-1,8-naftiridin-2(1H)-ona en forma de sólido amarillo (0,146 g, 80%).

Peso molecular: 427,93

Espectrometría de masas: 392 $(M + H)^+$

Grado de actividad in vitro: A

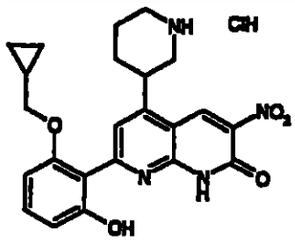
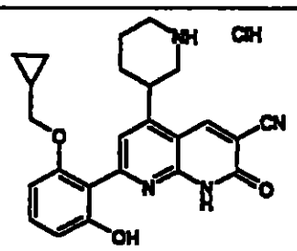
Grado de actividad celular: (A549)-A

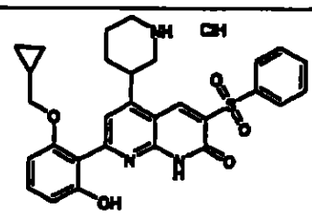
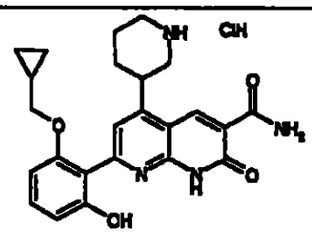
RMN de ^1H (500 MHz, DMSO-d_6): 0,34 (2H, m), 0,58 (2H, m), 1,28 (1H, m), 1,91 (4H, m), 2,89 (1H, d a, J= 6,6 Hz), 3,00 (1H, dd, J= 10,4, 12,3 Hz), 3,37 (2H, dd, J= 12,3, 12,6 Hz), 6,57 (2H, d, J= 8,2 Hz), 6,67 (1H, d, J= 9,8 Hz), 7,23 (1H, t, J= 8,2 Hz), 7,99 (1H, s), 8,21 (1H, d, J= 9,8 Hz), 9,02 (1H, a), 9,14 (1H, a), 12,45 (1H, s a).

Ejemplos 25-5 a 25-8

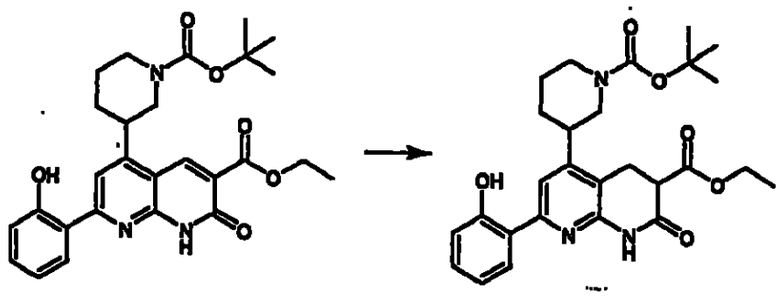
Los compuestos de la tabla 8 se prepararon de acuerdo con un procedimiento sintético similar al de los Ejemplos 25-1 a 25-4

Tabla 8

Ej. nº	Estructura	Peso molec	Masa	*In vitro*	A549	RMN
25-05		472,93	437	A	B	(500 MHz, DMSO-d_6): 0,33 (2H, dd, J= 4,7, 9,1 Hz), 0,56 (2H, m), 1,25 (1H, m), 1,94 (4H, m), 2,90 (1H, a), 3,00 (1H, t, J= 12,3 Hz), 3,40 (2H, d a, J= 12,3 Hz), 6,59 (2H, d, J= 8,2 Hz), 7,27 (1H, t, J= 8,2 Hz), 8,03 (1H, s), 9,02 (1H, s), 11,57 (1H, s), 13,32 (1H, a).
25-06		452,94	417	A	A	(500 MHz, DMSO-d_6): 0,32 (2H, dd, J= 4,7, 9,1 Hz), 0,57 (2H, m), 1,25 (1H, m), 1,93 (4H, m), 2,89 (1H, d a, J= 7,3 Hz), 2,97 (1H, dd, J= 11,4, 11,7 Hz), 3,39 (2H, t, J= 14,5 Hz), 6,59 (2H, d, J= 8,5 Hz), 7,26 (1H, t, J= 8,5 Hz), 8,00 (1H, s), 8,81 (1H, a), 9,01 (1H, s), 9,26 (1H, a), 11,66 (1H, s), 13,13 (1H, s).

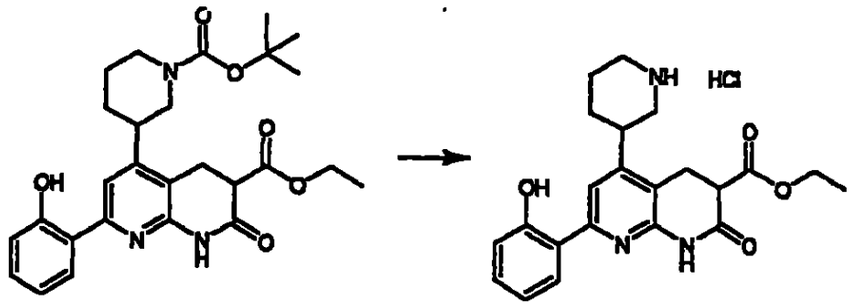
25-07		568,10	532	A	A	(500 MHz, DMSO-d_6): 0,32 (2H, m), 0,57 (2H, m), 1,25 (1H, m), 1,95 (4H, m), 2,93 (1H, d a, J= 11,0 Hz), 3,06 (1H, dd, J= 11,0, 12,0 Hz), 6,58 (2H, dd, J= 2,5, 8,2 Hz), 7,25 (1H, t, J= 8,2 Hz), 7,64 (2H, t, J= 7,6 Hz), 7,74 (1H, t, J= 7,6 Hz), 8,04 (3H, m), 8,85 (1H, a), 9,01 (1H, s), 9,35 (1H, a), 11,47 (1H, a), 12,93 (1H, s)
25-08		470,96	435	A	A	(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,58 (2H, m), 1,28 (1H, m), 1,90 (4H, m), 2,91 (1H, d, J= 11,3 Hz), 3,06 (1H, dd, J= 11,3, 12,3 Hz), 6,59 (2H, d, J= 8,2 Hz), 7,26 (1H, t, J= 8,2 Hz), 7,90 (1H, d, J= 3,5 Hz), 8,06 (1H, s), 8,81 (1H, a), 9,00 (1H, d, J= 3,5 Hz), 9,02 (1H, s), 9,31 (1H, a), 11,80 (1H, a), 13,07 (1H, s).

Ejemplo 26-1



(1) A una suspensión fría (0°C) de 5-[1-(*terc*-butoxicarbonil)-3-piperidinil]-7-(2-hidroxifenil)-2-oxo-1,2-dihidro-1,8-naftiridin-3-carboxilato de etilo (0,050 g, 0,101 mmol) en THF (2,0 ml) en atmósfera de argón se añadió $LiBH_4$ (0,004 g, 0,20 mmol).

Se dejó calentar la mezcla hasta temperatura ambiente y se continuó agitando durante 3 horas. La mezcla resultante se enfrió con agua, y se repartió entre acetato de etilo y una solución saturada de cloruro de amonio. La fase orgánica separada se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El producto se purificó mediante cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 3,2) proporcionando 5-[1-(*terc*-butoxicarbonil)-3-piperidinil]-7-(2-hidroxifenil)-2-oxo-1,2,3,4-tetrahidro-1,8-naftiridin-3-carboxilato de etilo. (0,027 g, rendimiento; 54%).



(2) El 5-[1-(*terc*-butoxicarbonil)-3-piperidinil]-7-(2-hidroxifenil)-2-oxo-1,2,3,4-tetrahidro-1,8-naftiridin-3-carboxilato de etilo (0,024 g, 0,048 mmol) se trató en condiciones ácidas de manera similar a la descrita en el Ejemplo 1-1 proporcionando 7-(2-hidroxifenil)-2-oxo-5-(3-piperidinil)-1,2,3,4-tetrahidro-1,8-naftiridin-3-carboxilato de etilo (0,019 g, rendimiento; 91%).

Peso molecular: 431,92

Espectrometría de masas: 396 $(M + H)^+$

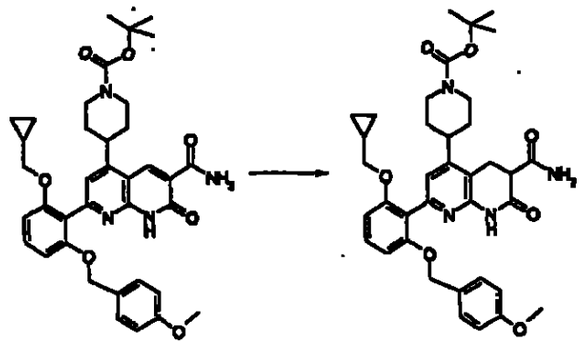
Grado de actividad in vitro: A

Grado de actividad celulaR: (A549)-A

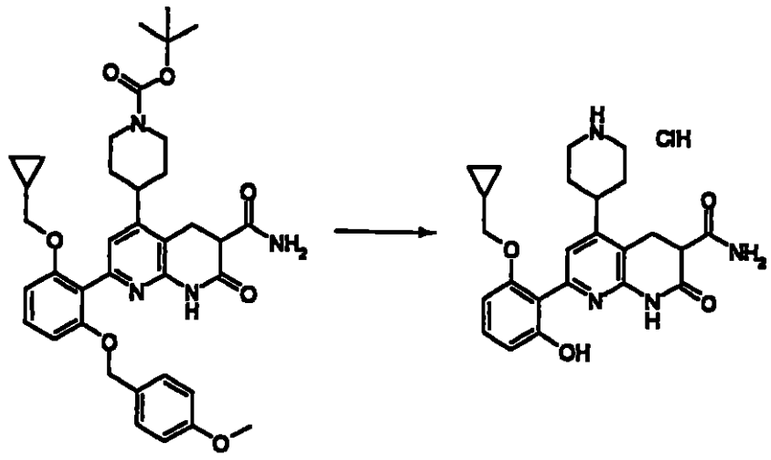
RMN de ^1H (500 MHz, DMSO-d_6): 1,16-1,21 (3H, m), 1,83-1,95 (4H, m), 2,87-2,94 (1H, m), 3,18-3,37 (6H, m), 4,12-4,17 (2H, m), 6,90-6,93 (2H, m), 7,29 (1H, t, J= 7,88

Hz), 7,73 (1H, s), 8,03 (1H, d, J= 7,88 Hz), 8,81-8,90 (1H, m), 9,23-9,30 (1H, m), 11,33 (1H, s).

Ejemplo 26-2



A una solución fría (0°C) de 4-(6-(aminocarbonil)-2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-7-oxo-7,8-dihidro-1,8-naftiridin-4-il)-1-piperidincarboxilato. (0,200 g, 0,305 mmol) que se obtuvo en la etapa (1) del Ejemplo 25-3, en alcohol metílico (5,0 ml) en atmósfera de argón se añadió $NaBH_4$ (0,010 g, 0,367 mmol). La mezcla se dejó calentar hasta temperatura ambiente y se continuó agitando durante 12 horas. La mezcla de la reacción se enfrió con agua y se extrajo con acetato de etilo. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida proporcionando 4-(6-(aminocarbonil)-2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)-oxi]fenil}-7-oxo-5,6,7,8-tetrahidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo, (0,133 g, rendimiento; 67%).



A una solución agitada de 4-(6-(aminocarbonil)-2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)-oxi]fenil}-7-oxo-5,6,7,8-tetrahidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo (0,120 g, 0,187 mmol) en 1,4-dioxano (3 ml) se añadió HCl 4 N en dioxano (1 ml). La mezcla se agitó a temperatura ambiente durante 2 horas. El precipitado resultante se recogió por filtración, se lavó con acetonitrilo y se secó a presión reducida proporcionando clorhidrato de 7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(4-piperidinil)-1,2,3,4-tetrahidro-1,8-naftiridin-3-carboxamida. (0,080 g, rendimiento; 90%).

Peso molecular: 472,98

Espectrometría de masas: 437 $(M + H)^+$

Grado de actividad in vitro: A

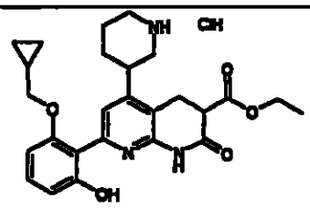
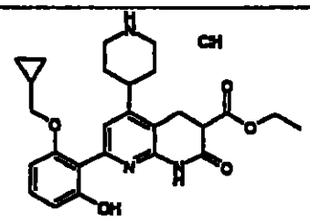
Grado de actividad celular: (A549)-A

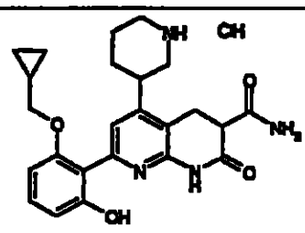
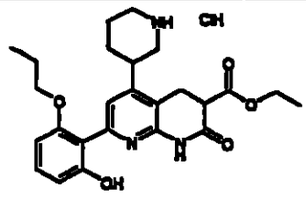
RMN de ^1H (500 MHz, DMSO-d_6): 0,33 (2H, d, J= 4,4 Hz), 0,60 (2H, d, J= 6,3 Hz), 1,33-1,39 (1H, m), 1,77-1,91 (5H, m), 3,06-3,10 (2H, m), 3,20 (3H, d, J= 8,2 Hz), 3,86 (2H, dd, J= 2,2, 7,1 Hz), 6,53 (2H, dd, J= 8,2, 7,0 Hz), 7,16 (1H, t, J= 8,2 Hz), 7,20 (1H, s), 7,56 (1H, s), 7,84 (1H, s), 11,02 (1H, s).

Ejemplos 26-3 a 26-6

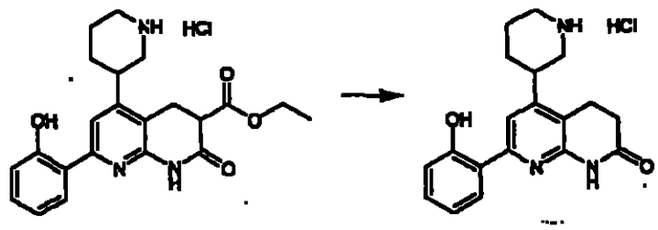
Los compuestos de la tabla 9 fueron preparados de acuerdo con un procedimiento similar al de los Ejemplos 26-1 a 26-2.

Tabla 9

Ej. nº	Estructura	Peso molec	Masa	*In vitro*	A549	RMN
26-03		502,02	466	A	A	(300 MHz, DMSO-d_6): 0,31-0,36 (2H, m), 0,56-0,60 (2H, m), 1,17 (3H, t, J= 7,2 Hz), 1,26 (1H, m), 1,82-1,90 (4H, m), 2,84-2,89 (2H, m), 3,23-3,39 (6H, m), 3,80-3,89 (2H, m), 4,16 (2H, q, J= 7,2 Hz), 6,52 (2H, d, J= 8,3 Hz), 7,16 (1H, t, J= 8,3 Hz), 7,85 (1H, s), 9,17 (1H, a), 9,39 (1H, a), 11,17 (1H, s).
26-04		502,02	466	A	A	(500 MHz, DMSO-d_6): 0,30-0,33 (2H, m), 0,56-0,59 (2H, m), 1,17 (3H, t, J= 7,2 Hz), 1,36 (1H, m), 1,86-1,92 (4H, m), 3,06-3,09 (2H, m), 3,18–3,23 (2H, m), 3,30-3,38 (3H, m), 3,80 (1H, m), 3,85-3,87 (2H, d, J= 7,0 Hz), 4,12 (2H, q, J= 7,2 Hz), 6,51 (1H, d, J= 8,2 Hz), 6,53 (1H, d, J= 8,2 Hz), 7,16 (1H, t, J= 8,2 Hz), 7,83 (1H, s), 8,96 (1H, a), 9,03 (1H, a), 11,16 (1H, s).

26-05		472,98	437	A	A	(500 MHz, DMSO-d_6): 0,36 (2H, m), 0,60 (2H, m), 1,30 (1H, m), 1,73-1,94 (4H, m), 2,94 (2H. m). 6,52, 6,53 (2H, d x 2, J= 8,2 Hz). 7,16 (1H, t, J= 8,2 Hz), 7,22. 7,23 (1H, a x 2), 7,54, 7,59 (1H, a s x 2), 7,85, 7,87 (1H, s x 2), 8,86 (1H, a), 9,15 (1H, a), 11,04, 11,04 (1H, s x 2).
26-06		490,00	454	A	A	(500 MHz, DMSO-d_6): 0,93 (3H, t, J= 7,3 Hz), 1,17 (3H, td. J= 3,5, 7,2 Hz), 1,74-1,79 (3H, m), 1,85-1,91 (3H, m), 2,87-2,89 (2H, m), 3,34-3,40 (3H, m), 3,80-3,85 (1H, m), 3,93-3,97 (2H, m), 4,14 (2H. q, J= 7,2 Hz), 6,52 (1H, d, J= 8,2 Hz), 6,57 (1H, d, J= 8,5 Hz), 7,17 (1H, t, J= 8,2 Hz), 7,65 (1J, s), 8,86 (1H, a), 9,15 (1H, a), 11,13 (1H, s).

Ejemplo 27-1



Una solución de clorhidrato de 7-(hidroxifenil)-2-oxo-5-(3-piperidinil)-1,2,3,4-tetrahidro-1,8-naftiridin-3-carboxilato de etilo (0,012 g, 0,023 mmol) que se obtuvo en la etapa (2) del Ejemplo 26-1, en HCl 2,5N (3,0 ml), se calentó a reflujo durante 4

horas. Después de enfriarse a temperatura ambiente, la mezcla se concentró a presión reducida. El producto se lavó con acetonitrilo y se secó a presión reducida proporcionando clorhidrato de 7-(2-hidroxifenil)-5-(3-piperidinil)-3,4-dihidro-1,8-naftiridin-2(1H)-ona (0,007 g, rendimiento; 70%).

Peso molecular: 359,86

Espectrometría de masas: 324 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

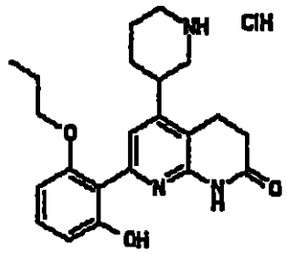
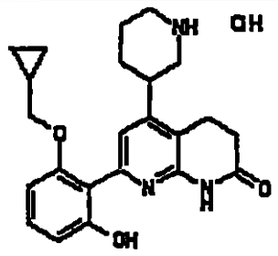
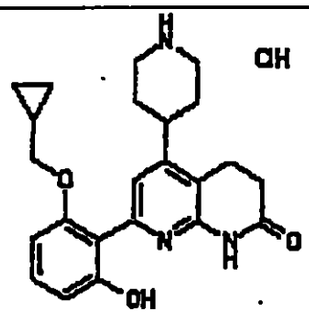
RMN de ^1H (500 MHz, DMSO-d_6): 1,83-1,94 (4H, m), 2,57-2,64 (2H, m), 2,89-3,01 (3H, m), 3,19-3,37 (4H, m), 6,88-6,93 (2H, m), 7,28 (1H, t, J= 8,2 Hz), 7,69 (1H, s), 8,01 (1H, d, J= 7,9 Hz), 8,90 (1H, a), 9,16 (1H, a), 10,99 (1H, s).

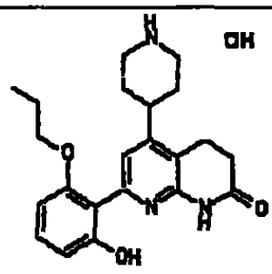
Ejemplos 27-2 a 27-5

Los compuestos de los Ejemplos 27-2 a 27-5 se sintetizaron de manera similar a la descrita en el Ejemplo 27-1

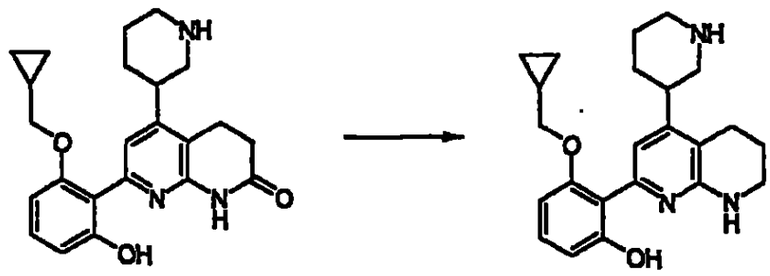
Los compuestos de la tabla 10 se prepararon de acuerdo con un procedimiento similar al del Ejemplo 27-1

Tabla 10

Ej nº	Estructura	Peso molec	Masa	*In vitro*	A549	RMN
27-02		417,94	382	A	A	(500 MHz, DMSO-d_6): 0,94 (3H, t, J= 7,5 Hz), 1,72-1,80 (2H, m), 1,87-1,89 (4H, m), 2,59-2,61 (2H, m), 2,88-2,91 (2H, m), 2,99-3,02 (2H, m), 3,26-3,33 (2H, m), 3,43 (1H, m), 3,95 (2H, m), 6,54 (1H, d, J= 8,2 Hz), 6,58 (H, d, J= 7,9 Hz), 7,18 (1H, t, J= 7,4 Hz), 7,64 (1H, s), 9,26 (1H, a), 10,84 (1H, s).
27-03		429,95	394	A	A	(300 MHz, DMSO-d_6):0,32-0,37 (2H, m), 0,56-0,62 (2H, m), 1,29 (1H, m), 1,75-1,83 (4H, m), 2,57-2,61 (2H, m), 2,88 (1H, m), 2,96-3,01 (2H, m), 3,33-3,36 (4H, m), 3,82-3,87 (2H, m), 6,52 (2H, d, J= 7,9 Hz), 7,15 (1H, t, J= 7,9 Hz), 7,83 (1H, s), 9,07 (1H, a), 10,81 (1H, s).
27-04		429,95	394	A	A	(500 MHz, DMSO-d_6): 0,31-0,34 (2H, m), 0,57-0,60 (2H, m), 1,33 (1H, m), 1,81-1,85 (2H, m), 1,90-1,93 (2H, m), 2,57 (2H, t, J= 7,2 Hz), 2,99 (2H, t, J= 7,2 Hz), 3,06-3,08 (2H, m), 3,18 (1H, m), 3,38-3,40 (2H, m), 3,85 (2H, d, J= 6,9 Hz), 6,52 (2H, d, J= 7,9 Hz), 7,15 (1H, t, J= 8,2 Hz), 7,80 (1H, s),

						8,52 (1H, a), 8,77 (1H, a), 10,80 (1H, s).
27-05		417,94	382	A	A	(500 MHz, DMSO-d_6): 0.93 (3H. t. J= 7,3 Hz), 1,80-1,84 (2H, m), 2,57-2,59 (2H, m), 2,99-3,08 (4H, m), 3,12 (1H, m), 3,36-3,39 (2H, m), 3,97 (2H, t, J= 7,7 Hz), 6,52 (1H, d, J= 8,2 Hz), 6,57 (1H, d, J= 8,5 Hz), 7,18 (1H, t, J= 8,2 Hz), 7,59 (1H, s), 9,03 (2H, a), 10,80 (1H, s).

Ejemplo 28-01



A una solución agitada de 7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-3,4-dihidro-1,8-naftiridin-2(1H)-ona (0,029 g, 0,074 mmol), que se obtuvo en el Ejemplo 27-3, en THF (1,5 ml), se añadió gota a gota Vitride® (tolueno disuelto al 70%, 0,500 ml). La mezcla se agitó con acetato de etilo a 65°C durante 1 hora. Después de enfriar hasta temperatura ambiente, la mezcla se inactivó con una solución saturada de tartrato de sodio y potasio. La mezcla se extrajo con acetato de etilo y agua. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El producto resultante se purificó mediante TLC preparativa (cloroformo /

metanol =4/1) proporcionando 3-(ciclopropilmetoxi)-2-[4-(3-piperidinil)-5,6,7,8-tetrahidro-1,8-naftiridin-2-il]fenol. (0,003 g, rendimiento; 11%).

Peso molecular: 379,51

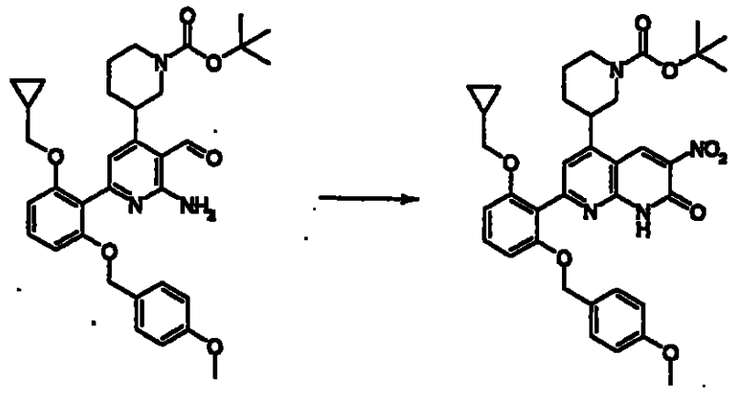
Espectrometría de masas: 380 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A459)-A

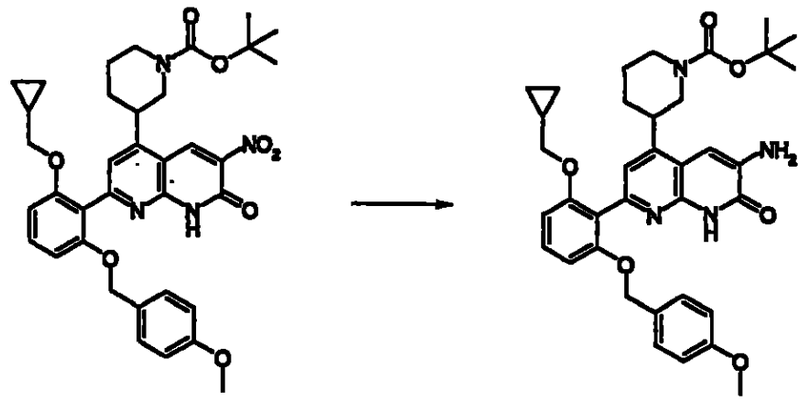
RMN de ^1H (500 MHz, $CDCl_3$): 0,42 (2H, m), 0,68 (2H, m), 1,35 (1H, m), 1,91 (1H, d, J= 12,0 Hz), 1,98 (2H, m), 2,63 (1H, dt, J= 2,8, 12 Hz), 2,77 (3H, m), 2,86 (1H, m), 3,11 (2H, dd, J= 2,3, 10,5 Hz), 3,40 (2H, dt, J= 2,8, 5,4 Hz), 3,83 (2H, d, J= 6,9 Hz), 4,75 (1H, s a), 6,38 (1H, dd, J= 1,3, 8,2 Hz), 6,59 (1H, dd, J= 1,3, 8,2 Hz), 7,09 (1H, t, J= 8,2 Hz), 7,78 (1H, s), 14,69 (1H, a).

Ejemplo 29-01

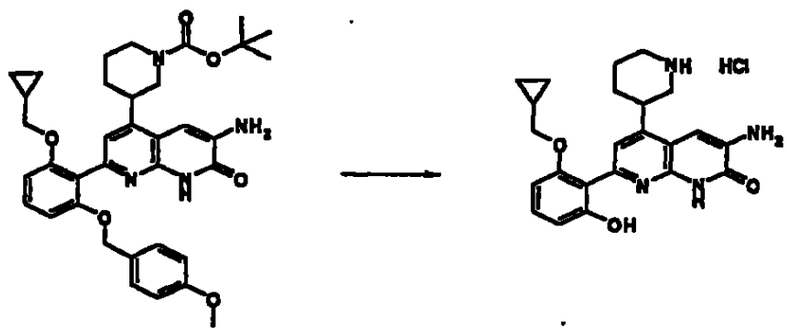


(1) A una solución agitada de 3-(2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3-formil-4-piridinil)-1-piperidincarboxilato de *terc*-butilo. (0,100 g, 0,170 mmol), que se obtuvo en la etapa (1) del Ejemplo 25-2, y nitroacetato de etilo (0,060 ml, 0,510 mmol) en etanol (5 ml) se añadió piperidina (0,050 ml, 0,510

mmol). Se agitó la mezcla a 75°C durante 18 horas y se concentró a presión reducida. El residuo se extrajo con acetato de etilo y agua. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo resultante (líquido) se purificó mediante cromatografía en columna sobre gel de sílice (hexano / acetato de etilo = 3/1 – 3/2) proporcionando 3-(2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-6-nitro-7-oxo-7,8-dihidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo. (0,105 g, rendimiento; 94%).



(2) A una mezcla agitada de 3-(2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-6-nitro-7-oxo-7,8-dihidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo (0,085 g, 0129 mmol), polvo de hierro (0,300 g), etanol (4,5 ml) y agua (0,5 ml) se añadió cloruro de amonio (0,100 g). La mezcla se agitó a 85°C durante 30 minutos. Después de enfriar a temperatura ambiente, se filtró la mezcla a través Celite®. El filtrado se concentró a presión reducida. El residuo se extrajo con acetato de etilo y agua. La fase orgánica separada se lavó con salmuera, se secó sobre SO_4Na_2, se filtró y se concentró a presión reducida proporcionando 3-(6-amino-2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]-fenil}-7-oxo-7,8-dihidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo (0,068 g, rendimiento; 84%).



(3) A continuación se eliminó el resto bencilo y el carbamato de *terc*-butilo de forma similar a la descrita en la etapa (2) del Ejemplo 25-4, proporcionando un clorhidrato de 3-amino-7-[2(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-1,8-naftiridin-2(1H)-ona

Peso molecular: 442,95

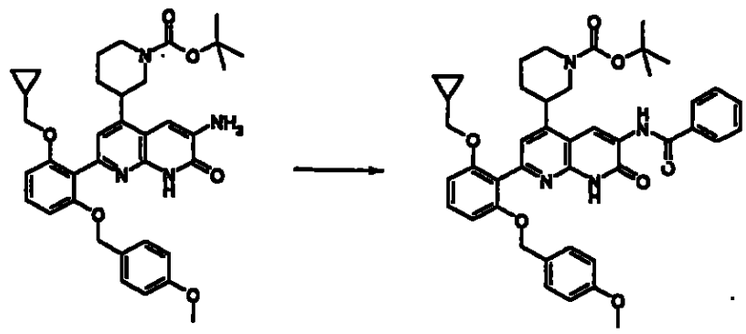
Espectrometría de masas: 407 $(M + H)^+$

Grado de actividad in vitro: A

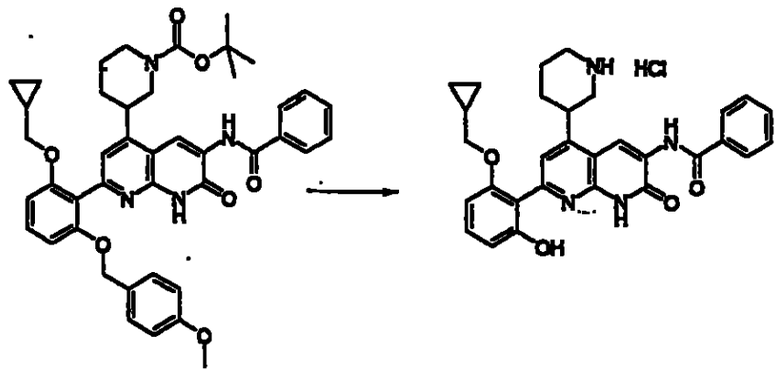
Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,35 (2H, m), 0,62 (2H, m), 1,32 (1H, m), 1,73 (1H, ddd, J= 4,1, 8,2, 8,2 Hz), 1,93 (3H, m), 2,90 (1H, dd, J= 11,7, 12,3 Hz), 3,11 (1H, dd, J= 11,0, 11,7 Hz), 6,54 (2H, d, J= 8,2 Hz), 6,93 (1H, s), 7,17 (1H, t, J= 8,2 Hz), 7,99 (1H, s), 9,10 (1H, a), 9,28 (1H, a), 12,55 (1H, s).

Ejemplo 29-2



A una solución agitada de 3-(6-amino-2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-7-oxo-7,8-dihidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo (0,068 g, 0,109 mmol), que se obtuvo en la etapa (2) del Ejemplo 29-1, y trietilamina (0,05 ml, 0,327 mmol) en cloruro de metileno (3 ml) se añadieron cloruro de benzoílo (0,01 ml, 0,109 mmol) y 4-dimetilaminopiridina (0,001 g, 0,01 mmol). La mezcla se agitó a temperatura ambiente durante 19 horas y se vertió en agua. La mezcla se extrajo con acetato de etilo. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo resultante se purificó mediante cromatografía en columna sobre gel de sílice (hexano / acetato de etilo = 5/1 – 3/2) proporcionando 3-{2-{2-(ciclopropilmetoxi)-6-[(4-metoxi)-oxibencil]fenil}-7-oxo-[1-fenil-metanoil)-amino]-7,8-dihidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo (0,022 g, rendimiento; 28%).



A continuación se eliminó el resto bencilo y el carbamato de *terc*-butilo de manera similar a la descrita en la etapa (2) del Ejemplo 25-4 proporcionando clorhidrato de N-[7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,2-dihidro-1,8-naftiridin-3-il]-benzamida.

Peso molecular: 547,06

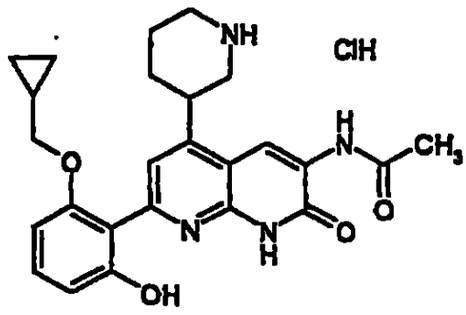
Espectrometría de masas: 511 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

RMN de ^1H (500 MHz, DMSO-d_6): 0,34 (2H, m), 0,59 (2H, m), 1,29 (1H, m), 1,80-2,08 (4H, m), 2,96 (1H, a), 3,18 (1H, dd, J= 11,4, 11,7 Hz), 6,59 (2H, d, J= 8,2 Hz), 7,23 (1H, t, J= 8,2 Hz), 7,61 (2H, t, J= 7,9 Hz), 7,68 (1H, m), 8,01 (2H, m), 8,04 (1H, s), 8,80 (1H, a), 9,03 (2H, s), 9,61 (1H, s), 13,13 (1H, s).

Ejemplo 29-3



De manera similar a la del Ejemplo 29-2, se preparó clorhidrato de N-[7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,2-dihidro-1,8-naftiridin-3-il]-benzamida.

Peso molecular: 484,99

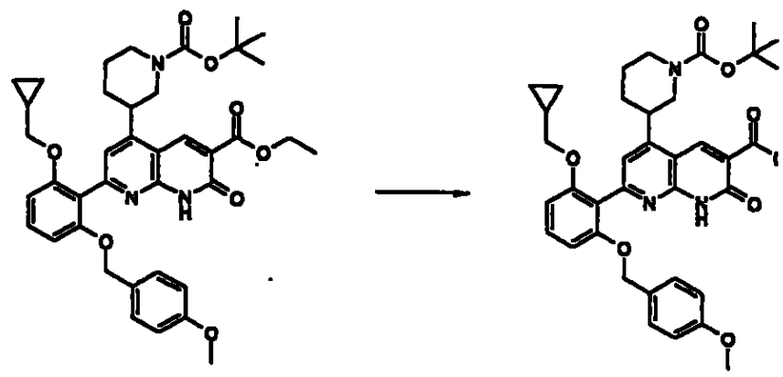
Espectrometría de masas: 449 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

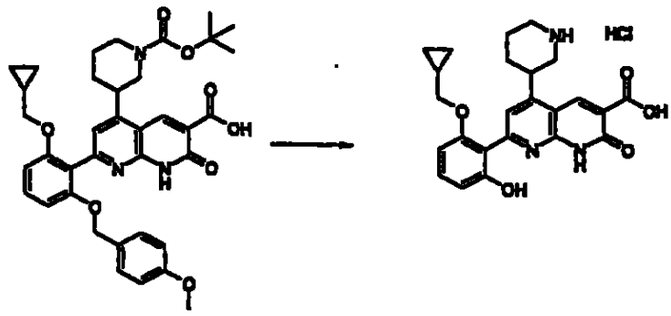
(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,59 (2H, m), 1,28 (1H, m), 1,76 (1H, m), 1,89 (1H, m), 1,98 (1H, m), 2,92 (1H, dd, J= 11,4, 12,0 Hz), 3,17 (1H, dd, J= 11,0, 12,0 Hz), 6,57 (2H, d, J= 8,5 Hz), 7,21 (1H, t, J= 8,5 Hz), 7,99 (1H, s), 8,78 (1H, a), 8,94 (1H, s), 9,02 (1H, a), 9,69 (1H, s), 11,92 (1H, a), 12,93 (1H, s).

Ejemplo 30-1



(1) A una solución agitada de 5-[1-(*terc*-butoxicarbonil)-3-piperidinil]-7-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil]fenil}-2-oxo-1,2-dihidro-1,8-naftiridin-3-carboxilato de etilo (0,276 g, 0,403 mmol), que se obtuvo de manera similar a la de la etapa (1) del Ejemplo 29-1 utilizando malonato de dietilo en vez de nitroacetato de etilo, en tetrahidrofurano (4 ml) y agua (1 mililitro) se añadió hidróxido de litio monohidratado (0,015 g, 0,605 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas y se aciduló (pH 3-4) con una solución en agua de ácido clorhídrico 1N. La mezcla se extrajo con acetato de etilo. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a vacío proporcionando clorhidrato del ácido 5-[1-(*terc*-butoxicarbonil)-3-piperidinil]-7-{2-(ciclopropilmetoxi)-

6-[(4-metoxibencil)oxi]fenil}2-oxo-5-piperidin-3-il-1,2-dihidro[1,8]naftiridin-3-carboxílico (0,259 g, rendimiento; 98%).



(2) Seguidamente se eliminó el resto bencilo y el carbamato de *terc*-butilo de manera similar a la descrita en la etapa (2) del Ejemplo 25-4, proporcionando clorhidrato de ácido 7-(2-ciclometoxipropil-6-hidroxifenil)-2-oxo-5-piperidin-3-il-1,2-dihidro-[1,8]naftiridin-3-carboxílico.

Peso molecular: 471,94

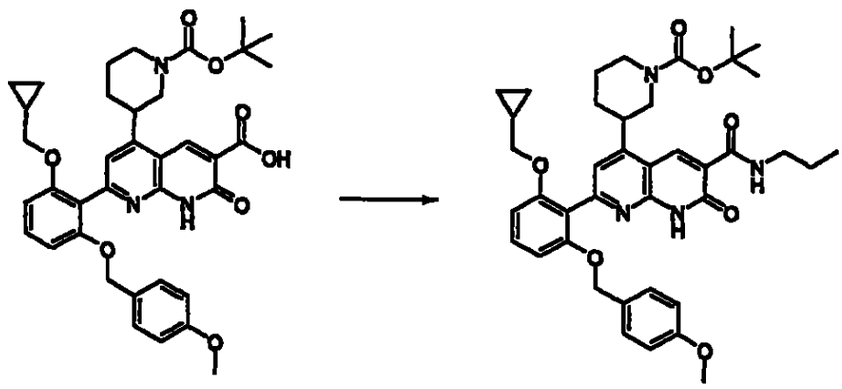
Espectrometría de masas: 436 $(M + H)^+$

Grado de actividad in vitro: A

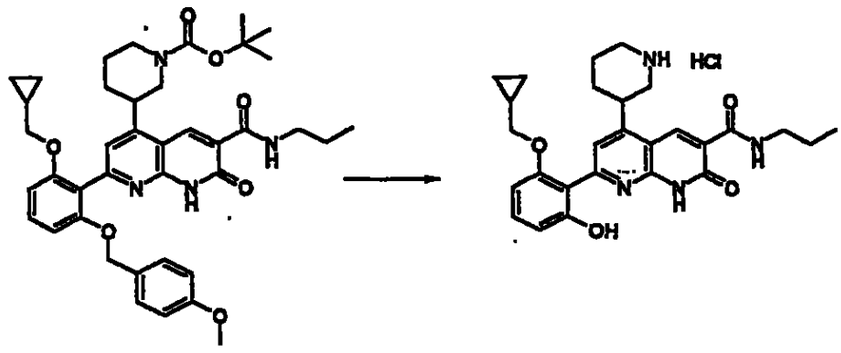
Grado de actividad celular: (A549)-B

(500 MHz, DMSO-d_6): 0,30-0,33 (2H, m), 0,54-0,55 (2H, m), 1,23 (1H, m), 1,92-1,98 (4H, m), 2,91 (1H, m), 3,04 (1H, m), 3,39-3,41 (3H, m), 3,86-3,89 (3H, m), 6,61 (2H, d, J= 8,5 Hz), 7,27 (1H, t, J= 8,2 Hz), 8,07 (1H, s), 8,72 (1H, s), 9,24 (1H, s), 13,74 (1H, s), 14,43 (1H, s).

Ejemplo 31-1



(1) A una solución agitada de ácido 5-[1-(*terc*-butoxicarbonil)-3-piperidinil]-7-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-2-oxo-1,2-dihidro-1,8-naftiridin-3-carboxílico (0,200 g, 0,305 mmol), que se obtuvo en la etapa (1) del Ejemplo 30-1, y 1-hidroxibenzotriazol hidratado (0,062 g, 0,457 mmol) en dimetilformamida (4 ml) se añadió clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0,070 g, 0,366 mmol). Se agitó la mezcla a temperatura ambiente durante 18 horas, y después se extrajo con acetato de etilo y agua. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo resultante se purificó mediante cromatografía en columna sobre gel de sílice (hexano / acetato de etilo = 1/1) proporcionando 3-{2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-7-oxo-6-[propilamino)-carbonil]-7,8-dihidro-1,8-naftiridin-4-il}-1-piperidincarboxilato de *terc*-butilo (0,129 g, rendimiento; 61%).



(2) A continuación se eliminó el resto bencilo y el carbamato de *terc*-butilo de manera similar a la descrita en la etapa (2) del Ejemplo 25-4 proporcionando 7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-N-propil-1,2-dihidro-1,8-naftiridin-3-carboxamida.

Peso molecular: 513,04

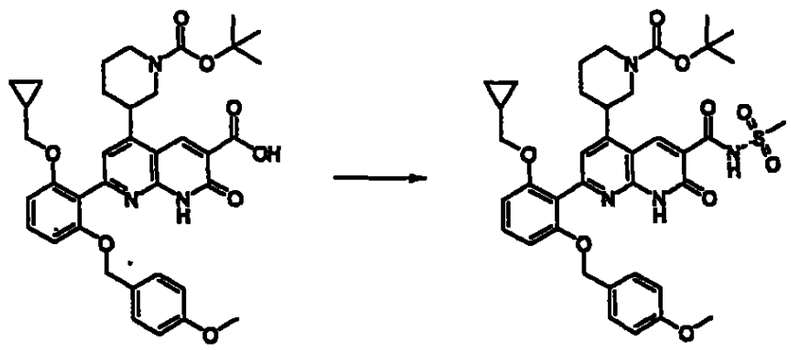
Espectrometría de masas: 477 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

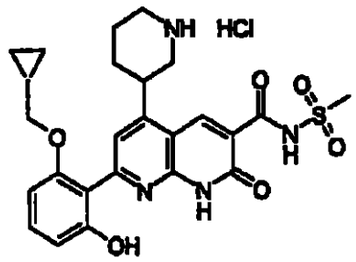
RMN de ^1H (500 MHz, DMSO-d_6): 0,33 (2H, m), 0,57 (2H, m), 0,94 (3H, t, J= 7,3 Hz), 1,27 (1H, m), 1,58 (2H, tq, J= 7,3, 7,3 Hz), 1,92 (4H, m), 2,90 (1H, m), 3,06 (1H, t, J= 12,3 Hz), 6,59 (2H, d, J= 8,2 Hz), 7,26 (1H, t, J= 8,2 Hz), 8,07 (1H, s), 9,01 (1H, s), 9,69 (1H, t, J= 6,0 Hz), 11,80 (1H, s).

Ejemplo 31-2



A una solución agitada de metanosulfonamida (0,026 g, 0,628 mmol) y trietilamina (0,030 ml, 0,229 mmol) en tolueno (2 ml) se añadió cloruro de trimetilsililo (0,020 ml, 0,229 mmol). La mezcla se agitó a 90°C durante 1 hora, y después se concentró a presión reducida. Al residuo diluido con diclorometano (2 ml) se añadió,

sucesivamente, trietilamina (0,020 ml, 0,155 mmol), 4,4-dimetilaminopiridina (0,002 g, 0,015 mmol), hexafluorofosfato de benzotriazol-1-iloxi-tris(dimetilamino)fosfonio (0,040 g, 0,091 mmol) y ácido 5-[1-(*terc*-butoxicarbonil)-3-piperidinil]-7-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-2-oxo-1,2-dihidro-1,8-naftiridin-3-carboxílico (0,050 g, 0,076 mmol). La mezcla se agitó a temperatura ambiente durante 6 horas. La mezcla se extrajo con acetato de etilo y agua. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo resultante se purificó con TLC preparativa (hexano / acetato de etilo = 1/1 x 2) proporcionando 3-(2-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-6-{[(metilsulfonil)-amino]carbonil}-7-oxo-7,8-dihidro-1,8-naftiridin-4-il)-1-piperidincarboxilato de *terc*-butilo (0,024 g, rendimiento; 43%).



A continuación se eliminó el resto bencilo y el carbamato de *terc*-butilo de manera similar a la descrita en la etapa (2) del Ejemplo 25-4 proporcionando clorhidrato de N-{[7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,2-dihidro-1,8-naftiridin-3-il]carbonil}metanosulfonamida.

Peso molecular: 549,05

Espectrometría de masas: 513 $(M + H)^+$

Grado de actividad in vitro: A

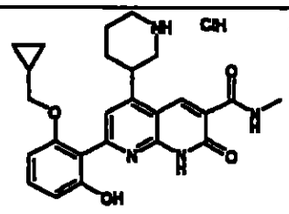
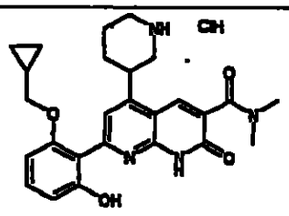
Grado de actividad celular: (A549)-B

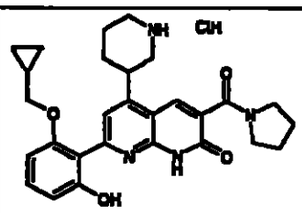
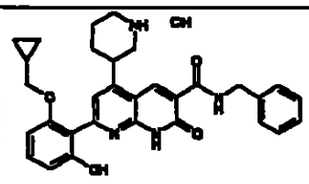
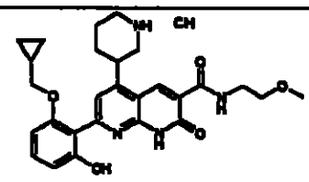
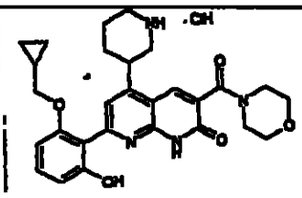
RMN de ^{1}H (500 MHz, DMSO-d_6): 0,33 (2H, m), 0,55 (2H, m), 1,25 (1H, m), 1,95 (4H, m), 2,92 (1H, a), 3,06 (1H, t, J= 12,0 Hz), 3,40 (2H, t, J= 11,7 Hz), 3,45 (3H, s), 6,61 (2H, d, J= 8,2 Hz), 7,28 (1H, t, J= 8,2 Hz), 8,09 (1H, s), 8,74 (1H, a), 9,08 (1H, s), 11,62 (1H, a), 12,72 (1H, a), 13,56 (1H, a).

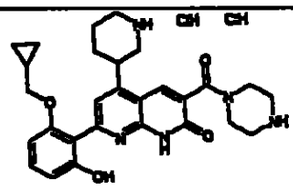
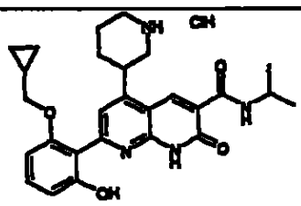
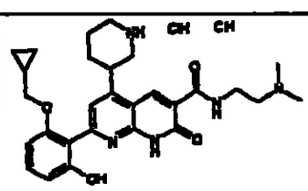
Ejemplos 31-3 a 31-27

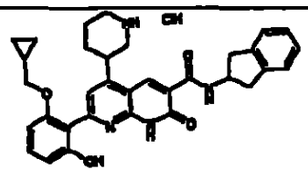
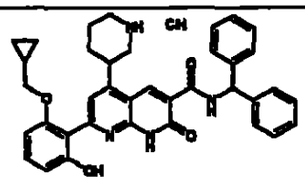
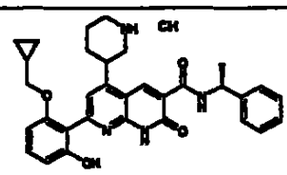
Los compuestos de la tabla 11 se prepararon de acuerdo con un procedimiento sintético similar al de los Ejemplos 31-1 a 31-2.

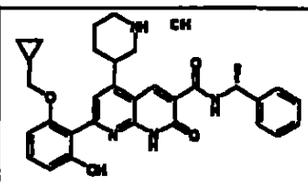
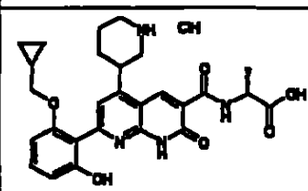
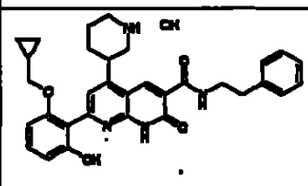
Tabla 11

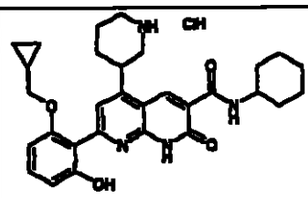
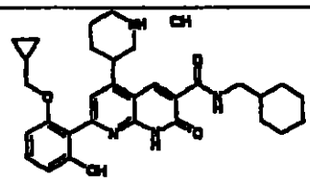
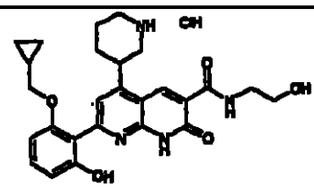
Ej. nº	Estructura	Peso molec	Masa	*In vitro*	A549	RMN
31-03		484,99	449	A	A	(500 MHz, DMSO-d_6): 0,34 (2H, m), 0,57 (2H, m), 1,27 (1H, m), 1,92 (4H, m), 2,91 (3H, d, J= 4,7 Hz), 3,05 (1H, t, J= 12,3 Hz), 6,59 (2H, d, J=8,2 Hz), 7,26 (1H, t, J= 8,2 Hz), 8,06 (1H, s), 9,00 (1H, s), 9,53 (1H, q, J= 4,7 Hz), 11,79 (1H, s)
31-04		499,01	463	A	B	(500 MHz, DMSO-d_6): 0,34 (2H, m), 0,57 (2H, m), 1,27 (1H, m), 1,94 (4H, m), 2,92 (3H, s), 3,00 (3H, s), 6,58 (2H, d, J= 8,2 Hz), 7,24 (1H, t, J= 8,2 Hz), 8,00 (1H, s), 8,19 (1H, s), 8,58 (1H, a), 9,10 (1H, a), 11,84 (1H, a), 12,72 (1H, s).

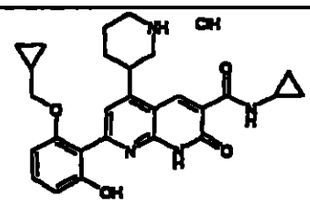
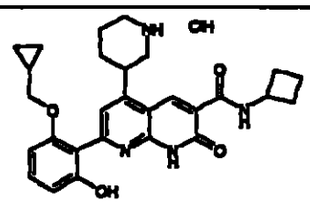
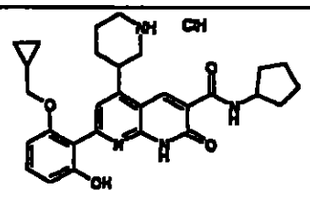
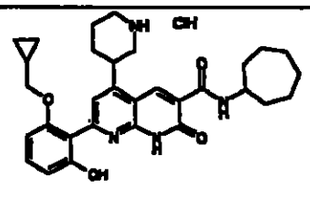
31-05		525,05	489	A	B	(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,57 (2H, m), 1,25 (1H, m), 1,89 (9H, m), 2,90 (1H, m), 2,98 (1H, dd, J=11,4, 12,6 Hz), 6,58 (2H, d, J= 8,2 Hz), 7,24 (1H, t, J= 2,5 Hz), 8,00 (1H, s), 8,22 (1H, d, J= 2,5 Hz), 8,46 (1H, a), 9,05 (1H, a), 11,82 (1H, a), 12,74 (1H, s).
31-06		561,09	525	A	A	(500 MHz, DMSO-d_6):0,33 (2H, m), 0,57 (2H, m), 1,27 (1H, m), 1,92 (4H, m), 2,91 (1H, m), 3,06 (1H, t, J= 12,3 Hz), 4,61 (2H, d, J= 6,0 Hz), 6,59 (2H, d, J= 8,5 Hz), 7,28 (2H, m), 7,37 (4H, m), 8,08 (1H, s), 9,05 (1H, s), 10,07 (1H, t, J= 6,0 Hz), 11,80 (1H, s).
31-07		529,04	493	A	A	(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,57 (2H, m), 1,27 (1H, m), 1,92 (4H, m), 2,91 (1H, m), 3,07 (1H, t, J= 12,3 Hz), 3,50 (2H, m), 3,55 (2H, m), 6,60 (2H, d, J= 8,2 Hz), 7,26 (1H, t, J= 8,2 Hz), 8,07 (1H, s), 9,02 (1H, s), 9,78 (1H, m), 11,80 (1H, s).
31-08		541,05	505	A	B	(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,57 (2H, m), 1,26 (1H, m), 1,93 (4H, m), 2,90 (1H, m), 2,98 (1H, dd, J= 11,3, 12,0 Hz), 3,73 (1H, a), 3,88 (2H, m), 6,58 (2H, d, J= 8,2 Hz), 7,24 (1H, t, J= 8,2 Hz), 8,00 (1H, s), 8,63 (1H, a), 9,06 (1H, d a, J= 10,7 Hz),

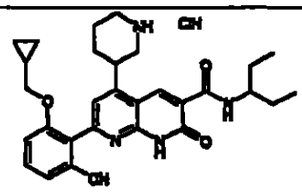
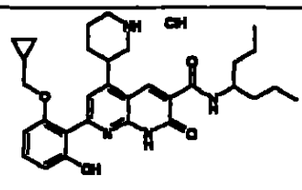
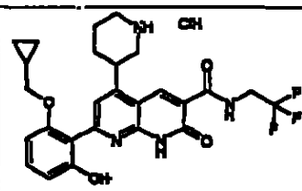
						11,85 (1H, a), 12,73 (1H, s).
31-09		576,53	504	A	C	(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,57 (2H, m), 1,26 (1H, m), 1,94 (4H, m), 2,90 (1H, m), 2,98 (1H, dd, J= 10,7, 11,4 Hz), 3,18 (4H, s a), 3,88 (5H, m), 6,58 (2H, d, J= 8,2 Hz), 7,24 (1H, t, J= 8,2 Hz), 8,00 (1H, s), 8,38 (1H, s), 9,03-9,21 (4H, a), 11,81 (1H. a), 12,78 (1H, s).
31-10		513,04	477	A	A	(500 MHz, DMSO-d_6): 0,34 (2H, m), 0,57 (2H, m), 1,23 (6H, d, J= 6,6 Hz), 1,88-1,99 (4H, m), 2,91 (1H, m), 3,07 (1H, dd, J= 11,0, 12,0 Hz), 4,11 (1H, dq, J= 6,6, 7,6 Hz), 6,59 (2H, d, J= 8,2 Hz), 7,26 (1H, t, J= 8,2 Hz), 8,07 (1H, s), 8,72 (1H, a), 9,01 (1H, s), 9,59 (1H, d, J= 7,6 Hz), 11,80 (1H, a), 13,13 (1H, s).
31-11		578,04	506	A	A	(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,56 (2H, m), 1,26 (1H, m), 1,88-1,99 (4H, m), 2,85 (6H, s), 3,11 (1H, dd, J= 11,0, 12,3 Hz), 3,75 (2H, t, J= 5,7 Hz), 6,59 (2H, d, J= 8,2 Hz), 7,27 (1H, t, J= 8,2 Hz), 8,07 (1H, s), 8,83 (1H, a), 9,01 (1H, s), 9,14 (1H, a), 9,66 (1H, a), 9,83 (1H, t, J= 6,0 Hz), 11,75 (1H, s), 13,18 (1H, s).

31-12		587,12	551	A	A	(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,57 (2H, m), 1,26 (1H, m), 1,88-1,99 (4H, m), 2,92 (3H, dd, J= 5,4, 10,7 Hz), 3,07 (1H, t, J= 12,3 Hz), 4,74 (1H, ddd, J= 6,9, 6,9, 12,6 Hz), 6,59 (2H, d, J= 8,2 Hz), 7,19 (2H, m), 7,28 (3H, m), 8,06 (1H, s), 9,03 (1H, s), 9,91 (1H, d, J= 6,9 Hz), 11,76 (1H, s), 13,09 (1H, a).
31-13		637,18	601	A	A	(500 MHz, DMSO-d_6): 0,32 (2H, m), 0,56 (2H, m), 1,25 (1H, m), 1,88-1,97 (4H, m), 2,90 (1H, m), 3,05 (1H, t, J= 12,3 Hz), 6,33 (1H, d, J= 7,9 Hz), 6,60 (2H, d, J= 8,2 Hz), 7,28 (3H, m), 7,38 (8H, m), 8,04 (1H, s), 9,03 (1H, s), 10,07 (1H, d, J= 7,9 Hz), 11,69 (1H, s), 13,20 (1H, a)
31-14		575,11	539	A	A	(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,56 (2H, m), 1,26 (1H, m), 1,53 (3H, d, J= 6,9 Hz), 1,86-1,98 (4H, m), 2,91 (1H, m), 3,06 (1H, m), 5,19 (1H, dq, J= 6,9, 7,3 Hz), 6,59 (3H, d, J= 8,2 Hz), 7,28 (2H, m), 7,39 (4H, m), 8,06 (1H, d, J= 2,9 Hz), 8,71 (1H, t a, J= 11,7 Hz), 9,01 (1H, d, J= 2,9 Hz), 9,09 (1H, t a, J= 11,7 Hz), 10,11 (1H, dd, J= 5,7, 7,6 Hz), 11,78 (1H, a), 13,16 (1H, s).

31-15		575,11	539	A	A	(500 MHz, DMSO-d_6): 0,33 (2H. m), 0,56 (2H, m), 1.26 (1H, m), 1.53 (3H, d, J= 6,9 Hz), 1,86-1,98 (4H, m), 2,91 (1H, m), 3,06 (1H, m), 5,19 (1H, dq, J= 6,9, 7,3 Hz), 6,59, 6,59 (2H. d x 2, J= 8,2 Hz), 7,28 (2H, m), 7,39 (4H, m), 8,06 (1H, d, J= 2,9 Hz), 8,73 (1H, t a, J= 11,7 Hz), 9,00 (1H, d, J= 2,9 Hz), 9,16 (1H, t a, J= 11,4 Hz), 10,11 (1H, dd, J= 5,7, 7,6 Hz), 11,78 (1H, a), 13,16 (1H, s).
31-16		543,02	507	A	B	(500 MHz, DMSO-d_6):0.34 (2H. m). 0,57 (2H, m), 1,28 (1H, m), 1,44 (3H, d, J= 7,3 Hz), 1,88-1,99 (4H, m), 2,92 (1H, m), 3,07 (1H, dd, J= 11,4, 12,0 Hz), 4,53 (1H, m), 6,59, 6,61 (2H, d x 2, J= 8,2 Hz), 7,27 (1H, t, J= 8,2 Hz), 8,08 (1H, s), 8,79 (1H, a), 9,02 (1H, s), 9,28 (1H, a), 10,07, 10,08 (1H, d x 2, J= 6,9 Hz), 13,17 (1H, s).
31-17		575,11	539	A	B	(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,56 (2H, m), 1,26 (1H, m), 1,88-1,99 (4H, m), 2,88 (2H, t, J= 7,3 Hz), 3,07 (1H, dd, J= 11,7, 12,0 Hz), 3,63 (2H, dt, J= 6,3, 7,3 Hz), 6,59 (2H, d, J= 8,2 Hz), 7,21-7,33 (6H, m), 8,05 (1H, s), 8,69 (1H, a), 8,99 (1H, d a, J= 5,1 Hz), 9,01 (1H, s), 9,73 (1H, t, J= 6,3 Hz), 11,74 (1H, s a), 13,11 (1H, s).

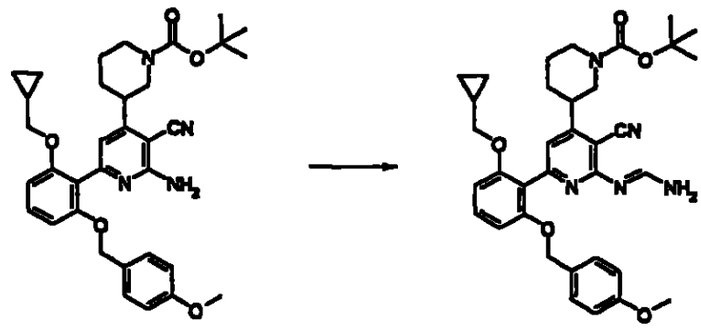
31-18		553,11	517	A	A	(500 MHz, $CDCl_3$): 0,41-0,47 (2H, m), 0,65-0,77 (2H, m), 0,77-0,92 (1H, m), 1,32-1,42 (1H, m), 1,78-1,84 (1H, m), 1,84-1,97 (2H, m), 2,15-2,24 (1H, m), 2,72 (1H, dd, J= 2,8, 12,0 Hz), 2,80-2,88 (m, 1H), 3,16-3,26 (1H, m), 3,34-3,46 (2H, m), 3,91 (2H, d, J= 6,9 Hz), 5,95 (2H, s a), 6,42 (1H, dd, J= 1,0, 8,2 Hz), 6,73 (1H, dd, J= 1,0, 8,2 Hz), 7,23-7,26 (1H, m), 8,63 (1H, s), 8,69 (1H, s), 15,00 (1H, a).
31-19		567,13	531	A	C	(500 MHz, DMSO-d_6): 0.33 (2H, m), 0,56 (2H, m), 1,02 (2H, m), 1,14-1,26 (4H, m), 1,53 (1H, a), 1,64 (1H, d a, J= 11,4 Hz), 1,72 (4H, m), 1,93 (4H, m), 2,92 (1H, a), 3,07 (1H, t, J= 12,0 Hz), 6,59 (2H, d, J= 8,2 Hz), 7,26 (1H, t, J= 8,2 Hz), 8,05 (1H, s), 8,90 (1H, a), 9,00 (1H, a), 9,01 (1H, s), 9,73 (1H, d, J= 11,7 Hz), 11,74 (1H, s), 13,12 (1H, a).
31-20		515.01	479	A	B	(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,56 (2H, m), 1,27 (1H, m), 1,93 (4H, m), 2,91 (1H, m), 3,07 (1H, t, J= 12,0 Hz), 3,39 (2H, a), 3,44 (2H, dd, J= 5,7, 6,0 Hz), 3,56 (2H, dd, J= 5,4, 5,7 Hz), 6,59 (2H, d, J= 8,2 Hz), 7,26 (1H, t, J= 8,2 Hz), 8,07 (1H, s), 9,02 (1H, s), 9,79 (1H, d, J= 5,4 Hz), 11,82 (1H, s), 13,13 (1H, a).

31-21		511,03	475	A	A	(500 MHz, DMSO-d_6): 0,34 (2H, m), 0,58 (2H, m), 0,79 (2H, m), 1,26 (1H, m), 1,91 (4H, m), 2,93 (2H, m), 3,07 (1H, t, J= 12,0 Hz), 6,60 (2H, d, J= 8,2 Hz), 7,26 (1H, t, J= 8,2 Hz), 8,06 (1H, s), 8,99 (1H, s), 9,66 (1H, d, J= 4,4 Hz), 11,76 (1H, s), 13,13 (1H, a).
31-22		525,05	489	A	A	(500 MHz, DMSO-d_6): 0,33 (2H, m), 0,56 (2H, m), 1,26 (1H, m), 1,74 (2H, m), 1,87-2,05 (6H, m), 2,91 (1H, m), 3,05 (1H, t, J= 12,3 Hz), 4,46 (1H, m), 6,59 (2H, d, J= 8,2 Hz) 7,26 (1H, t, J= 8,2 Hz), 8,06 (1H, s), 8,99 (1H, s), 9,84 (1H, d, J= 7,6 Hz), 11,79 (1H, s), 13,13 (1H, a).
31-23		539,08	503	A	A	(500 MHz, DMSO-d_6): 0,34 (2H, m), 0,56 (2H, m), 1,26 (1H, m), 1,50 (2H, m), 1,62 (2H, m), 1,71 (2H, m), 1,88-1,99 (6H, m), 2,92 (1H, m), 3,06 (1H, t, J= 12,0 Hz), 6,59 (2H, d, J= 8,2 Hz), 7,26 (1H, t, J= 8,2 Hz), 8,06 (1H, s), 9,01 (1H, s), 9,72 (1H, d, J= 6,9 Hz), 11,77 (1H, s), 13,12 (1H, a).
31-24		567,13	531	A	A	(500 MHz, DMSO-d_6): 0,34 (2H, m), 0,56 (2H, m), 1,26 (1H, m), 1,59 (10H, m), 1,87-1,99 (6H, m), 2,90 (1H, m), 3,06 (1H, t, J= 11,7 Hz), 4,07 (1H, m), 6,59 (2H, d, J= 8,5 Hz), 7,26 (1H, t, J= 8,5 Hz), 8,06 (1H, s), 9,01 (1H, s), 9,78 (1H, d, J= 7,9 Hz),

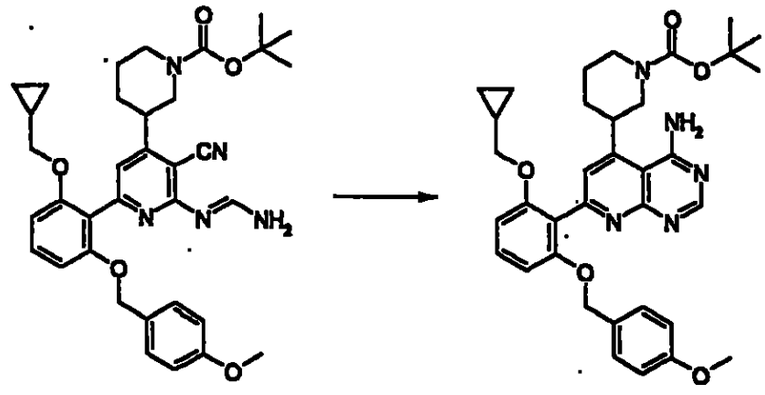
						11,78 (1H, s), 13,12 (1H, a).
31-25		541,10	505	A	A	(500 MHz, DMSO-d_6): 0,34 (2H, m), 0,56 (2H, m), 0,90 (6H, t, J= 8,2 Hz), 1,27 (1H, m), 1,51 (2H, m), 1,61 (2H, m), 1,88-1,99 (4H, m), 2,92 (1H, m), 3,07 (1H, t, J= 12,0 Hz), 6,60 (2H, d, J= 8,2 Hz), 7,26 (1H, t, J= 8,2 Hz), 8,07 (1H, s), 8,67 (1H, a), 8,98 (1H, a), 9,03 (1H, s), 9,54 (1H, d, J= 8,8 Hz), 11,78 (1H, s), 13,12 (1H, a).
31-26		569,15	533	A	A	(500 MHz, DMSO-d_6): 0,34 (2H, m), 0,56 (2H, m), 0,90 (6H, t, J= 7,3 Hz), 1,25-1,54 (9H, m), 1,88-1,99 (4H, m), 2,92 (1H, m), 3,06 (1H, t, J= 12,3 Hz), 4,07 (1H, m), 6,59 (2H, d, J= 8,2 Hz), 7,26 (1H, t, J= 8,2 Hz), 8,07 (1H, s), 8,69 (1H, a), 9,00 (1H, a), 9,03 (1H, s), 9,51 (1H, d, J= 9,1 Hz), 11,78 (1H, s), 13,11 (1H, a).
31-27		552,99	517	A	A	(500 MHz, DMSO-d_6): 0,34 (2H, m), 0,57 (2H, m), 1,27 (1H, m), 1,88-1,99 (4H, m), 2,92 (1H, m), 3,06 (1H, t, J= 12,3 Hz), 4,28 (2H, m), 6,60 (2H, d, J= 8,2 Hz), 7,27 (1H, t, J= 8,2 Hz), 8,08 (1H, s), 9,07 (1H, s), 10,12 (1H, d, J= 6,6 Hz), 11,76 (1H, s), 13,26 (1H, a).

Ejemplo 32-1

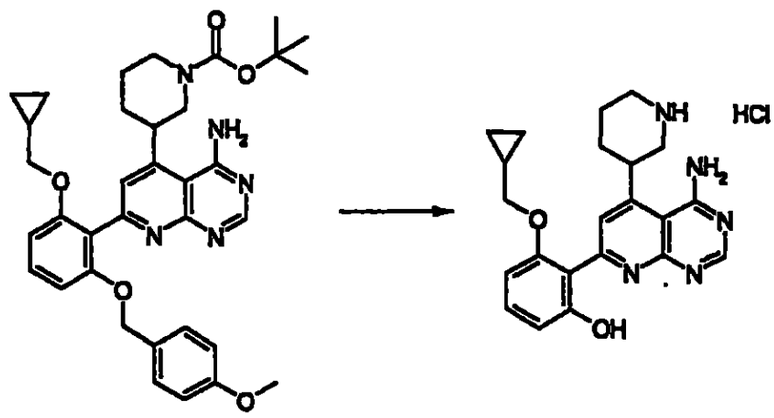
Utilizando los compuestos de pártida 1G, 2B y otros materiales, se preparó 3-(2-amino-3-ciano-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-4-piridinil)-1-piperidincarboxilato de *terc*-butilo de manera similar a la de la etapa (1) Ejemplo 1-1.



A una solución de 3-(2-amino-3-ciano-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-4-piridinil)-1-piperidincarboxilato de *terc*-butilo (0,580 g, 0,999 mmol) en ortoformiato de trietilo (1,2 ml) se añadió sulfato de amonio (0,004 g, 0,030 mmol) y la mezcla se agitó a temperatura ambiente durante la noche y se concentró a presión reducida. El residuo se trituró con hexano y éter isopropílico, y se secó a presión reducida proporcionando 3-(2-{[(1E)-aminometilidino]amino}-3-ciano-6-{2-(ciclopropil-metoxi(-6-[(4-metoxi-bencil)oxi]fenil}-4-piridinil)-1-piperidincarboxilato de *terc*-butilo en forma de sólido marrón (0,543 g, rendimiento; 89%).



A una solución de 3-(2-{[(1E)-aminometilideno]amino}-3-ciano-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-4-piridinil)-1-piperidincarboxilato de *terc*-butilo (0,1805 g, 0,289 mmol) en MeOH (5 ml) y tolueno (5 ml) se añadió ácido trifluoracético (0,01 ml). La mezcla se dejó durante 20 días y se concentró a presión reducida. Se purificó por cromatografía en columna sobre gel de sílice (CH_2Cl_2 / MeOH = 50/1 a 20/1) proporcionando 3-(4-amino-7-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]-fenil}pirido[2,3-d]pirimidin-5-il)-1-piperidincarboxilato de *terc*-butilo en forma de aceite incoloro (0,026 g, rendimiento; 15%).



A continuación se eliminó el resto bencilo y el carbamato de *terc*-butilo de manera similar a la descrita en la etapa (2) del Ejemplo 25-4 proporcionando clorhidrato de 2-[4-amino-5-(3-piperidinil)pirido[2,3-d]pirimidin-7-il]-3-(ciclopropilmetoxi)fenol en forma de polvo amarillo (0,004 g, 24%).

Peso molecular: 391,48

Espectrometría de masas: 392 $(M + H)^+$

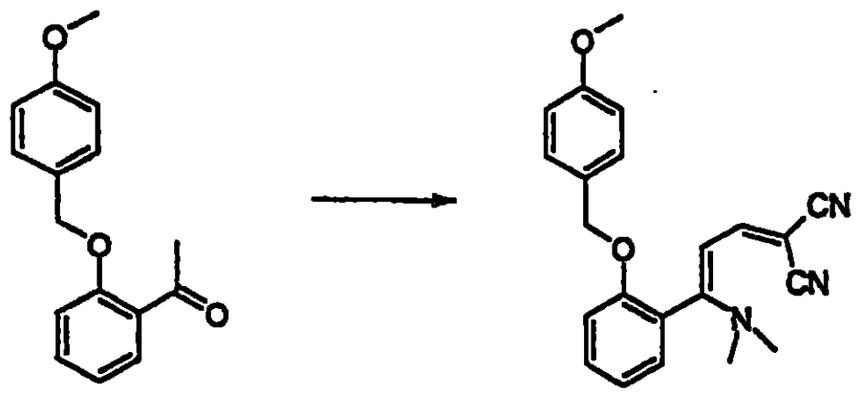
Grado de actividad in vitro: C

Grado de actividad celular: (A549)-B

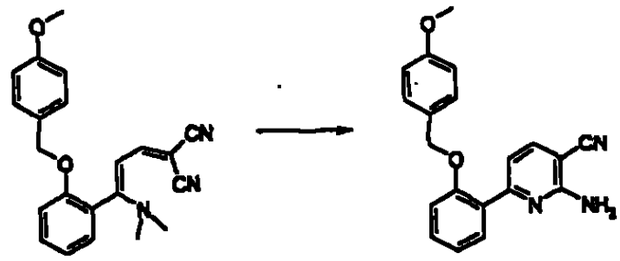
RMN de ^1H (500 MHz, $CDCl_3$): 0,41-0,47 (2H, m), 0,65-0,77 (2H, m), 0,77-0,92 (1H,

m), 1,32-1,42 (1H, m), 1,78-1,84 (1H, m), 1,84-1,97 (2H, m), 2,15-2,24 (1H, m), 2,72 (1H, dd, J= 2,8, 12,0 Hz), 2,80-2,88 (m, 1H), 3,16-3,26 (1H, m), 3,34-3,46 (2H, m), 3,91 (2H, d, J= 6,9 Hz), 5,95 (2H, s a), 6,42 (1H, dd, J= 1,0, 8,2 Hz), 6,73 (1H, dd, J= 1,0, 8,2 Hz), 7,23-7,26 (1H, m), 8,63 (1H, s), 8,69 (1H, s), 15,00 (1H, a).

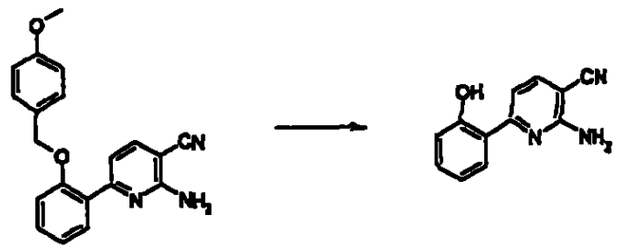
Ejemplo 33-1



A una solución de cloruro de oxalilo (3,63 g, 28,6 mmol) en acetonitrilo (5,00 ml) a temperatura ambiente se añadió DMF (5,00 ml). Después de 10 minutos, se añadió una solución de 2-(4-metoxifenilmetoxi)acetofenona (3,33 g, 13,0 mmol) (compuesto de partida 1D) en DMF (50ml), y se continuó agitando durante la noche. A la mezcla de reacción se añadió malonitrilo (1,03 g, 15,6 mmol) y Et_3N (75 ml, 52,0 mmol) sucesivamente y la mezcla de reacción se vertió en agua y seguidamente se extrajo con éter. La fase orgánica separada se lavó con salmuera, y se secó sobre Mg SO_4, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice ($CHCl_3$) proporcionando 2-((2Z)-3-(dimetilamino)-3-{2-[(4-metoxibencil)-oxi]fenil}-2-propenilideno)malononitrilo (1,27 g, rendimiento; 27%).



A una solución fría (-78°C) de 2-((2Z)-3-(dimetilamino)-3-{2-[(4-metoxibencil)-oxi]fenil}-2-propenilidina)malononitrilo (1,26 g, 3,51 mmol) en MeOH se añadió NH_3 líquido y la mezcla se calentó a 120°C en un tubo cerrado durante la noche. Después de enfriar a la temperatura ambiente, la mezcla se vertió en agua y la mezcla resultante se extrajo con acetato de etilo. La fase orgánica separada se lavó con salmuera y se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El residuo bruto de purificó por cromatografía en columna sobre gel de sílice (hexano / acetato de etilo = 70/30) proporcionando 2-amino-6-({2-[(4-metoxibencil)oxi]fenil}nicotinonitrilo (0,050 g, rendimiento; 4,3%).



Una mezcla de 2-amino-6-({2-[(4-metoxibencil)oxi]fenil}nicotinonitrilo (0,050 g, 0,151 mmol), ácido trifluoracético (3,00 ml), anisol (0,50 ml) y agua (0,50 ml) se agitó a temperatura ambiente durante la noche. La mezcla se diluyó en THF y a continuación se añadió hexano para producir un precipitado. El precipitado se recogió por filtración y se lavó con hexano, y seguidamente se secó a presión reducida proporcionando 2-amino-6-(2-hidroxifenil)nicotinonitrilo. (0,026 g, rendimiento: 82%).

Peso molecular: 211,23

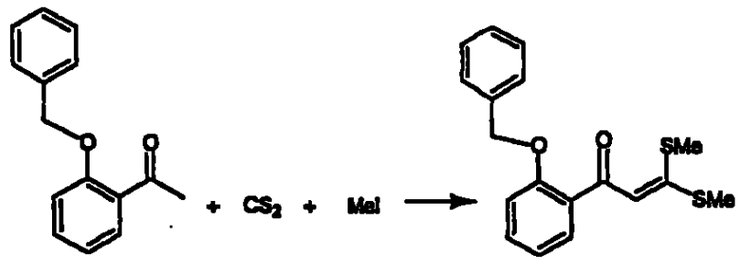
Espectrometría de masas: 212 $(M + H)^+$

Grado de actividad in vitro: B

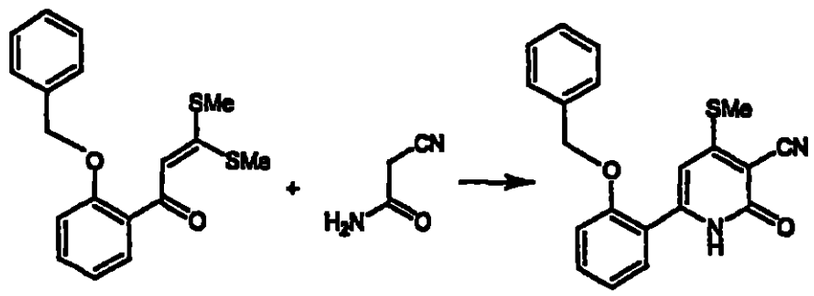
Grado de actividad celular: (A549)-B

RMN de ^1H (500 MHz, DMSO-d_6): 6,87-6,92 (2H, m), 7,31-7,39 (4H, m), 7,94 (1H, d, J= 8,3 Hz), 8,01 (1H, d, J= 8,3 Hz), 13,38 (1H, s a).

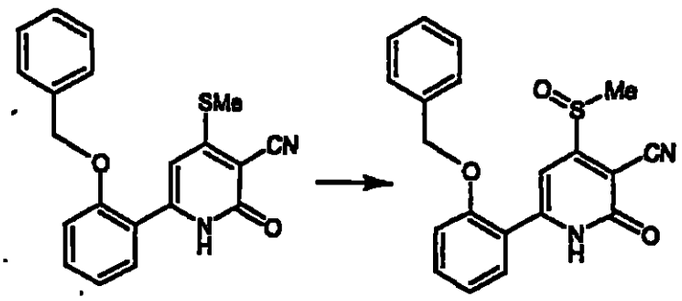
Ejemplo 34-1



(1) A una solución de 2-(benciloxi)acetofenona (5,66 g, 25 mmol) (compuesto de partida 1A) en tolueno (40ml) se añadió disulfuro de carbono (6,0 ml, 99,8 mmol) y yoduro de metilo (10ml, 245 mmol). A la mezcla se añadió hidruro de sodio (suspensión del 60%, 2,00 g, 50 mmol) y N,N-dimetilacetamida (10 ml). La mezcla resultante se agitó a temperatura ambiente durante 1 hora y se calentó a reflujo durante 2 horas. Después de enfriar a la temperatura ambiente, la mezcla de reacción se repartió entre CH_2Cl_2 y agua. Se separó la fase orgánica y se lavó con agua, se secó y se concentró a presión reducida. El residuo sólido se trituró con éter diisopropílico proporcionando 1-[2-(bencil)fenil]-3,3-bis(metiltio)-2-propen-1-ona en forma de sólido amarillo claro (5,17 g, rendimiento; 63%).

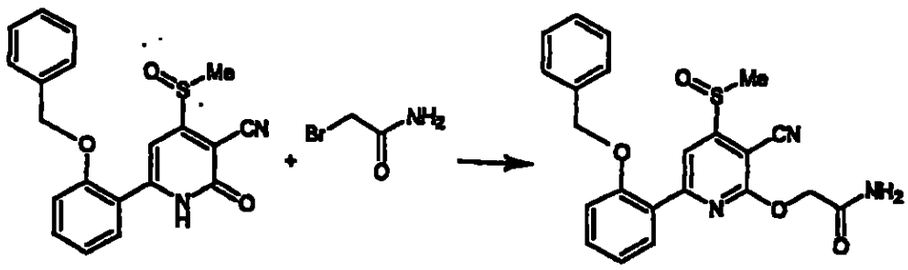


(2) A una suspensión de cianoacetamida (1,27 g, 15,1 mmol) en 2-propanol (50 ml) se añadió hidruro de sodio (suspensión del 60%, 0,605 g, 15,1 mmol). La mezcla se agitó a temperatura ambiente durante 10 minutos. A esta mezcla se añadió en una porción 1-[2-(bencil)fenil]-3,3-bis(metiltio)-2-propen-1-ona (5,00 g, 15,1 mmol). La mezcla resultante se calentó a reflujo durante 4 horas. Después de enfriar a temperatura ambiente, la mezcla se diluyó en HCl 1N. El precipitado resultante de recogió por filtración y se lavó con EtOH proporcionando 6-[2-(benciloxi)fenil]-4-(metiltio)-2-oxo-1,2-dihidro-nicotinonitrilo en forma de sólido cristalino amarillo (4,43 g, rendimiento; 84%).

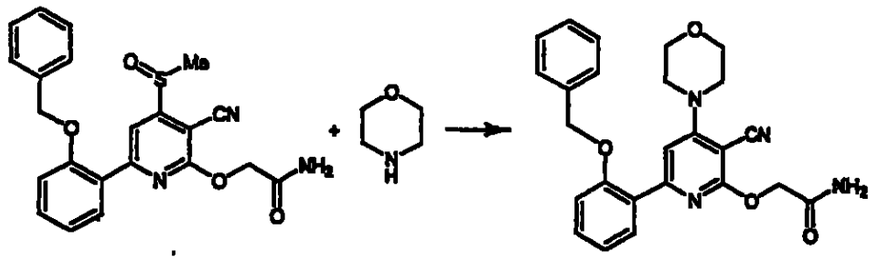


(3) A una solución fría (0°C) de 6-[2-(benciloxi)fenil]-4-(metiltio)-2-oxo-1,2-dihidro-nicotinonitrilo (4,00 g, 11,5 mmol) en CH_2Cl_2 se añadió ácido m-cloroperbenzoico (mCPBA) (69%, 3,45 g, 13,8 mmol) en una porción. La mezcla de reacción a 0°C se agitó a temperatura ambiente durante 1 hora, se enfrió con una solución saturada de $NaHCO_3$ (80 ml) incluyendo $Na_2S_2O_3$ $0,5H_2O$ (5 g), y se diluyó con CH_2Cl_2. La fase

orgánica separada se lavó con una solución de $NaHCO_3$, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo sólido se trituró con éter diisopropílico proporcionando 6-[2-(benciloxi)fenil]-4-(metilsulfinil)-2-oxo-1,2-dihidro-nicotinonitrilo en forma de sólido amarillo (4,00 g, rendimiento; 96%).

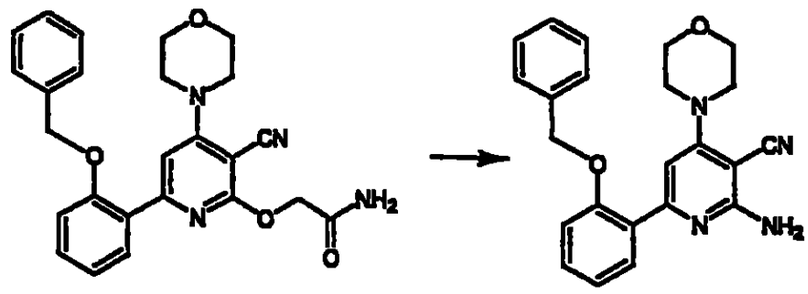


(4) Una mezcla de 6-[2-(benciloxi)fenil]-4-(metilsulfinil)-2-oxo-1,2-dihidro-3-piridinacarbonitrilo (2,97 g, 8,16 mmol), bromoacetamida (1,27 g, 9,21 mmol) y K_2CO_3 (1,43 g, 10,4 mmol) en DMF (30 ml) se agitó a 60°C durante 1,5 horas. La mezcla de reacción se vertió en agua y el precipitado resultante se recogió por filtración. El sólido obtenido se lavó con acetona proporcionando 2-{[6-[2-(benciloxi)fenil]-3-ciano-4-(metilsulfinil)-2-piridinil]oxi}acetamida en forma de sólida (2,09 g, rendimiento; 61%).

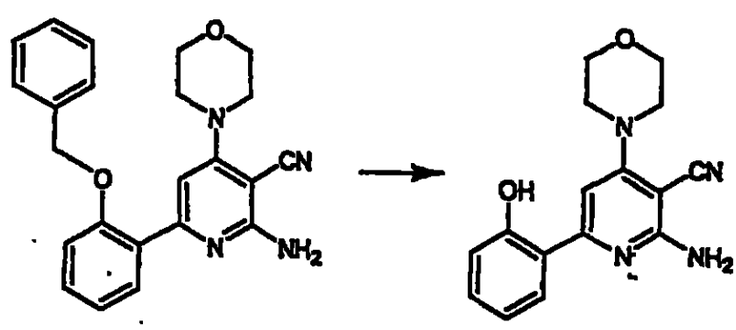


(5) Una mezcla de 2-{[6-[2-(benciloxi)fenil]-3-ciano-4-(metilsulfinil)-2-piridinil]oxi}acetamida (300 mg, 0,71 mmol) y morfolina (1,0 ml) se agitó a 130°C durante 1 hora, y seguidamente se le añadió agua. El precipitado resultante se recogió por filtración y se secó a presión reducida proporcionando 2-{[6-[2-(benciloxi)fenil]-3-ciano-4-(morfolinil)-2-piridinil]oxi}acetamida en forma de sólido amarillo (304 mg,

rendimiento; 96%).



(6) A una solución de 2-{[6-[2-(benciloxi)fenil]-3-ciano-4-(morfolinil)-2-piridinil]oxi}acetamida (318 mg, 0,72 mmol) en DMF (1 ml) se añadió K_2CO_3 (198 mg, 1,43 mmol) y la mezcla se agitó a 130°C durante 24 horas. La mezcla se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró a presión reducida. Se purificó por cromatografía en columna sobre gel de sílice (hexano /acetato de etilo = 3/1 a 2/1) seguido de una trituración con éter diisopropílico proporcionando 2-amino-6-[2-(benciloxi)fenil]-4-(morfolinil)nicotinonitrilo en forma de sólido blanco (141 mg, rendimiento; 51%).



(7) Seguidamente se eliminó el resto bencilo de la misma manera descrita en la etapa (2) del Ejemplo 1-1. El residuo se trituró con Et_2O y se secó a presión reducida proporcionando 2-amino-6-(2-hidroxifenil)-4-(4-morfolinil)nicotinonitrilo en forma sólida (68 mg, rendimiento; 76%).

Peso molecular: 296,33

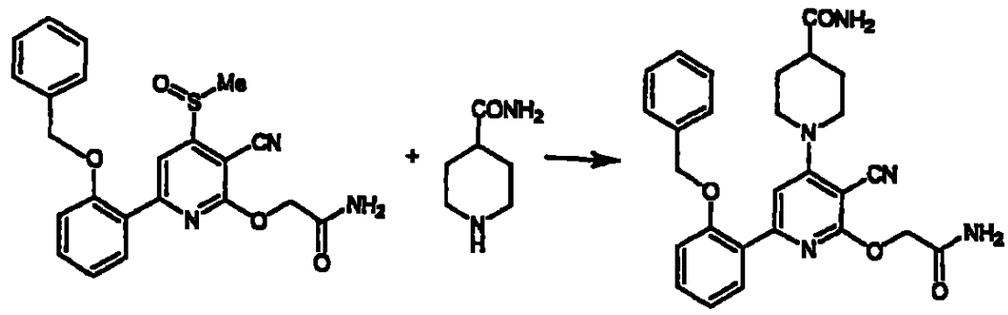
Espectrometría de masas: 297 $(M + H)^+$

Grado de actividad in vitro: B

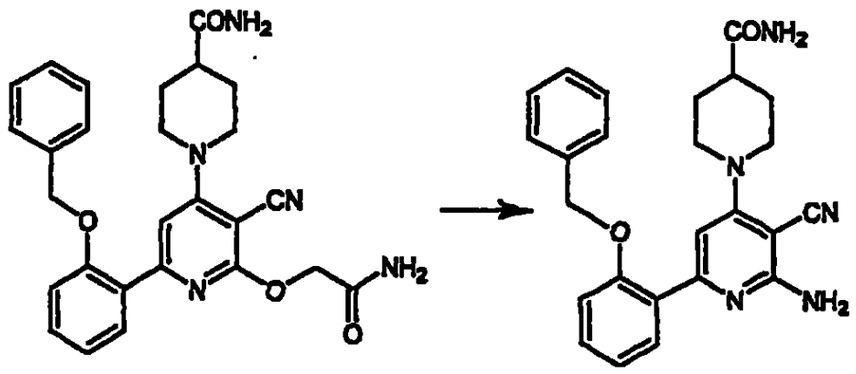
Grado de actividad celular: (A549)-C

RMN de ^1H (300 MHz, DMSO-d_6): 3,44-3,54 (4H, m), 3,68-3,78 (4H, m), 6,77-6,90 (3H, m), 7,08 (2H, s a), 7,25-7,35 (1H, m), 7,92-8,00 (1H, m), 13,77 (1H, s).

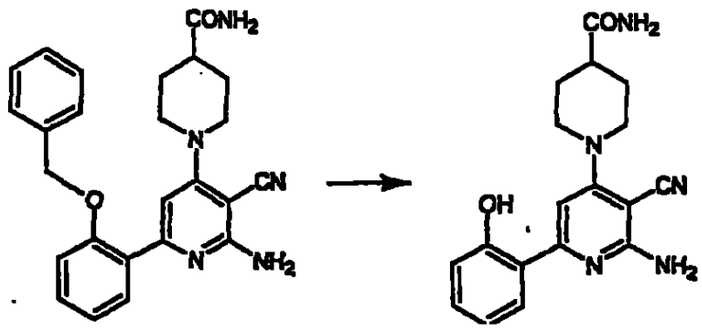
Ejemplo 34-2



A una mezcla de 2-{[6-[2-(benciloxi)fenil]-3-ciano-4-(metilsulfinil)-2-piridinil]-oxi}acetamida (500 mg, 1,19 mmol) que se obtuvo en la etapa (4) del Ejemplo 34-1, y isonipecotamida (228 mg, 1,78 mmol) en DMF (2 ml) se agitó a 130°C durante 5 horas. Después de enfriar a la temperatura ambiente, la mezcla se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró a presión reducida proporcionando 1-{2-(2-amino-2-oxoetoxi)-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}-4-piperidincarboxamida en forma sólida (485 mg, rendimiento; 84%).



Una mezcla de 1-{2-(2-amino-2-oxoetoxi)-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}-4-piperidincarboxamida (485 mg, 1,00 mmol) y K_2CO_3 (280 mg, 2,03 mmol) en DMF (2,5 ml) se agitó a 130°C durante 28 horas. Después de enfriar a la temperatura ambiente, la mezcla se diluyó con agua y el precipitado resultante se recogió por filtración. El precipitado se lavó con EtOH y CH_2Cl_2 proporcionando 1-{2-amino-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}-4-piperidincarboxamida en forma de sólido (119 mg, rendimiento; 28%).



Seguidamente se eliminó el resto bencilo de manera similar a la de la etapa (2) del Ejemplo 1-1 proporcionando 1-[2-amino-3-ciano-6-(2-hidroxifenil)-4-piridinil]-4-piperidincarboxamida en forma sólida (19 mg, rendimiento; 36%).

Peso molecular: 337,38

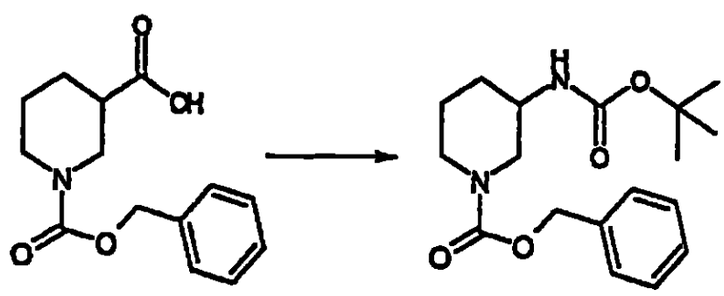
Espectrometría de masas: 338 $(M + H)^+$

Grado de actividad in vitro: B

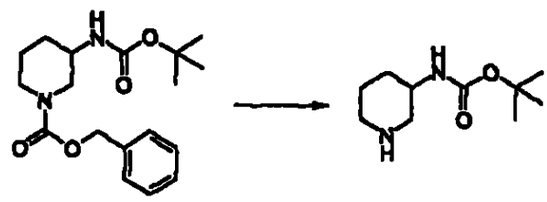
Grado de actividad celular: (A549)-C

RMN de ^1H (300 MHz, DMSO-d_6): 1,58-1,77 (2H, m), 1,77-1,90 (2H, m), 2,30-2,46 (1H, m), 2,98-3,15 (2H, m), 3,97 (2H, d, J= 12,8 Hz), 6,73-6,90 (4H, m), 7,10 (2H, s), 7,22-7,36 (2H, m), 7,94 (1H, d, J= 7,2 Hz), 13,85 (1H, s).

Ejemplo 34-3

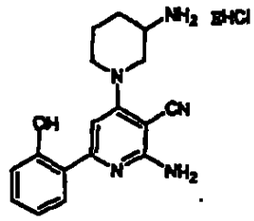


A una solución de ácido 1-[(benciloxi)carbonil]-3-piperidincarboxílico (3,00 g, 11,4 mmol) y Et_3N (1,56 ml, 11,4 mmol) en t-BuOH (30 ml) se añadió difenilfosforilazida (DPPA) (2,46 ml, 11,4 mmol) y la mezcla se calentó a reflujo durante 21 horas. Después de enfriar a la temperatura ambiente, la mezcla se concentró a presión reducida y el producto se repartió entre acetato de etilo y una solución en agua de $NaHCO_3$. La fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$ y salmuera, se secó sobre Na_2SO_4 y se concentró a presión reducida. Se purificó por cromatografía en columna sobre gel de sílice (hexano / acetato de etilo = 4/1 a 3/1) proporcionando 3-[(*terc*-butoxicarbonil)amino]-1-piperidincarboxilato de bencilo en forma sólida (2,22 g, rendimiento; 58%).



Una mezcla de 3-[(*terc*-butoxicarbonil)amino]-1-piperidincarboxilato de bencilo 2,25 g, 6,73 mmol) y Pd al 10%/C (0,229 g) en EtOH se agitó a temperatura ambiente en atmósfera de hidrógeno (1 atm) durante 14 horas. Se separó el catalizador por filtración a través de Celite® y el filtrado se concentró a presión reducida proporcionando 3-piperidinilcarbamato de *terc*-butilo en forma sólida (1,22 g, rendimiento; 91%).

El 3-piperidinilcarbamato de *terc*-butilo resultante y 2-{[6-[2-(benciloxi)fenil]-3-ciano-4-(metilsulfinil)-2-piridinil]oxi}acetamida se utilizaron como materiales de partida para preparar clorhidrato de 2-amino-4-(3-amino-1-piperidinil)-6-(2-hidroxifenil)nicotinonitrilo de manera similar a la descrita en el Ejemplo 34-1.



Peso molecular: 345,83

Espectrometría de masas: 310 $(M + H)^+$

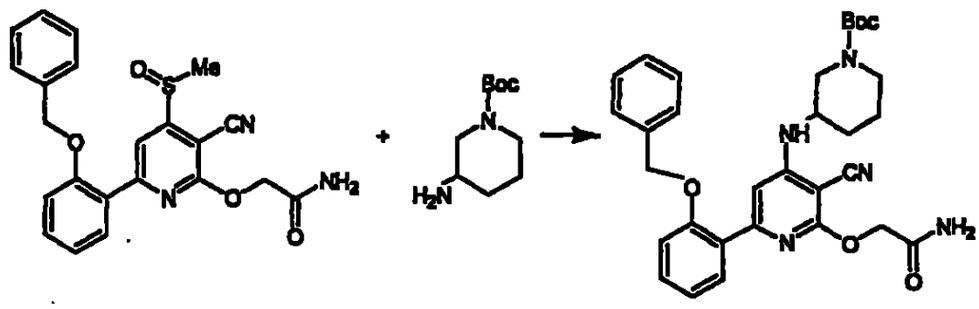
Grado de actividad in vitro: B

Grado de actividad celular: (A459)-B

RMN de ^1H (500 MHz, DMSO-d_6): 1,59-1,76 (2H, m), 1,82-1,95 (1H, m), 2,02-2,14 (1H, m), 3,27-3,50 (3H, m), 3,90-4,05 (1H, m), 4,08-4,22 (1H, m), 6,80 (1H, s), 6,92

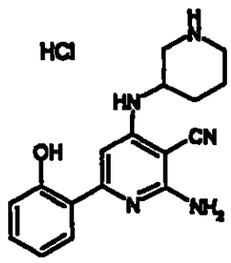
(1H, t, J= 7,6 Hz), 6,96-7,06 (1H, m), 7,37 (1H, t, J= 6,9 Hz), 7,79 (3H, s a), 8,39 (3H, s a), 13,25 (1H, s a).

Ejemplo 34-4



Una mezcla de 2-{[6-[2-(benciloxi)fenil]-3-ciano-4-(metilsulfinil)-2-piridinil]oxi}acetamida (500 mg, 1,19 mol) que se obtuvo en la etapa (4) del Ejemplo 34-1 y 3-amino-1-piperidincarboxilato de *terc*-butilo (555 mg, 2,77 mmol) en DMF (0,6 ml) se agitó a 130°C durante 24 horas. Después de enfriar hasta temperatura ambiente, la mezcla se repartió entre acetato de etilo y agua. La fase orgánica se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó por cromatografía en columna sobre gel de sílice (hexano //acetato de etilo = 1/1) proporcionando 3({2-(metoxicarbamoil)-6-[2-(benciloxi)fenil]-3-ciano-4-piridinil}amino)-1-piperidincarboxilato de *terc*-butilo en forma de espuma (360 mg, rendimiento; 64%).

Utilizando el compuesto resultante, se preparó clorhidrato de 2-amino-6-(2-hidroxifenil)-4-(3-piperidinilamino) nicotinonitrilo de manera similar a la descrita en el Ejemplo 34-2.



Peso molecular: 345,83

Espectrometría de masas: 310 $(M + H)^+$

Grado de actividad in vitro: A

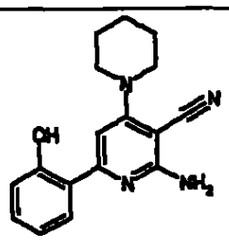
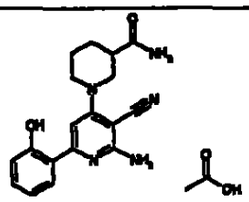
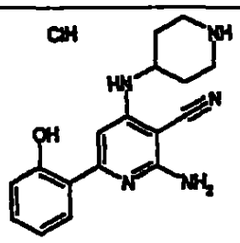
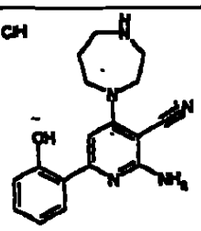
Grado de actividad celular: (A459)-A

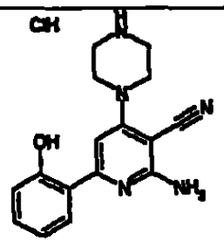
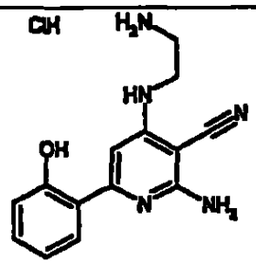
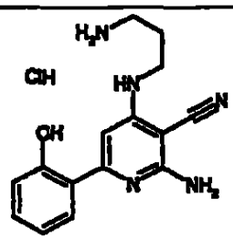
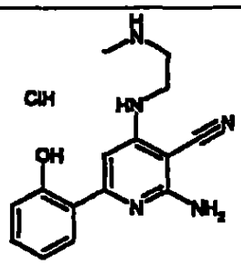
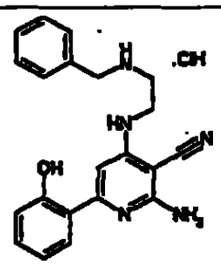
RMN de ^1H (300 MHz, DMSO-d_6): 1,68-2,06 (4H, m), 2,66-2,96 (2H, m), 3,17-3,38 (2H, m), 4,23 (1H, s a), 6,73 (1H, s), 6,92 (1H, t, J= 7,5 Hz), 7,01 (1H, d, J= 7,5 Hz), 7,37 (1H, t, J= 7,5 Hz), 7,55 (3H, a), 7,78 (1H, d, J= 7,5 Hz), 9,20 (2H, s a), 13,20 (1H, a).

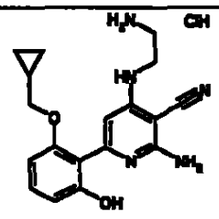
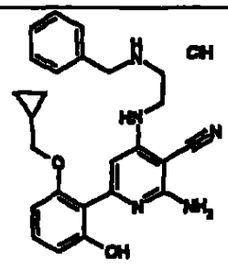
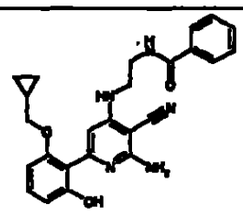
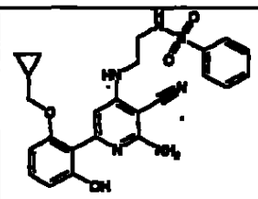
Ejemplos 34-5 a 34-19

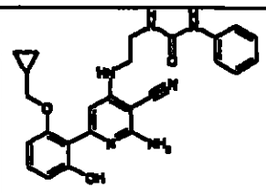
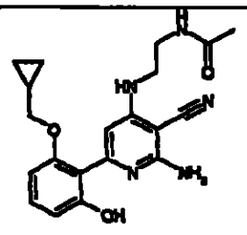
Los compuestos de la tabla 12 fueron preparados de acuerdo con un procedimiento de síntesis similar al del Ejemplo 34-4

Tabla 12

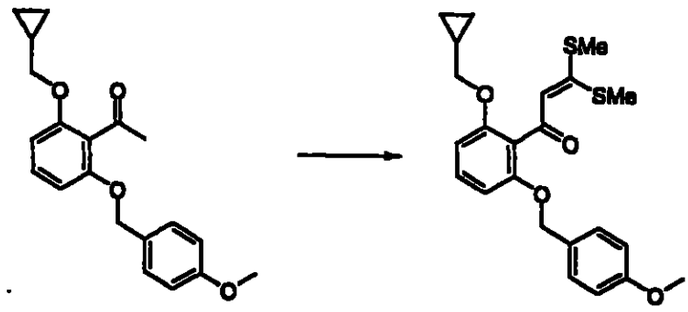
Ej. nº	Estructura	Peso molec	Masa	*In vitro*	A-459	RMN
34-05		294,36	295	D		(300 MHz, DMSO-d_6): 1,64 (6H, s a), 3,48 (4H, s a), 6,76 (1H, s), 6,78-6,89 (2H, m), 6,98 (1H, s a), 7,28 (1H, t, J= 7,2 Hz), 7,93 (1H, d, J= 7,2 Hz), 13,86 (1H, s a).
34-06		397,44	338	C	C	(300 MHz, DMSO-d_6): 1,49-1,71 (2H, m), 1,71-1,87 (1H, m), 1,91 (3H, s), 1,87-2,02 (1H, m), 2,37-2,54 (1H, m), 2,94-3,08 (1H, m), 3,09 (1H, dd, J= 11,3, 12,8 Hz), 3,88-4,04 (2H, m), 6,76-6,92 (4H, m), 7,01 (2H, s), 7,24-7,33 (1H, m), 7,34 (1H, s a), 7,95 (1H, d, J= 7,2 Hz), 11,92 (1H, a).
34-07		345.83	310	A	B	(500 MHz, DMSO-d_6): 1,90 (2H, s a), 1.96 (2H, s a), 2,98 (2H, s a), 3,31 (2H, s a), 4,07 (1H, s a), 6,67-6,75 (1H, m), 6,90-6,99 (1H, m), 7,04 (1H, s a), 7,30-7,47 (1H, m), 7,63 (1H, s a), 7,81 (3H, a), 8,84 (1H, s a), 9,09 (1H, s a), 12,94 (1H, a).
34-08		345.83	310	B	B	(500 MHz, DMSO-d_6): 2,20 (2H, s a), 3,24 (2H, s a), 3,36 (2H, s a), 3,91 (2H, s a), 4,09 (2H, s a), 6,69 (1H, s), 6,94 (1H, t, J= 7,6 Hz), 7,03 (1H, d, J= 7,9 Hz), 7,37 (1H, t, J= 7,9 Hz), 7,68 (1H, d, J= 7,3 Hz), 7,84 (2H, a), 9,36 (2H, s a), 13,15 (1H, a).

34-09		331,81	296	A	B	(500 MHz, DMSO-d_6): 3,26 (4H, s a), 3,86 (4H, s a), 6,86 (1H, s), 6,92 (1H, t, J= 7,5 Hz). 6.93-7,03 (1H, m), 7,36 (1H, t, J= 7,5 Hz), 7,70 (1H, a), 7,82 (1H, d, J= 7,5 Hz), 9,57 (2H, a).
34-10		305,77	270	A	A	(500 MHz, DMSO-d_6): 2,92-3,07 (2H, m), 3,71 (2H, s a), 6,71 (1H, d, J= 2,8 Hz), 6,94 (1H, t, J= 7,6 Hz), 7,03-7,11 (1H, m), 7,38 (1H, t, J= 7,6 Hz), 7,71 (1H, s a), 7,95 (3H. a), 8,13 (3H, s a), 12,98 (1H, a).
34-11		319,80	284	A	B	(500 MHz, DMSO-d_6): 1,81-1.95 (2H. m). 2,79-2,91 (2H, m), 3,45-3,63 (2H, m), 6,67 (1H, s), 6,92-6,98 (1H, m). 7,10 (1H, d, J= 8,2 Hz), 7,35-7,43 (1H, m), 7,63 (1H, d, J= 7,6 Hz), 7,85-8,55 (6H, m), 12,80 (1H, a).
34-12		319,80	284	A	A	(500 MHz, DMSO-d_6): 2,55-2,61 (3H, m), 3,08 (2H, s a), 3,77 (2H, s a), 6,73 (1H, s), 6,94 (1H, t, J= 7,6 Hz), 7,02-7,11 (1H, m), 7,38 (1H, t, J= 7,6 Hz), 7,74 (1H, a), 7,96 (2H, a), 9,06 (2H, a), 12,99 (1H, a).
34-13		395,90	360	A	A	(500 MHz, DMSO-d_6): 3,11 (2H, s a), 3,77-3,93 (2H, m), 4,15-4,23 (2H, m), 6,76 (1H, s), 6,90-6,98 (1H, m), 7,07 (1H, d, J= 8,2 Hz), 7,33-7,48 (4H, m), 7,55-7,64 (2H, m), 7,66-7,79 (1H, m), 7,98 (3H, a), 9,57 (2H, s a), 12,97 (1H, a)

34-14		375,86	340	A		(500 MHz, DMSO-d_6): 0,26-0,37 (2H, m), 0,44-0,55 (2H, m), 1,11-1,20 (1H, m), 2,95 (2H, s a), 3,63 (2H, s a), 3,84 (2H, d, J= 6,9 Hz), 6,51-6,72 (3H, m), 7,26 (1H, t, J= 8,4 Hz), 7,75-8,35 (6H, m), 10,39 (1H, a), 12,89 (1H, a).
34-15		465,99	430	A	A	(500 MHz, DMSO-d_6): 0,26-0.37 (2H, m). 0,44-0,55 (2H, m), 1,10-1,22 (1H, m), 3,11 (2H, s a), 3,74 (2H, s a), 3,85 (2H, d, J= 6,6 Hz), 4,18 (2H, s a), 6,50-6,74 (3H; m), 7,22-7,32 (1H, m), 7,39-7,48 (3H, m), 7,52-7,58 (2H, m), 7,86 y 8,21 (2H, a), 9,21 y 10,35 (2H, a), 12,81 (1H, a).
34-16		443,51	444	A	A	(500 MHz, DMSO-d_6): 0,25-0,37 (2H, m), 0,47-0,57 (2H, m), 1,22-1,33 (1H, m), 3,41-3,54 (4H, m), 3,83 (2H, d, J= 6,9 Hz). 6,39-6,49 (2H, m), 6,60-7,00 (3H, m), 7,14 (1H, t, J= 8,2 Hz), 7,23 (1H, s a), 7,43 (2H, t, J= 7,3 Hz), 7,51 (1H, t, J= 7,3 Hz), 7,80 (2H, d, J= 7,3 Hz), 8,62 (1H, s a), 14,39 (1H, a).
34-17		479,56	480	A	C	(500 MHz, DMSO-d_6): 0,25-0,36 (2H, m), 0,47-0,58 (2H, m), 1,18-1,30 (1H, m), 2,96 (2H, q, J= 6,0 Hz), 3,33 (2H, q, J= 6,0 Hz), 3,82 (2H, d, J= 6,9 Hz), 6,40-6,48 (2H, m), 6,60 (1H, t, J= 6,0 Hz), 6,76 (2H, s), 7,07 (1H, s), 7,13 (1H, t, J= 8,2 Hz), 7,52 (2H, t, J= 7,3 Hz), 7,59 (1H, t, J= 7,3 Hz), 7,75 (2H, d, J= 7,3 Hz), 7,80 (1H, t, J= 6,0 Hz), 14,28 (1H, s a).

34-18		458,52	459	A	A	(500 MHz, DMSO-d_6): 0,26-0,37 (2H, m), 0,50-0,62 (2H, m), 1,22-1,34 (1H, m), 3,35 (4H, s a), 3,83 (2H, d, J= 6,9 Hz), 6,33 (1H, s a), 6,40-6,48 (2H, m), 6,80 (2H, a), 6,85-6,92 (1H, m), 7,10-7,25 (4H,m), 7,37 (2H, d, J= 7,6 Hz), 8,57 (1H, s), 14,44 (1H, a).
34-19		381,44	382	A	A	(300 MHz, $CDCl_3$): 0,31-0,41 (2H, m), 0,60-0,70 (2H, m), 1,21-1,38 (1H, m), 1,96 (3H, s), 3,40-3,50 (4H, m), 3,84 (2H, d, J= 7,2 Hz), 5,60 (2H, s a), 6,11 (1H, s a), 6,37 (1H, d, J= 8,3 Hz), 6,53 (1H, d, J= 8,3 Hz), 7,13 (1H, t, J= 8,3 Hz), 7,35 (1H, s), 7,48 (1H, s a), 14,44 (1H, s a).

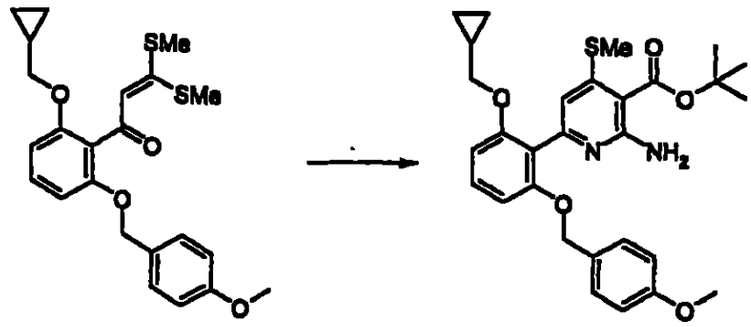
Ejemplo 35-1



A una suspensión de *terc*-butóxido de potasio (0,809 g, 6,128 mmol) en THF (5 ml) se añadió una solución de 1-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]-fenil}etanona (1,00 g, 3,064 mmol) (compuesto de partida 1G) en THF (5 ml) seguido de disulfuro de carbono (0,23 ml, 3,83 mmol) y yoduro de metilo (0,57 ml, 9,19 mmol) sucesivamente. La mezcla resultante se agitó a temperatura ambiente durante 40 minutos, y a

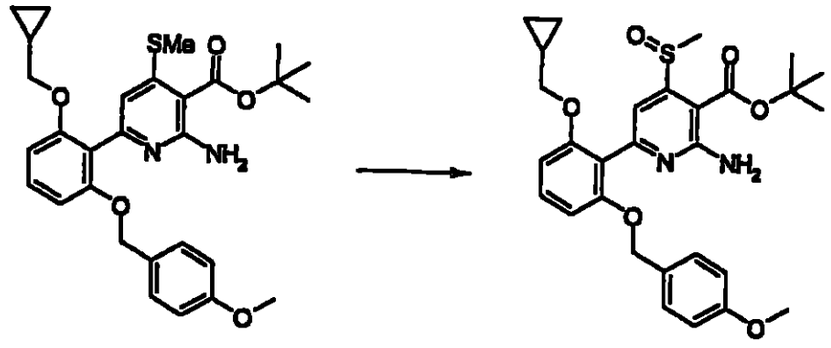
457
456

continuación se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó por cromatografía en columna sobre gel de sílice. (hexano/acetato de etilo = 4/1 a 3/1) proporcionando 1-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3,3-bis(metilsulfinil)-2-propen-1-ona en forma de aceite amarillo pálido (0,825 g, rendimiento; 63%).

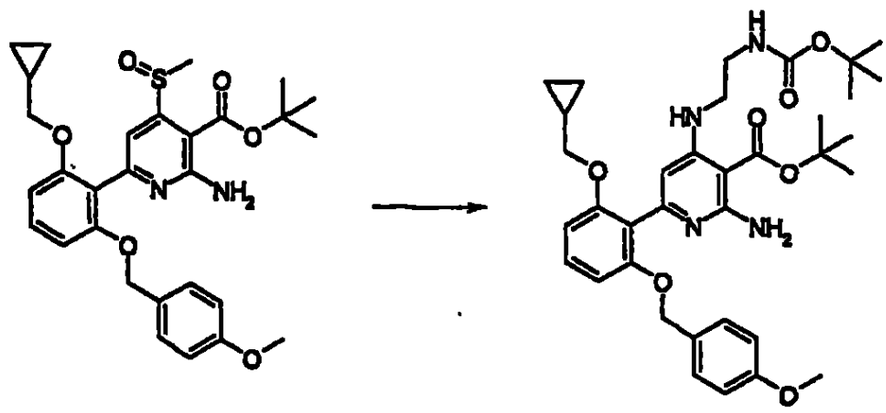


A una suspensión de NaH (60%, 0,056 g, 1,39 mmol) en THF (3 ml) se añadió una solución de cianoacetato de t-butilo (0,197 g, 1,392 mmol) en THF (1 ml) en una porción. Después de 10 minutos, se añadió una solución de 1-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-3,3-bis(metilsulfinil)-2-propen-1-ona (0,500 g, 1,16 mmol) en THF (3 ml) seguido de dibenzo-18-corona-6 (0,013 g, 0,035 mmol). La mezcla resultante se calentó a reflujo durante 4 horas. Después de enfriarse a temperatura ambiente, la mezcla se repartió entre una solución de ácido acético 0,1 N y CH_2Cl_2. Se separó la fase orgánica, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El aceite residual se disolvió en 1,2-dicloroetano (1 ml) y ácido acético (1 ml) y se añadió acetato de amonio (1,20 g, 15,57 mmol). La mezcla se agitó a 120°C durante 0,5 horas. Después de enfriarse a la temperatura ambiente, la mezcla se repartió entre acetato de etilo y una solución acuosa saturada de $NaHCO_3$ y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó por cromatografía en

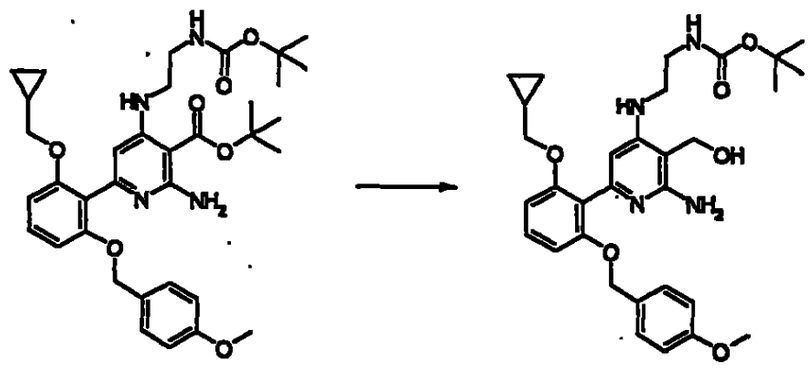
columna sobre gel de sílice (hexano / acetato de etilo = 4/1 a 3/1) proporcionando 2-amino-6-{2-ciclometoxipropil)-6-[(4-metoxibencil)oxi]fenil}-4-(metil-sulfinil)nicotinato de *terc*-butilo en forma de aceite amarillo pálido (0,177 g, rendimiento; 29%).



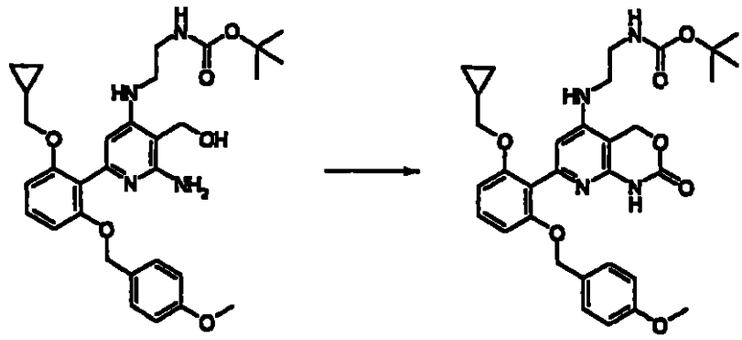
A una solución fría (0°C) de 2-amino-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}-4-(metilsulfanil)nicotinato de *terc*-butilo (1,72 g, 3,30 mmol) en CH_2Cl_2 (20 ml) se añadió m-CPBA (69%, 0,82 g, 3,30 mmol). La mezcla de reacción se agitó a 0°C durante 15 minutos, se enfrió con una solución saturada de $NaHCO_3$ (20 ml) que contiene $Na_2S_2O_3$ (1 g). Se separó la fase orgánica, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó por cromatografía en columna sobre gel de sílice /hexano / acetato de etilo = 3/2 a 1/1) proporcionando 2-amino-6-{2-ciclometoxipropil)-6-[(4-metoxibencil)oxi]fenil}-4-(metilsulfinil)nicotinato de *terc*-butilo en forma de polvo blanco (1,112 g, rendimiento; 63%).



Una mezcla de 2-amino-6-{2-ciclometoxipropil)-6-[(4-metoxibencil)oxi]fenil}-4-(metilsulfinil)nicotinato de *terc*-butilo (0,118 g, 0,219 mmol) y etilenodiamina (0,29 ml) se agitó a 100°C durante 8 horas. Después de enfriarse a temperatura ambiente, la mezcla se repartió entre acetato de etilo y agua. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo se disolvió en CH_2Cl_2 (2 ml) y se añadió bicarbonato de di-*terc*-butilo (0,060 g, 0,275 mmol). La mezcla se agitó a temperatura ambiente durante 2 horas y se concentró a presión reducida. El residuo se purificó por cromatografía en columna proporcionando 2-amino-4-({2-[(*terc*-butoxicarbonill)amino]etil}amino}-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)oxi]fenil}nicotinato de *terc*-butilo en forma de espuma (0,121 g, rendimiento; 92%).

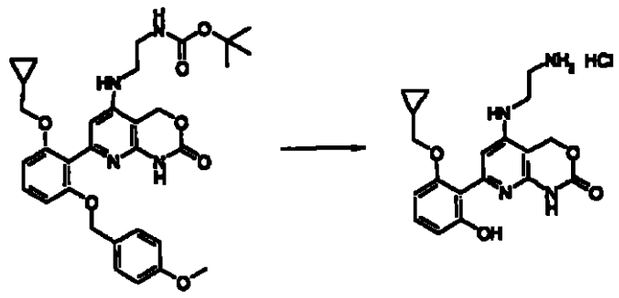


A una solución fría (0°C) de 2-amino-4-({2-[(*terc*-butoxicarbonill)amino]etil}amino)-6-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)-oxi]fenil}nicotinato de *terc*-butilo (0,113 g, 0,178 mmol) en THF (5 ml) se añadió una solución de Vitride® (3,4 M, 1,0ml, 3,4 mmol). La mezcla se agitó a 0°C durante 0,5 horas, se enfrió con una solución saturada de ácido tartárico sódico potásico, y seguidamente se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida proporcionando un sólido, que se trituró con acetato de etilo y éter diisopropílico proporcionando 2-{[2-amino-6-{2-(ciclopropilmetoxi)-6-[4-metoxibencil)-oxi]-fenil}-3-(hidroximetil)-4-piridinil]amino}etilcarbamato de *terc*-butilo como un sólido rosado (0,078 g, rendimiento; 78%).



A una solución fría (0°C) de 2-{[2-amino-6-{2-ciclometoxipropil)-6-[(4-metoxibencil)oxi]fenil}-3-(hidroximetil)-4-pridinil]amino}etilcarbamato de *terc*-butilo (0,50 g, 0,089 mmol) y Et_3N (0,074 ml, 0,531 mmol) en THF (10 ml) se añadió trifosgeno (0,013 g, 0,044 mmol) en una porción. La mezcla se agitó a 0°C durante 1 hora y seguidamente se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. Se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo) proporcionando 2-[(7-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)-oxi]fenil}-2-oxo-1,4-dihidro-2H-pirido[2,3]oxazin-5-il)amino]etilcarbamato de *terc*-butilo en forma de aceite

incoloro (0,036 g, rendimiento; 69%).



A una solución de 2-[(7-{2-(ciclopropilmetoxi)-6-[(4-metoxibencil)-oxi]fenil}-2-oxo-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-5-il)amino]etilcarbamato de *terc*-butilo (0,032 g, 0,054 mmol) en 1,4 dioxano (1 ml) se añadió HCl 4 N en 1,4-dioxano (1 ml). La mezcla se agitó a temperatura ambiente durante la noche. El precipitado resultante se recogió por filtración, se lavó con acetato de etilo proporcionando el clorhidrato de 5-[(2-aminoetil)amino]-7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-2-ona en forma sólida (0,013 g, rendimiento; 59%).

Peso molecular: 406,87

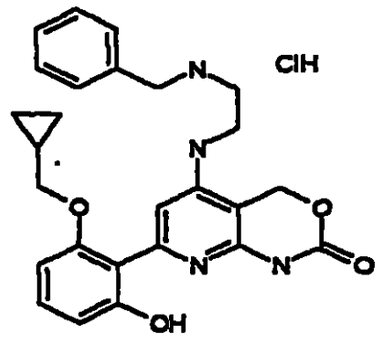
Espectrometría de masas: 370 $(M + H)^+$

Grado de actividad in vitro: A

Grado de actividad celular: (A549)-A

RMN-H^1 (500 MHz, DMSO-d_6): 0,26-0,36 (2H, m), 0,47-0,57 (2H, m), 1,15-1,25 (1H, m), 2,96-3,07 (2H, m), 3,50-3,60 (2H, m), 3,85 (2H, d, J= 6,9 Hz), 5,45 (2H, s a), 6,57 (1H, d, J= 8,2 Hz), 6,56-6,68 (1H, m), 6,96 (1H, s a), 7,24 (1H, t, J= 8,2 Hz), 7,75 (1H, a), 8,18 (3H, s a), 10,86 (1H, a).

Ejemplo 35-2



De manera similar a la del Ejemplo 35-1, se preparó clorhidrato de 5-(2-bencilamino-etilamino)-6-(2-ciclopropilmetoxi-6-hidroxifenil)-1,4-dihidro-pirido[2,3-d][1,3]oxazin-2-ona

Peso molecular: 497,00

Espectrometría de masas: 461 $(M + H)^+$

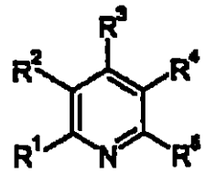
Grado de actividad in vitro: A

(500 MHz, DMSO-d_6): 0,26-0,35 (2H, m), 0,45-0,58 (2H, m), 1,10-1,28 (1H, m), 3,16 (2H, s a), 3,67 (2H, a), 3,85 (2H, d, J= 6,8 Hz), 4,13-4,25 (2H, m), 5,43 (2H, s a), 6,50-6,65 (2H, m), 7,04 (1H, s a), 7,22 (1H, t, J= 8,3 Hz), 7,35-7,50 (4H, m), 7,50-7,65 (3H, m), 9,44 (2H, a), 10,74 (1H, a).

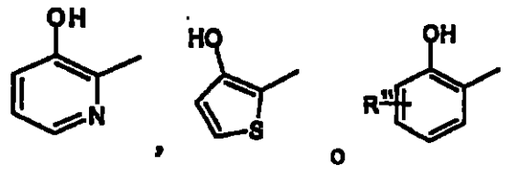
Habiendo descrito como antecede la presente invención se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un derivado de piridina de fórmula (I)



en la que R^1 representa



en la que R^{11} es hidrógeno, alquilo C_{1-6}, halógeno, hidroxi, alcoxi C_{1-12}, nitro, amino, alquil C_{1-6}-sulfonilamino, alcoxi C_{1-6}-carbonilo, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, alcanoil C_{1-6}-amino, fenilalquil C_{1-6}-amino, fenilsulfonilamino o $-O-(CH_2)_n-R^{111}$,

representando n un número entero seleccionado de 0 a 6, y R^{111} es alquenilo C_{2-6}, benzoílo, difenilmetiló, di(alquil C_{1-6})amino, alcanoílo C_{1-6}, alcoxi C_{1-6}-carbonilo, o un anillo saturado o insaturado de 3 a 10 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo formado por S, O y N como heteroátomos y está opcionalmente sustituido con alquilo C_{1-6}, mono o dihalógeno, alquilo C_{1-6} sustituido con halógeno, nitro, ciano, alcoxi C_{1-6}-carbonilo, fenilo, hidroxi, amino, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, alcanoil C_{1-6}-amino, alcoxi C_{1-6} o carbamoílo;

R^2 representa hidrógeno o halógeno;

R^3 representa hidrógeno o 1,2,3,6-tetrahidropiridina,

$-CR^{31}R^{32}R^{33}$,

en la que R^{31} es hidrógeno o alquilo C_{1-6},

R^{32} es hidrógeno, α-aminobencilo, alquilo C_{1-6} opcionalmente sustituido con uno o dos sustituyentes seleccionados del grupo formado por hidroxi, amino, fenilo sustituido con amino, fenilo, fenilo sustituido con halógeno y fenilo sustituido con alcoxi C_{1-6}, o un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 átomos seleccionados del grupo formado por S, O y N como heteroátomos y opcionalmente sustituido con alquilo C_{1-6}, y

R^{33} es hidrógeno, amino, alcoxi C_{1-6}-carbonilamino, alquenil C_{2-6}-oxicarbonilamino, piperidin-alquil C_{1-6}-carbonilamino, piperidinil-alquil C_{1-6}-carbonilamino, o

R^{32} y R^{33} pueden formar, junto con el átomo de carbono adyacente, un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo formado por N, O y S como heteroátomos, estando dicho anillo opcionalmente sustituido con fenilalquilo C_{1-6}, fenilalquilo C_{1-6} sustituido con alcoxi C_{1-6}, alquilo C_{1-6}, amino, ciano, hidroxi, carbamoílo, carboxi, alquil C_{1-6}-amino, alcoxi C_{1-6}-carbonilo, di(alquil C_{1-6})amino, bencilamino, alquil C_{1-6}-sulfonilo, piperidin-alquil C_{1-6}-carbonilo o opcionalmente condensado con benceno;

o

$-NR^{34}R^{35}$,

en la que R^{34} es hidrógeno o alquilo C_{1-6}, y

R^{35} es hidrógeno, un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo formado por N, O y S como heteroátomos, o $-(CH_2)_m-NR^{351}R^{352}$ (m representa cualquier número entero de 1 a 6).

representando R^{351} hidrógeno, alquilo C_{1-6},

R^{352} representa hidrógeno, alquilo C_{1-6}, alcanoílo C_{1-6}, fenilo sustituido con alquilo C_{1-6}, benzoílo, alcanoílo C_{1-6}, fenilaminocarbonilo, fenilsulfonilo o

R^{34} y R^{35} pueden formar, junto con el átomo de N adyacente, un anillo heterocíclico saturado de 5 a 8 miembros, y el dicho anillo puede contener como átomos distintos del átomo de N adyacente opcionalmente NH, S u O distintos del átomo de N adyacente y estar opcionalmente sustituido con carbamoílo, amino o alquilo C_{1-6};

R^4 representa hidroxicarbonilo, alcanoílo C_{1-6}, carbamoílo, nitro, ciano, carboxilo, alcoxi C_{1-6}-carbonilo, alquil C_{1-6}-carbamoílo, alquil C_{1-6}-amino, heteroarilo de 5 a 10 miembros-(hidroxi)metilo, heteroarilo de 5 a 10 miembros-alquilo C_{1-6}, o metilo sustituido con hidroxi y un anillo cíclico saturado de 5 a 7 miembros, alquilo C_{1-6} opcionalmente sustituido con un sustituyente seleccionado del grupo formado por

hidroxi, alcoxi C_{1-6}, alquil C_{1-6}-sulfonilamino, alquil C_{1-6}-carbonilamino, arilo C_{5-10}, aril C_{5-10}-sulfonilo, aril C_{5-10}-sulfanilo, ariloxi C_{5-10}, imidazolilo o pirrolidinoxi sustituido con dioxo,

$-(CH_2)_pNHCOR^{41}$, $-(CH_2)_pNHC(=S)R^{41}$

en las que p representa cualquier número entero de 1 a 6 y R^{41} representa alcoxi C_{1-6}, amino, fenilamino, alquilo C_{1-6}, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, cicloalquil C_{3-10}-amino,

R^3 y R^4 pueden formar junto con los átomos de carbono en el anillo de piridina, monocicloalquilo o bicicloalquilo de 4 a 10 miembros opcionalmente interrumpidos por NH y opcionalmente sustituidos con bencilo, =NH o =O;

R^5 representa $NR^{51}R^{52}$,

en la que R^{51} es hidrógeno, alquilo C_{1-6},

R^{52} es hidrógeno, alquilo C_{1-6}, fenilo, bencilo, alcanoílo C_{1-6}, o $NR^{51}R^{52}$ puede formar un anillo saturado de 5 a 6 miembros que contiene opcionalmente NH u O como otros heteroátomos distintos del átomo de N adyacente,

o

R^4 y R^5 pueden formar,

$-R^{40}-CO-NH-$

$-R^{40}-SO_2-NH-$

$-R^{40}-C(=S)-NH-$

$-R^{40}-CH_2-NH-$

en las que dicho $-R^{40}-$ representa $-CHR^{401}-O-$, $-CH_2-N\ R^{401}-$, $-CO-NR^{401}-$, $-CH_2-CHR^{401}-$, $-CH=CR^{401}-$, (siendo R^{401} alcanoílo C_{1-6}, alquilo C_{1-6}, fenilo, alquil C_{1-6}-sulfonilo, cicloalquil C_{3-8}-aminocarbonilo, hidrógeno, halógeno, nitro, amino, ciano, benzoilamino, fenilsulfonilo, carbamoílo, hidroxicarbonilo, alcoxi C_{1-6}-carbonilo, alquil C_{1-12}-aminocarbonilo, alquil C_{1-6}-aminocarbonilo sustituido con halógeno, alcanoil C_{1-6}-amino, alquil C_{1-6}-amino, di(alquil C_{1-6})aminocarbonilo, di(alquil C_{1-6})aminoalquil C_{1-6}-aminocarbonilo, hidroindenilaminocarbonilo, difenilmetilaminocarbonilo, pirrolidinocarbonilo, alcoxi C_{1-6}-alquil C_{1-6}-aminocarbonilo, morfolinocarbonilo, piperazinocarbonilo, fenilalquil C_{1-6}-aminocarbonilo, hidroxicarbonilalquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-aminocarbonilo, cicloalquil C_{3-8}-alquil C_{1-6}-aminocarbonilo, hidroxialquil C_{1-6}-aminocarbonilo, carboxietilaminocarbonilo, alquil C_{1-6}-sulfonilaminocarbonilo),

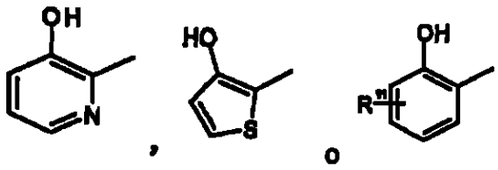
$-CR^{41}=N-NH-$ (R^{41} es hidrógeno, amino o alcanoil C_{1-6}-amino),

$-CR^{42}=N-C=N-$ (R^{42} es hidrógeno o amino).

o una de sus sales.

2. El compuesto o una de sus sales de acuerdo con la reivindicación 1, en la que:

R^1 representa



en la que R^{11} es hidrógeno, alquilo C_{1-6}, halógeno, hidroxi, alcoxi C_{1-12}, amino, alcanoil C_{1-6}-amino, fenilalquil C_{1-6}-amino, fenilsulfonilamino o $-O-(CH_2)_n-R^{111}$,

representando n un número entero seleccionado de 1 a 6, y R^{111} es alquenilo C_{2-6}, benzoílo, difenilmetilo, di(alquil C_{1-6})amino, alcanoílo C_{1-6}, alcoxi C_{1-6}-carbonilo, o un anillo saturado o insaturado de 3 a 10 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo formado por S, O y N como heteroátomos y está opcionalmente sustituido con alquilo C_{1-6}, mono o dihalógeno, alquilo C_{1-6} sustituido con halógeno, nitro, ciano, alcoxi C_{1-6}-carbonilo, fenilo;

R^2 representa hidrógeno;

R^3 representa hidrógeno o 1,2,3,6-tetrahidropiridina,

$-CR^{31}R^{32}R^{33}$,

en la que R^{31} es hidrógeno o alquilo C_{1-6},

R^{32} es hidrógeno, α-aminobencilo, alquilo C_{1-6} opcionalmente sustituido con uno o dos sustituyentes seleccionados del grupo formado por hidroxi, amino, fenilo sustituido con

amino, fenilo, fenilo sustituido con halógeno y fenilo sustituido con alcoxi C_{1-6}, o un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 átomos seleccionados del grupo formado por S, O y N como heteroátomos y opcionalmente sustituido con alquilo C_{1-6}, y

R^{33} es hidrógeno, amino, alcoxi C_{1-6}-carbonilamino, alquenil C_{2-6}-oxicarbonilamino, piperidino-alquil C_{1-6}-carbonilamino, o

R^{32} y R^{33} pueden formar, junto con el átomo de carbono adyacente, un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo formado por N, O y S como heteroátomos, estando dicho anillo opcionalmente sustituido con fenilalquilo C_{1-6}, fenilalquilo C_{1-6} sustituido con alcoxi C_{1-6}, alquilo C_{1-6}, amino, carboxi, alquil C_{1-6}-amino, alcoxi C_{1-6}-carbonilo, di(alquil C_{1-6})amino, bencilamino, alquil C_{1-6}-suifonilo, piperidino-alquil C_{1-6}-carbonilo o opcionalmente condensado con benceno;

o

$-NR^{34}R^{35}$,

en la que R^{34} es hidrógeno y

R^{35} es hidrógeno, un anillo saturado de 5 a 8 miembros que tiene de 0 a 3 heteroátomos seleccionados del grupo formado por N, O y S como heteroátomos, o $-(CH_2)_m-NR^{351}R^{352}$ (m representa cualquier número entero de 1 a 6).

en la que R^{351} representa hidrógeno, alquilo C_{1-6},

R^{352} representa hidrógeno, alquilo C_{1-6}, alcanoílo C_{1-6}, fenilo sustituido con alquilo C_{1-6}, benzoílo, alcanoílo C_{1-6}, fenilaminocarbonilo, fenilsulfonilo o

R^{34} y R^{35} pueden formar, junto con el átomo de N adyacente, un anillo heterocíclico saturado de 5 a 8 miembros, y dicho anillo puede contener opcionalmente como átomos distintos del átomo de N adyacente NH, S u O distintos del átomo de N adyacente y estaro pcionalmente sustituido con carbamoílo, amino o alquilo C_{1-6};

R^4 representa hidroxicarbonilo, alcanoílo C_{1-6}, carbamoílo, ciano, carboxilo, alcoxi C_{1-6}-carbonilo, alquil C_{1-6}-carbamoílo, alquil C_{1-6}-amino, heteroarilo de 5 a 10 miembros-(hidroxi)metilo, heteroarilo de 5 a 10 miembros-alquilo C_{1-6}, o metilo sustituido con hidroxi y un anillo cíclico saturado de 5 a 7 miembros, alquilo C_{1-6} opcionalmente sustituido con un sustituyente seleccionado del grupo formado por hidroxi, alcoxi C_{1-6}, alquil C_{1-6}-sulfonilamino, alquil C_{1-6}-carbonilamino, arilo C_{5-10}, aril C_{5-10}-sulfanilo, aril C_{5-10}-sulfenilo, ariloxi C_{5-10}, imidazolilo o pirrolidinoxi sustituido con dioxo,

$-(CH_2)_pNHCOR^{41}$, $-(CH_2)_pNHC(=S)R^{41}$

en las que p representa cualquier número entero de 1 a 6 y R^{41} representa alcoxi C_{1-6}, amino, fenilamino, alquilo C_{1-6}, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, cicloalquil C_{3-10}-amino,

R^3 y R^4 pueden formar junto con los átomos de carbono en el anillo de piridina,

monocicloalquilo o bicicloalquilo de 4 a 10 miembros opcionalmente interrumpidos por NH y opcionalmente sustituidos con bencilo, =NH o =O;

R^5 representa $NR^{51}R^{52}$,

en la que R^{51} es hidrógeno, alquilo C_{1-6},

R^{52} es hidrógeno, alquilo C_{1-6}, fenilo, bencilo, alcanoílo C_{1-6} o $NR^{51}R^{52}$ puede formar piperidino,

o

R^4 y R^5 pueden formar

$-R^{40}-CO-NH-$, $-R^{40}-SO_2-NH-$
$-R^{40}-C(=S)-NH-$ o
$-R^{40}-CH_2-NH-$,

representando dicho $-R^{40}-$ $-CHR^{401}-O-$, $-CH_2-N\ R^{401}-$, $-CO-NR^{401}-$, (siendo R^{401} hidrógeno, alcanoílo C_{1-6}, alcoxi C_{1-6}-carbonilo, alquilo C_{1-6}, fenilo, alquil C_{1-6}-sulfonilo, cicloalquil C_{3-8}-aminocarbonilo, alquil C_{1-6}-aminocarbonilo, carbamoílo, di(alquil C_{1-6})aminocarbonilo, $-CH_2-CHR^{402}-$, $-CH=CR^{402}-$, (siendo R^{402} hidrógeno, halógeno, nitro, amino, ciano, benzoilamino, fenilsulfonilo, carbamoílo, hidroxicarbonilo, alcoxi C_{1-6}-carbonilo, alquil C_{1-12}-aminocarbonilo, alquil C_{1-6},-aminocarbonilo sustituido con halógeno, alcanoil C_{1-6}-amino, alquil C_{1-6}-amino, di(alquil C_{1-6})aminocarbonilo, di(alquil C_{1-6})amino-alquil C_{1-6}-aminocarbonilo,

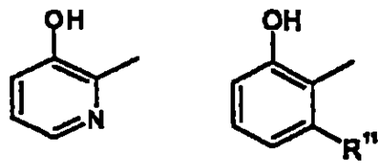
hidroindenilaminocarbonilo, difenilmetilaminocarbonilo, pirrolidinocarbonilo, alcoxi C_{1-6}-alquil C_{1-6}-aminocarbonilo, morfolinocarbonilo, piperazinocarbonilo, fenil-alquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-aminocarbonilo, hidroxicarbonil-alquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-alquil C_{1-6}-aminocarbonilo, hidroxialquil C_{1-6}-aminocarbonilo, carboxietilaminocarbonilo, metilsulfonilaminocarbonilo).

$-CR^{41}=N-NH-$ (R^{41} es hidroxi, amino o alcanoil C_{1-6}-amino) o

$-CR^{42}=N-C=N-$ (R^{42} es amino).

o una de sus sales.

3. El compuesto o una de sus sales de acuerdo con la reivindicación 1, en el que $-R^1$ representa



o

en la que R^{11} es hidrógeno, alcoxi C_{1-12}, u $-O-(CH_2)_n-R^{111}$,

representando n un número entero seleccionado de 1 a 6, y R^{111} es fenilo, cicloalquilo C_{3-8};

R^2 representa hidrógeno;

R^3 representa 1,2,3,6-tetrahidropiridina,

$-CR^{31}R^{32}R^{33}$,

en la que R^{31} es hidrógeno,

y

R^{32} y R^{33} forman, junto con el átomo de carbono adyacente un anillo saturado de 5 a 8 miembros interrumpido por NH, estando dicho anillo opcionalmente sustituido con fenilalquilo C_{1-6}, fenilalquilo C_{1-6} sustituido con alcoxi C_{1-6}, alquilo C_{1-6}, amino, carboxi, alquil C_{1-6}-amino, alcoxi C_{1-6}-carbonilo, di(alquil C_{1-6})amino, bencilamino, alquil C_{1-6}-sulfonilo, piperidino-alquil C_{1-6}-carbonilo o opcionalmente condensado con benceno;

o

$-NR^{34}R^{35}$,

en la que R^{34} es hidrógeno y

R^{35} es $-(CH_2)_m-NR^{351}R^{352}$ (m representa cualquier número entero de 1 a 6).

en la que R^{351} representa hidrógeno, alquilo C_{1-6},

R^{352} representa hidrógeno, alquilo C_{1-6}, alcanoílo C_{1-6}, fenilo sustituido con alquilo C_{1-6}, benzoílo, alcanoílo C_{1-6}, fenilaminocarbonilo, fenilsulfonilo; y

R^4 representa ciano, alquilo C_{1-6} opcionalmente sustituido con hidroxi o alcoxi C_{1-6}, o

$-(CH_2)_pNHCOR^{41}$, $-(CH_2)_pNHC(=S)R^{41}$

en las que p representa cualquier número entero de 1 a 6 y R^{41} representa alcoxi C_{1-6}, amino, fenilamino, alquilo C_{1-6}, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, cicloalquil C_{3-10}-amino,

R^5 representa amino,

o

R^4 y R^5 pueden formar,

$-R^{40}-CO-NH-$, $-R^{40}-SO_2-NH-$
$-R^{40}-C(=S)-NH-$ o
$-R^{40}-CH_2-NH-$

representando dicho $-R^{40}-$ $-CHR^{401}-O-$, $-CH_2-NR^{401}-$, $-CO-NR^{401}-$, (en las cuales R^{401} es hidrógeno, alcanoílo C_{1-6}, alcoxi C_{1-6}-carbonilo, alquilo C_{1-6}, fenilo, alquil C_{1-6}-sulfonilo, cicloalquil C_{3-8}-aminocarbonilo, alquil C_{1-6}-aminocarbonilo, carbamoílo,

di(alquil C_{1-6})aminocarbonilo, $-CH_2-CHR^{402}-$, $-CH=CR^{402}-$, (en las cuales R^{402} es hidrógeno, halógeno, nitro, amino, ciano, benzoilamino, fenilsulfonilo, carbamoílo, hidroxicarbonilo, alcoxi C_{1-6}-carbonilo, alquil C_{1-12}-aminocarbonilo, alquil C_{1-6},-aminocarbonilo sustituido con halógeno, alcanoil C_{1-6}-amino, alquil C_{1-6}-amino, di(alquil C_{1-6})aminocarbonilo, di(alquil C_{1-6})amino-alquil C_{1-6}-aminocarbonilo, hidroindenilaminocarbonilo, difenilmetilaminocarbonilo, pirrolidinocarbonilo, alcoxi C_{1-6}-alquil C_{1-6}-aminocarbonilo, morfolinocarbonilo, piperazinocarbonilo, fenilalquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-aminocarbonilo, hidroxicarbonilalquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-alquil C_{1-6}-aminocarbonilo, hidroxialquil C_{1-6}-aminocarbonilo, carboxietilaminocarbonilo, metilsulfonilaminocarbonilo).

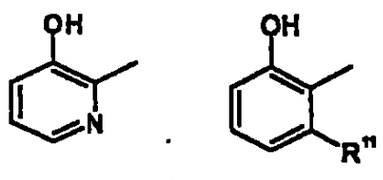
$-CR^{41}=N-NH-$ (R^{41} es hidroxi, amino o alcanoil C_{1-6}-amino) o

$-CR^{42}=N-C=N-$ (R^{42} es amino).

o una de sus sales.

4. El compuesto o una de sus sales de acuerdo con la reivindicación 1, en el que

$-R^1$ representa



o

en la que R^{11} es hidrógeno, alcoxi C_{1-6}, u $-O-CH_2-R^{111}$,

representando R^{111} fenilo, cicloalquilo C_{3-4};

R^2 representa hidrógeno;

R^3 representa 1,2,3,6-tetrahidropiridina,

$-CR^{31}R^{32}R^{33}$,

en la que R^{31} es hidrógeno,

y

R^{32} y R^{33} forman, junto con el átomo de carbono adyacente, piperidina o pirrolidina, estando dichas piperidina o pirrolidina opcionalmente sustituidas con alquilo C_1-C_6;

o

$-NR^{34}R^{35}$,

en la que R^{34} es hidrógeno y

R^{35} es $-(CH_2)_m-NR^{351}R^{352}$ (m representa cualquier número entero de 1 a 6).

en la que R^{351} representa hidrógeno, alquilo C_{1-6},

R^{352} representa hidrógeno, alquilo C_{1-6}, alcanoílo C_{1-6}, fenilo sustituido con alquilo C_{1-6}, benzoílo, alcanoílo C_{1-6}, fenilaminocarbonilo, fenilsulfonilo; y

R^4 representa ciano, hidroximetilo, o $-CH_2NHCOR^{41}$,

representando R^{41} alcoxi C_{1-6}, amino, fenilamino, alquilo C_{1-6}, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, cicloalquil C_{3-10}-amino,

R^5 representa amino,

o

R^4 y R^5 pueden formar,

$-R^{40}-CO-NH-$ o $-R^{40}-CH_2-NH-$,

representando dicho $-R^{40}-$ $-CHR^{401}-O-$, $-CH_2-NR^{401}-$, $-CO-NR^{401}-$, (siendo R^{401} hidrógeno, alcanoílo C_{1-6}, alcoxi C_{1-6}-carbonilo, alquilo C_{1-6}, fenilo, alquil C_{1-6}-sulfonilo, cicloalquil C_{3-8}-aminocarbonilo, alquil C_{1-6}-aminocarbonilo, carbamoílo, di(alquil C_{1-6})aminocarbonilo, $-CH_2-CHR^{402}-$, $-CH=CR^{402}-$, (siendo R^{402} hidrógeno, halógeno, nitro, amino, ciano, benzoilamino, fenilsulfonilo, carbamoílo, hidroxicarbonilo, alcoxi C_{1-6}-carbonilo, alquil C_{1-12}-aminocarbonilo, alquil C_{1-6},-aminocarbonilo sustituido con halógeno, alcanoil C_{1-6}-amino, alquil C_{1-6}-amino, di(alquil C_{1-6})aminocarbonilo, di(alquil C_{1-6})amino-alquil C_{1-6}-aminocarbonilo,

hidroindenilaminocarbonilo, difenilmetilaminocarbonilo, pirrolidinocarbonilo, alcoxi C_{1-6}-alquil C_{1-6}-aminocarbonilo, morfolinocarbonilo, piperazinocarbonilo, fenilalquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-aminocarbonilo, hidroxicarbonilalquil C_{1-6}-aminocarbonilo, cicloalquil C_{3-8}-alquil C_{1-6}-aminocarbonilo, hidroxialquil C_{1-6}-aminocarbonilo, carboxietilaminocarbonilo, metilsulfonilaminocarbonilo),

o una de sus sales.

5. El compuesto de acuerdo con la reivindicación 1 seleccionado del grupo constituido por los siguientes compuestos:

7-(2-hidroxifenil)-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-2-ona;
2-amino-6-[2-(benciloxi)-6-hidroxifenil]-4-(3-piperidinil)nicotinonitrilo;
2-amino-6-(2-hidroxi-6-propoxifenil)-4-(3-piperidinil)nicotinonitrilo;
2-[6-amino-5-(hidroximetil)-4-(3-piperidinil)-2-piridinil]-3-(benciloxi)fenol;
7-[2-(benciloxi)-6-hidroxifenil]-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3d][1,3]oxazin-2-ona;
7-[2-(hidroxifenil)-5-(3-piperidinil)-3,4-dihidro-1,8-naftiridin-2(1H)-ona;
2-amino-6-[2-(ciclobutilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)nicotinonitrilo;
2-[6-amino-5-(hidroximetil)-4-(3-piperidinil)-2-piridinil]-3-propoxifenol;
7-(2-hidroxi-6-propoxifenil)-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3d][1,3]oxazin-2-ona;
7-(2-hidroxi-6-propoxifenil)-2-oxo-5-(3-piperidinil)-1,2,3,4-tetrahidro-1,8-naftiridin-3-carboxilato de etilo;
7-(2-hidroxi-6-propoxifenil)-5-(3-piperidinil)-3,4-dihidro-1,8-naftiridin-2(1H)-ona;

2-[6-amino-5-(hidroximetil)-4-(3-piperidinil)-2-piridinil]-3-(ciclopropilmetoxi)fenol;

2-[6-amino-5-(hidroximetil)-4-(4-piperidinil)-2-piridinil]-3-(ciclopropilmetoxi)fenol;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-3,4-dihidro-1,8-naftiridin-2(1H)-ona;

7-(2-ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,2,3,4-tetrahidro-1,8-naftiridin-3-carboxilato de etilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(4-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-2-ona;

6'-amino-5'-(hidroximetil)-4'-(3-piperidinil)-2,2'-bipiridin-3-ol;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(4-piperidinil)-3,4-dihidro-1,8-naftiridin-2(1H)-ona;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-3-fluoro-5-(3-piperidinil)-1,8-naftiridin-2(1H)-ona;

7-(2-hidroxi-6-propoxifenil)-5-(4-piperidinil)-1,4-dihidro-2H-pirido[2,3d][1,3]oxazin-2-ona;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-2-ona;

3-(ciclopropilmetoxi)-2-[5-(3-piperidinil)-1,4-dihidro-2H-pirido[2,3-d][1,3]oxazin-7-il]fenol;

2-[6-amino-5-(hidroximetil)-4-(3-piperidinil)-2-piridinil]-3-(neopentiloxi)fenol;

2-[6'-amino-5'-(hidroximetil)-1,2,5,6-tetrahidro-3,4'-bipiridin-2'-il]fenol;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-1,8-naftiridin-2(1H)-ona;

N-{[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]metil}acetamida;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,2-dihidro-1,8-

naftiridin-3-carboxamida;

3-acetil-7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-3,4-dihidropirido[2,3-d]pirimidin-2(1H)-ona;

2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(4-piperidinil)nicotinonitrilo;

2-amino-4-[(2-aminoetil)amino]-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]nicotinonitrilo;

N-{[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]metil}-N'-propilurea;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-5-(3-piperidinil)-3,4-dihidropirido[2,3-d]pirimidin-2(1H)-ona;

[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]-metilcarbamato de etilo;

2-amino-6-{2-hidroxi-6-[(4-metilpentil)oxi]fenil}-4-(4-piperidinil)nicotinonitrilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,2,3,4-tetrahidro-1,8-naftiridin-3-carboxamida;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-N-isopropil-2-oxo-5-(3-piperidinil)-1,2-dihidro-1,8-naftiridin-3-carboxamida;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido[2,3-d]pirimidin-3(2H)-carboxilato de etilo;

N-{[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]metil}urea;

2-amino-6-(2-hidroxi-6-propoxifenil)-4-(4-piperidinil)nicotinonitrilo;

N-ciclohexil-7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido[2,3-d]pirimidin-3(2H)-carboxamida;

2-amino-6-[2-(ciclobutilmetoxi)-6-hidroxifenil]-4-(4-piperidinil)nicotinonitrilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-N,N-dimetil-2-oxo-5-(3-piperidinil)-1,4-

dihidropirido[2,3-d]pirimidin-3(2H)-carboxamida;

2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(1-metil-3-piperidinil)nicotinonitrilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido[2,3-d]pirimidin-3(2H)-carboxamida;

[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]metilcarbamato de isopropilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido-[2,3-d]pirimidin-3(2H)-carboxilato de isopropilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido-[2,3-d]pirimidin-3(2H)-carboxilato de isobutilo;

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-2-oxo-5-(3-piperidinil)-1,4-dihidropirido-[2,3-d]pirimidin-3(2H)-carboxilato de neopentilo;

[2-amino-6-[2-(ciclopropilmetoxi)-6-hidroxifenil]-4-(3-piperidinil)-3-piridinil]metilcarbamato de neopentilo;

2-amino-6-[2-(hexiloxi)-6-hidroxifenil]-4-(4-piperidinil)nicotinonitrilo; y

7-[2-(ciclopropilmetoxi)-6-hidroxifenil]-N-etil-2-oxo-5-(3-piperidinil)-1,4-dihidropirido[2,3-d]pirimidin-3(2H)-carboxamida;

o una de sus sales.

6. Un medicamento que comprende el compuesto o una de sus sales de acuerdo con la reivindicación 1 como un ingrediente activo.

7. Una composición médica que comprende el compuesto o una de sus sales de

acuerdo con la reivindicación 1, junto con uno o más excipientes farmacéuticamente aceptables.

8. Un inhibidor de la quinasa β IκB que comprende el compuesto o una de su sales de acuerdo con la reivindicación 1 como un ingrediente activo.

9. Un agente antiinflamatorio que comprende el compuesto o una de sus sales de acuerdo con la reivindicación 1 como un ingrediente activo.

10. El agente antiinflamatorio de acuerdo con la reivindicación 9, usándose dicho agente para tratar o prevenir una enfermedad seleccionada del grupo formado por asma; rinitis alérgica; dermatitis atópica: urticaria; conjuntivitis; catarro vernal; artrorreumatismo crónico; lupus eritematoso sistémico; psoriasis; colitis diabrótica; síndrome de respuesta inflamatoria sistémica (SIRS); sepsis; polimiositis; dermatomiositis (DM); poliartritis nudosa (PN); enfermedad mixta del tejido conjuntivo (MCTD); síndrome de Sjoegren; y gota.

11. Un inmunosupresor que comprende el compuesto o una de sus sales de acuerdo con la reivindicación 1 como un agente activo.

12. Un agente para tratar la isquemia que comprende el compuesto o una de sus sales de acuerdo con la reivindicación 1 como un agente activo.

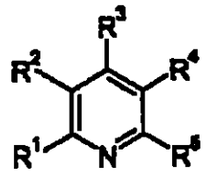
13. Un agente antitumoral que comprende el compuesto o una de sus sales de acuerdo con la reivindicación 1 como un agente activo.

14. Procedimiento para tratar enfermedades mediante la administración a un sujeto que lo necesite de una cantidad eficaz de un compuesto de acuerdo con la reivindicación 1.

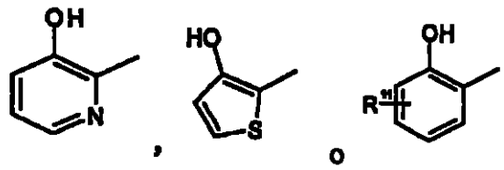
15. Uso de un compuesto de acuerdo con la reivindicación 1 para la preparación de un medicamento para el tratamiento del asma.

RESUMEN

Compuestos de piridina de fórmula general:



en la que -R^1 representa



en la que R^{11} representa hidrógeno, alquilo C_{1-6}, halógeno, hidroxi, alcoxi C_{1-12}, nitro, amino, alquil C_{1-6}-sulfonilamino, alcoxi C_{1-6}-carbonilo, alquil C_{1-6}-amino, di(alquil C_{1-6})amino, alcanoil C_{1-6}-amino, fenilalquil C_{1-6}-amino, fenilsulfonilamino o $-O-(CH_2)_n-R^{111}$; R^2 representa hidrógeno o halógeno; R^3 representa hidrógeno, $-CR^{31}R^{32}R^{33}$, o $-NR^{34}R^{35}$; R^4 es hidrógeno, carbamoílo, CN, carboxilo, etc.; R5 es amino, alquilamino C_{1-6}, di(alquil C_{1-6})amino, etc. o una de sus sales. El compuesto presenta una actividad antiinflamatoria excelente y otras actividades biológicas.

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484

Industria y Com rcio

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***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	9005688	17/03/2003	13,478,560.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	7 TRAMITES DE SOL. DE DISENOS INDUS	400,000.00
		TOTAL : $	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Odo 00698-841-014-5

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