Q.F.

CSA481104

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creciones

PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 08-34096

54. **TÍTULO** NUEVOS DERIVADOS IMIDAZOPIRIDINA

51. **CLASIFICACIÓN INTERNACIONAL** (O 7.D 471/04 ; A61K 31/437

71. **SOLICITANTE** LABORATORIOS ALMIRALL S.A.

DOMICILIO BARCELONA, ESPAÑA

74. **APODERADO** EMILIO FERRERO

C.C. 438.019 de Usàquen

22. **BOGOTÁ, D. C.,**

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PET

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE:

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

(2) SOLICITANTE (71)

Nombre: **LABORATORIOS ALMIRALL S.A.** sociedad constituida y existente bajo las leyes de España.

Dirección: Ronda del General Mitre 151, 08022 Barcelona, España

Domicilio: Barcelona, España

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

(3) REPRESENTANTE O APODERADO

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Dirección: Carrera 4ª. No. 72-35
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Fax: 211 86 50
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Domicilio: Bogotá, Colombia.

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

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(5) PCT (86)

Solicitud Internacional No. PCT/EP2006/009620 Fecha: 05 de octubre de 2006
Publicación Internacional No. WO 2007/039297 A1 Fecha: 12 de abril de 2007

(6) Título (54)

NUEVOS DERIVADOS IMIDAZOPIRIDINA

(7) Clasificación Internacional (51) C07D 471/004

(8) Prioridad SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	ES	06 de octubre de 2005	P200502433

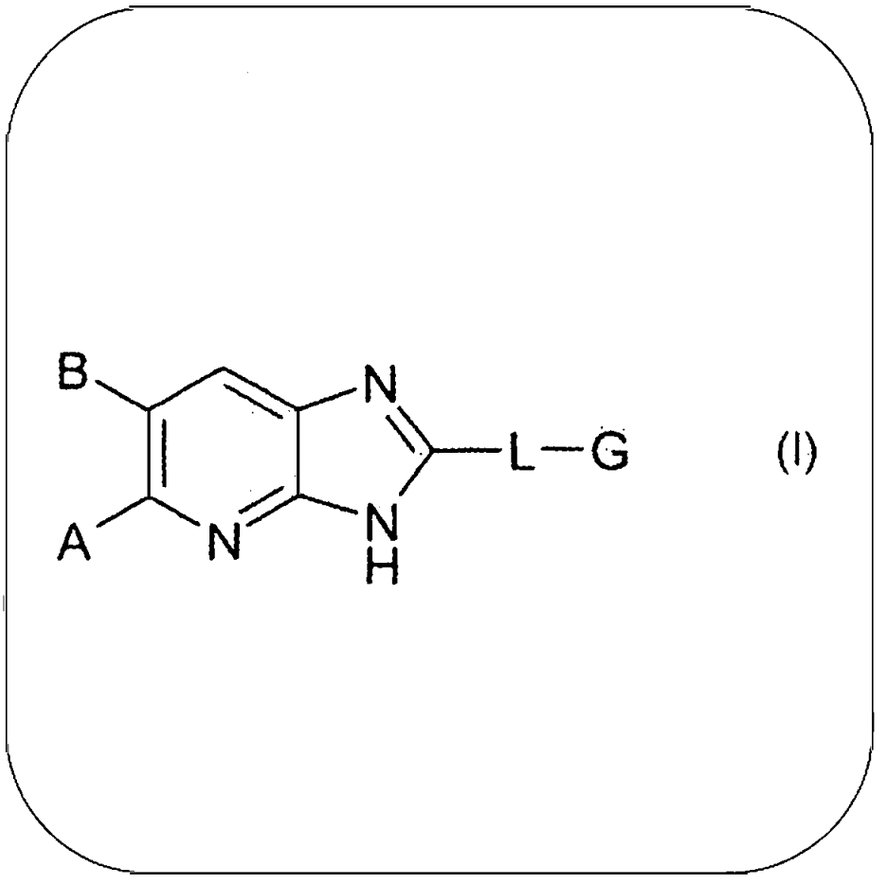
(9) **Comprobante de pago No.:** 08-23.420 **Fecha:** 17 de marzo de 2008

(10) **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 501.000.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: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



(I)

12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA :

C.C. 438.019 de Usaquén T.P. 31.929

SCT

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2007/039297 A1

   Descripción:

   Páginas 79 en el idioma original

   Páginas 80 en español

   Reivindicaciones: Número (s) 14

   Figuras: Número (s)

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

3. ☐ **Forma PCT/ISA/237.** Opinión Escrita De La Administración Encargada De La Búsqueda

4. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

5

576

CAVELIER ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 - COLOMBIA

188 **Poder general otorgado en el exterior con autenticación notarial y Apostille para patentes, modelos de utilidad y diseños industriales, marcas de fábrica y de servicio, nombres comerciales, enseñas, nombres de dominio, lemas comerciales y licencias.**

6734
6921

REPRESENTACION Y PODER

La que suscribe, LABORATORIOS ALMIRALL, S.A.

sociedad organizada y existente de conformidad con las leyes de España

domiciliada en Ronda del General Mitre 151, 08022 Barcelona, designa a EMILIO FERRERO, tpa. 31929; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y DANIEL PEÑA, tpa. 65620, domiciliados en la Carrera 4ª N° 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 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, conferimos poder a los abogados arriba nombrados, para obtener la protección de nuestra propiedad industrial y contra la competencia desleal, a cuyo efecto autorizamos a los dichos apoderados para que nos representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, renuncia voluntaria, y 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.

Firmado en la ciudad de Barcelona, el 23 de enero de 2007

COMO NOTARIO ENCARGADO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE PRESENTADO A LA VISTA
26 MAR 2008
FABIO MENDEZ BARAJAS
NOTARIO (E)

Pío Orviz / Pedro Berga
Apoderados

Legalización Consular

LEGITIMACION: Yo, SALVADOR CARBALLO CASADO, Notario del Ilustre Colegio Notarial de Catalunya, con residencia en Barcelona, doy fe:-- Que reputo legítimas y auténticas, las firmas y rúbricas que anteceden, de DON PIO ORVIZ DIAZ y DON PEDRO BERGA MARTI, por ser de mí conocidas, puestas en este documento, en su condición de apoderados de "LABORATORIOS ALMIRALL, S.A." (antes "ALMIRALL PRODESFARMA, S.A.) en uso de los poderes que dicha Sociedad les tienen conferidos, los cuales están debidamente inscritos en el Registro Mercantil de Barcelona.-----------------
Esta legitimación se hace a los efectos previstos en el artículo 207.2 del Reglamento Notarial, en virtud de acta en la que ha quedado debidamente acreditada la representación de dichos señores en nombre de la Sociedad, de esta misma fecha y protocolo, número 186 .------------------------
Anotado en mi Libro Indicador del año 2007 (Sección Segunda). Asiento 2.-------------------
En Barcelona, a treinta y uno de enero de dos mil siete.--

0,10 0,05 €

SELLO DE LEGITIMACIONES Y LEGALIZACIONES

FE PÚBLICA NOTARIAL

CONSEJO GENERAL DEL NOTARIADO ESPAÑOL
NOTARIADO EUROPA
0091508366

NOTARIA DE ... BARCELONA

EL SIGNO, FIRMA Y RÚBRICA DEL NOTARIO QUE OBRA EN ESTE FOLIO, HA SIDO ... Y ANOTADO ... 3943 /2007 ... EN ... DEL COLEGIO NOTARIAL DE CATALUÑA.

COMO NOTARIO ... DE BOGOTA HAGO CONSTAR QUE ES FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

26 MAR 2008

PABLO ... ARAJAS
NOTA...

6

PAPEL EXCLUSIVO PARA DOCUMENTOS NOTARIALES

7R8634233

10/2006

A P O S T I L L E

(Convention de La Haye du 5 octobre 1961)

1. País **ESPAÑA**----------
   El presente documento público----------
2. ha sido firmado por D. SALVADOR CARBALLO CASADO----------
3. quien actúa en calidad de Notario, en legitimación de firmas de don Pio Orviz Díaz y don Pedro Berga Martí, en documento de---- poder, en representación de Laboratorios Almirall, S.A., con--- forme Acta número 186/2007; de fecha 31 de enero de 2007.------
4. y está revestido del sello/timbre de su Notaría de --------- BARCELONA----------

CERTIFICADO

5. en BARCELONA---------- 6. el día 07 de febrero de 2007.---
7. por DON ANTONI BOSCH I CARRERA, Censor Segundo de la Junta----- Directiva del Colegio Notarial de Cataluña----------
8. bajo el número: -7943/2007----------
9. Sello/timbre : 10. Firma:

SELLO DE LEGITIMACIONES Y LEGALIZACIONES

FE PÚBLICA NOTARIAL

CONSEJO GENERAL DEL NOTARIADO ESPAÑOL

NOTARIADO EUROPA

NIHIL PRIUS FIDE

Antoni Bosch i Carrera
Censor Segundo

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

26 MAR 2008

PABLO MEN... NAJAS
NOTA...

6834

1163

787

CAVELIER ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 – COLOMBIA

A2B-IMIPYRID-001
35861

374

CESION

Yo, (nosotros) abajo firmado (s)

Nombre	Apellidos	Dirección	Firma
BERNAT	VIDAL JUAN	C/ Font, 11, 08396 St. Cebrià de Vallalta (Barcelona), España	
SILVIA	FONQUERNA POU	Pg de l' Havana 2-4, esc D, baixos 3, 08030 Barcelona, España	
PAUL ROBERT	EASTWOOD	C/ Palencia, 33, 2ª 1°, 08191 Rubí (Barcelona), España	
JOSE	AIGUADE BOSCH	C/ Sardenya 379 2-2 08025 Barcelona, España	
ARANZAZU	CARDUS FIGUERAS	C/ Balmes 14, 08780 Pallejá (Barcelona), España	
[illegible]ES	CARRANCO MORUNO	C/ Eusebi Güell N°98 1°4ª Sant Boi de llobregat (08830) Barcelona, España	
JACOB	GONZALEZ RODRIGUEZ	C/ Verge de Montserrat 6-8, 3° 2ª, 08980 Sant Feliu de Llobregat (Barcelona), España	
SERGIO	PAREDES APARICIO	C/ Navas de Tolosa 259, 5° 1ª 08026 Barcelona, España	

Declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es)

de la invención:

NUEVOS DERIVADOS IMIDAZOPIRIDINA

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad

LABORATORIOS ALMIRALL, S.A.
Ronda del General Mitre, 151
[illegible]022 Barcelona, España

constituida y existente de conformidad con las leyes de España

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.

Barcelona, -5 MAR. 2008

Legalización Consular

LEGITIMACIÓN: Yo, SALVADOR CARBALLO CASADO, Notario del Ilustre Colegio Notarial de Catalunya, con residencia en Barcelona, DOY FE: ----------

Que reputo legítimas y auténticas, las firma y rúbrica que anteceden, de DON BERNAT VIDAL JUAN, DOÑA SILVIA FONQUERNA POU, DON PAUL ROBERT EASTWOOD, DON JOSE AIGUADE BOSCH, DOÑA ARANZAZU CARDUS FIGUERAS, DOÑA INES CARRANCO MORUNO, DON JACOB GONZALEZ RODRIGUEZ y de DON SERGIO PAREDES APARICIO, puestas en nombre propio en este documento. ----

Esta legitimación se hace a los efectos previstos en el artículo 207.2 del Reglamento Notarial, en virtud de acta, de esta misma fecha y protocolo, número 408 .----------

Anotado en mi Libro Indicador del año 2008 , (Sección Segunda) Asiento nº. 167 .—

En Barcelona, a - 5 MAR. 2008

- 5 MAR. 2008

SELLO DE LEGITIMACIONES Y WAIVERS

NOTARIADO EUROPA

0114944286

EL SIGNO, FIRMA Y RÚBRICA DEL NOTARIO QUE OBRA EN ESTE FOLIO, HA SIDO APOSTILLADO Y ANOTADO BAJO EL NÚMERO 21026 DE 2008, EN EL LIBRO REGISTRO DEL COLEGIO NOTARIAL DE CATALUÑA.

PAPEL EXCLUSIVO PARA DOCUMENTOS NOTARIALES

8G7865495

09/2007

A P O S T I L L E

(Convention de La Haye du 5 octobre 1961)

1. País **ESPAÑA**----------
   El presente documento público----------
2. ha sido firmado por D. SALVADOR CARBALLO CASADO----------
3. quien actúa en calidad de Notario, en legitimación de firmas de don Bernat Vidal Juan, doña Silvia Fonquerna Pou, don Paul Robert Eastwood, don José Aiguadé Bosch, doña Aranzazu Cardús Figueras, doña Inés Carranco Moruno, don Jacob González Rodríguez y don Sergio Paredes Aparicio, en documento de cesión, conforme Acta número 408/2008, de fecha 5 de marzo de 2008.----
4. y está revestido del sello/timbre de su Notaría de BARCELONA----------

CERTIFICADO

5. en BARCELONA---------- 6. el día 12 de marzo de 2008.-----
7. por DON ANTONI BOSCH I CARRERA, Censor Segundo de la Junta Directiva del Colegio Notarial de Cataluña----------
8. bajo el número: -21026/2008----------
9. Sello/timbre : 10. Firma:

12 MAR. 2008

FE PÚBLICA NOTARIAL

CONSEJO GENERAL DEL NOTARIADO ESPAÑOL

NOTARIADO EUROPA

NIHIL PRIUS FIDE

COLEGIO NOTARIAL DE CATALUNYA

012582615 8

Antoni Bosch i Carrera
Censor Segundo

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International Bureau

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A61P 37/00 (2006.01) *A61P 11/00* (2006.01)

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(22) International Filing Date: 5 October 2006 (05.10.2006)

(25) Filing Language: English

(26) Publication Language: English

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P200502433 6 October 2005 (06.10.2005) ES

(71) Applicant *(for all designated States except US)*: **LABORATORIOS ALMIRALL, S.A.** [ES/ES]; Ronda del General Mitre 151, E-08022 Barcelona (ES).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **VIDAL JUAN, Bernat** [ES/ES]; C/Font, 11, E-08396 St. Cebrià de Vallalta (Barcelona) (ES). **PONQUERNA POU, Silvia** [ES/ES]; Pg de l'Havana 2-4, esc D, baixos 3, E-08030 Barcelona (ES). **EASTWOOD, Paul, Robert** [GB/ES]; C/Palencia, 33, 2a 1ª, E-08191 Rubi (Barcelona) (ES). **AIGUADE BOSCH, Jose** [ES/ES]; C/Sardenya 379, 2°2a, E-08025 Barcelona (ES). **CARDUS FIGUERAS, Aranzazu** [ES/ES]; C/Balmes 14, E-08780 Pallejà (Barcelona) (ES). **CARRANCO MORUNO, Ines** [ES/ES]; C/Buscbi Güell 98 1°4a, E-08830 Sant Boi de Llobregat (Barcelona) (ES). **GONZALEZ RODRIGUEZ, Jacob** [ES/ES]; C/Verge de Montserrat 6-8, 3°2a, E-08980 Sant Feliu de Llobregat (Barcelona) (ES). **PAREDES APARICIO, Sergio** [ES/ES]; C/Navas de Tolosa 259, 5°1a, E-08026 Barcelona (ES).

(74) Agents: **WINKLER, Andreas** et al.; Boehmert & Boehmert Anwaltssozietät, Hollerallee 32, 28209 Bremen (DE).

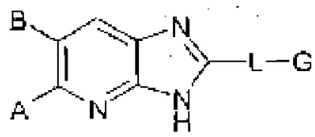
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZOPYRIDINE DERIVATIVES AS A2B ADENOSINE RECEPTOR ANTAGONISTS



(I)

(57) Abstract: New imidazopyridine derivatives of formula (I) are disclosed as antagonists of the A_{2B} adenosine receptor.

WO 2007/039297 A1

IMIDAZOPYRIDINE DERIVATIVES AS A2B ADENOSINE RECEPTOR ANTAGONISTS

The present invention relates to new antagonists of the A_{2B} adenosine receptor. These compounds are useful in the treatment, prevention or suppression of diseases and disorders known to be susceptible to improvement by antagonism of the A_{2B} adenosine receptor, such as asthma, chronic obstructive pulmonary disorder, pulmonary fibrosis, emphysema, allergic diseases, inflammation, reperfusion injury, myocardial ischemia, atherosclerosis, hypertension, retinopathy, diabetes mellitus, inflammatory gastrointestinal tract disorders, and/or autoimmune diseases.

Adenosine regulates several physiological functions through specific cell membrane receptors, which are members of the G-protein coupled receptor family. Four distinct adenosine receptors have been identified and classified: A_1, A_{2A}, A_{2B} and A_3.

The A_{2B} adenosine receptor subtype (see Feoktistov, I., Biaggioni, I. *Pharmacol. Rev.* 1997, *49*, 381-402) has been identified in a variety of human and murine tissues and is involved in the regulation of vascular tone, smooth muscle growth, angiogenesis, hepatic glucose production, bowel movement, intestinal secretion, and mast cell degranulation.

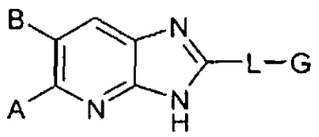
In view of the physiological effects mediated by adenosine receptor activation, several A_{2B} receptor antagonists have been recently disclosed for the treatment or prevention of, asthma, bronchoconstriction, allergic diseases, hypertension, atherosclerosis, reperfusion injury, myocardial ischemia, retinopathy, inflammation, gastrointestinal tract disorders, cell proliferation diseases and/or diabetes mellitus. See for example WO2005070926, WO2005042534, WO2005021548, WO2004106337, US2004176399, US2003229106, WO03002566, WO03/063800, WO03/042214, WO 03/035639, WO02/42298, EP 1283056, WO 01/16134, WO 01/02400, WO01/60350, WO 00/73307 or *Br. J. Pharmacol.* 2005, *145*, 1009-1015.

It has now been found that certain imidazopyridine derivatives are novel potent antagonists of the A_{2B} adenosine receptor and can therefore be used in the treatment or prevention of these diseases.

Further objectives of the present invention are to provide a method for preparing said compounds; pharmaceutical compositions comprising an effective amount of said

compounds; the use of the compounds in the manufacture of a medicament for the treatment of pathological conditions or diseases susceptible to improvement by antagonism of the A_{2B} adenosine receptor; and methods of treatment of pathological conditions or diseases susceptible to amelioration by antagonism of the A_{2B} adenosine receptor comprising the administration of the compounds of the invention to a subject in need of treatment.

Thus, the present invention is directed to new imidazopyridine derivatives of formula (I)



wherein:

A represents a monocyclic nitrogen-containing heteroaryl group optionally substituted by one or more substituents independently selected from the group comprising halogen atoms, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl- C_{1-4}alkyl, C_{1-4}alkoxy, aryl-C_{1-4}alkoxy, C_{1-4}alkylthio, mono or di-C_{1-4}alkylamino, trifluoromethyl, hydroxy and cyano groups;

B represents a monocyclic nitrogen-containing heteroaryl group optionally substituted by one or more substituents independently selected from the group comprising halogen atoms, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl- C_{1-4}alkyl, C_{1-4}alkoxy, aryl-C_{1-4}alkoxy, C_{1-4}alkylthio, mono or di-C_{1-4}alkylamino, trifluoromethyl, hydroxy and cyano groups;

L represents a linking group selected from the group comprising direct bond, -$(CRR')_n$-, -NR-, -S-, -O- and -CO-; wherein n is an integer from 0 to 2;

G represent a group selected from the group comprising –H, -OH, C_{3-7} cycloalkyl; C_{1-6} alkyl, aryl, heteroaryl and nitrogen-containing saturated heterocyclic rings, wherein the aryl, heteroaryl and nitrogen-containing saturated heterocyclic groups are unsubstituted or substituted by one or more groups selected from halogen atoms, C_{1-4} alkyl, C_{1-4} alkylthio, C_{1-4} alkoxy, mono- or di-C_{1-4} alkylamino, cyano, trifluoromethyl, –COOH and -CO-O-C_{1-4} alkyl groups;

R and R' are independently selected from hydrogen atoms and C_{1-4} alkyl groups;

and the pharmaceutically acceptable salts and N-oxides thereof.

As used herein the terms alkyl or lower alkyl embrace optionally substituted, linear or branched hydrocarbon radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms. Preferred substiuents on the alkyl groups are halogen atoms and hydroxy groups.

Examples include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *sec*-butyl and *tert*-butyl, *n*-pentyl, 1-methylbutyl, 2-methylbutyl, isopentyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, *n*-hexyl, 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 2-methylpentyl, 3-methylpentyl and iso-hexyl radicals.

As used herein, the term cycloalkyl embraces saturated carbocyclic radicals and, unless otherwise specified, a cycloalkyl radical typically has from 3 to 7 carbon atoms.

Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. When a cycloalkyl radical carries 2 or more substituents, the substituents may be the same or different. Preferred substiuents on the cycloalkyl groups are halogen atoms and hydroxy groups.

As used herein, unless otherwise provided, the term aryl radical embraces typically a C_5-C_{14} monocyclic or polycyclic aryl radical such as phenyl or naphthyl, anthranyl or phenanthryl. Optionally substituted phenyl is preferred. When an aryl radical carries 2 or more substituents, the substituents may be the same or different. Preferred substituents on the aryl radicals are halogen atoms and C_{1-4} alkyl, C_{1-4} alkylthio, C_{1-4} alkoxy, mono- or di-C_{1-4} alkylamino, cyano, trifluoromethyl, –COOH and -CO-O-C_{1-4} alkyl groups. Halogen atoms are particularly preferred.

As used herein, unless otherwise provided, the term heteroaryl radical embraces typically a 5- to 14- membered ring system comprising at least one heteroaromatic ring and containing at least one heteroatom selected from O, S and N. The term nitrogen-containing heteroaryl is used to designate heteroaryl groups which comprise at least one nitrogen atom forming part of the ring system. A heteroaryl radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom.

Examples of monocyclic heteroaryl radicals include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furyl, oxadiazolyl, oxazolyl, imidazolyl, thiazolyl, thiadiazolyl, thienyl, pyrrolyl, pyridinyl, triazolyl, imidazolidinyl and pyrazolyl radicals. Pyridyl, thienyl, furyl, pyridazinyl and pyrimidinyl radicals are preferred. Pyridyl and pyrimidinyl are the most preferred.

When a heteroaryl radical carries 2 or more substituents, the substituents may be the same or different. Preferred substituents on the heteroaryl radicals are halogen atoms and C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl- C_{1-4}alkyl, C_{1-4}alkoxy, aryl-C_{1-4}alkoxy, C_{1-4}alkylthio, mono or di-C_{1-4}alkylamino, trifluoromethyl, hydroxy –COOH, -CO-O-C_{1-4} alkyl and cyano groups.

As used herein, the term heterocyclic group embraces typically a non-aromatic, saturated or unsaturated C_3-C_{10} carbocyclic ring , such as a 5, 6 or 7 membered radical, in which one or more, for example 1, 2, 3 or 4 of the carbon atoms, preferably 1or 2, of the carbon atoms are replaced by a heteroatom selected from N, O and S. The term nitrogen-containing saturated heterocyclic ring is used to designate saturated heterocyclic groups which comprise at least one nitrogen atom forming part of the ring system. A heterocyclic radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom. When a heterocyclyl radical carries 2 or more substituents, the substituents may be the same or different. Preferred substiuents on the heterocyclic radicals are halogen atoms and C_{1-4} alkyl, C_{1-4} alkylthio, C_{1-4} alkoxy, mono- or di-C_{1-4} alkylamino, cyano, trifluoromethyl, –COOH and -CO-O-C_{1-4} alkyl groups.

Examples of monocyclic, nitrogen-containing heterocyclic radicals include piperidyl, pyrrolidyl, pyrrolinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolinyl, pirazolidinyl, quinuclidinyl, pyrazolyl. Piperidyl, piperazinyl and morpholinyl are preferred radicals.

As used herein, some of the atoms, radicals, moieties, chains or cycles present in the general structures of the invention are "optionally substituted". This means that these atoms, radicals, moieties, chains or cycles can be either unsubstituted or substituted in any position by one or more, for example 1, 2, 3 or 4, substituents, whereby the hydrogen atoms bound to the unsubstituted atoms, radicals, moieties, chains or cycles are replaced

by chemically acceptable atoms, radicals, moieties, chains or cycles. When two or more substituents are present, each substituent may be the same or different.

As used herein, the term halogen atom embraces chlorine, fluorine, bromine or iodine atoms typically a fluorine, chlorine or bromine atom, most preferably chlorine or fluorine. The term halo when used as a prefix has the same meaning.

As used herein, the term pharmaceutically acceptable salt embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or *p*-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases, for example alkyl amines, arylalkyl amines and heterocyclic amines.

Other preferred salts according to the invention are quaternary ammonium compounds wherein an equivalent of an anion (X-) is associated with the positive charge of the N atom. X- may be an anion of various mineral acids such as, for example, chloride, bromide, iodide, sulphate, nitrate, phosphate, or an anion of an organic acid such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, trifluoroacetate, methanesulphonate and *p*-toluenesulphonate. X- is preferably an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate, maleate, oxalate, succinate or trifluoroacetate. More preferably X- is chloride, bromide, trifluoroacetate or methanesulphonate.

As used herein, an N-oxide is formed from the tertiary basic amines or imines present in the molecule, using a convenient oxidising agent.

Preferred compounds of the invention are those wherein A represents an optionally substituted pyridine or an optionally substituted oxazole group. It is further preferred that A represents represents a pyridine ring either unsubstituted or substituted with one halogen atom.

In another embodiment of the present invention the group B represents an optionally substituted pyridine or pyrimidine group. It is further preferred that B represents a pyridine group which is unsubstituted or substituted by one or more halogen atoms

In an alternative embodiment of the present invention –L-G represents a moeity selected from the group consisting of hydrogen atoms, hydroxyl groups, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzyl, optionally substituted benzoyl, C_{3-7} cycloalkyl; C_{1-6} alkyl, optionally substituted morpholino, optionally substituted piperidino and optionally substituted piperazine groups wherein optionally substituted groups may carry from 0 to 2 substituents selected from the group consisting of halogen atoms, C_{1-4}alkyl, C_{1-4}alkylthio, C_{1-4}alkoxy, mono or di-C_{1-4}alkylamino, cyano, -(CO)OH, -(CO)O-C_{1-4}alkyl, trifluoromethyl, piperidinylmethyl, pyridinylmethyl, phenylamino and piperidinylamino.

Particular individual compounds of the invention for their use in the manufacture of a medicament for the treatment of a pathological condition or disease susceptible to improvement by antagonism of the A_{2B} adenosine receptor include:

6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one
2-Cyclopropyl-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
2-Cyclohexyl-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-methyl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
2-(4-Fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-(4-methoxyphenyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
N-{4-[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3H-imidazo[4,5-b]pyridin-2-yl]phenyl}-*N*,*N*-dimethylamine
6-(3-Fluoropyridin-4-yl)-2-(4-*tert*-butylphenyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-[4-(trifluoromethyl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine
Methyl 4-[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoate
4-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoic acid
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine
2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Fluoropyridin-4-yl)-2-[3-fluoro-4-(trifluoromethyl)phenyl]-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

2-(2,4-Dichloro-5-fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

2-(4-Fluorobenzyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

2-[1-(4-Chlorophenyl)-1-methylethyl]-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

(3,5-Difluorophenyl)[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone

N-(4-chlorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine

2-(4-Fluorophenyl)-5-pyridin-3-yl-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Chloropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5,6-Dipyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(3-Fluoropyridin-4-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(3-Chloropyridin-4-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(3-Chloropyridin-4-yl)-2-(4-fluorophenyl)-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Chloropyridin-4-yl)-5-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

6-(3-Chloropyridin-4-yl)-2-(4-fluorophenyl)-5-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

5-(3-Chloropyridin-4-yl)-2-(4-fluorophenyl)-6-(3-fluoropyridin-4-yl)-3*H*-imidazo[4,5-*b*]pyridine

5,6-Bis(3-chloropyridin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(1,3-Oxazol-2-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(1,3-Oxazol-2-yl)-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Fluoropyridin-4-yl)-5-(1,3-oxazol-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

6-(3-Fluoropyridin-4-yl)-5-(1,3-oxazol-2-yl)-3*H*-imidazo[4,5-*b*]pyridine

5-(1,3-Oxazol-5-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(1,3-Oxazol-5-yl)-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Fluoropyridin-4-yl)-5-(1,3-oxazol-5-yl)-3*H*-imidazo[4,5-*b*]pyridine

2-(3-Fluoro-4-methylphenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine.

2-(3-Fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Fluoropyridin-4-yl)-2,5-dipyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Fluoropyridin-4-yl)-2-pyrazin-2-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

3-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzonitrile

3-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoic acid;

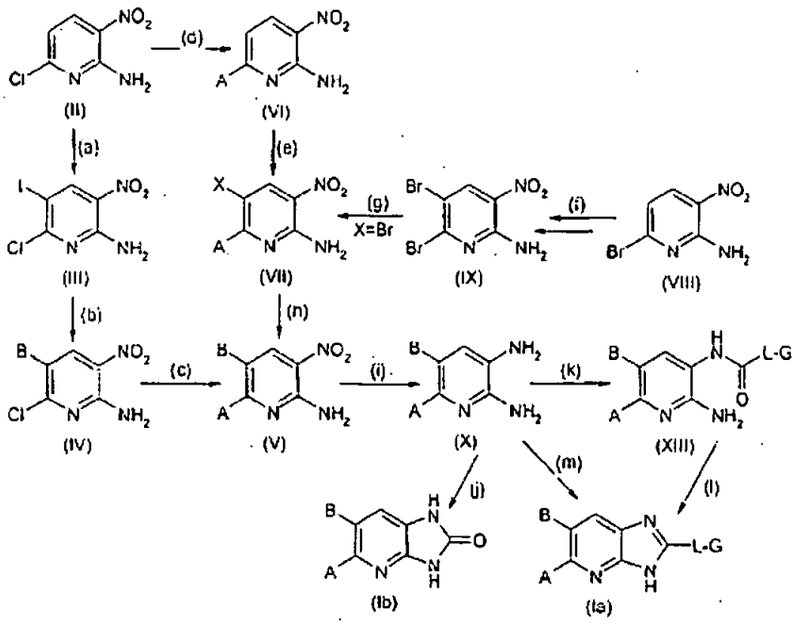
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-pyrimidin-5-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-pyridin-2-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
2-(3-Chloropyridin-4-yl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-(1-methyl-1*H*-imidazol-5-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-(methylthio)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
1-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]-1*H*-pyrazole-4-carboxylic acid
6-(3-Fluoropyridin-4-yl)-2-(1-methyl-1*H*-pyrazol-5-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-5-pyridin-3-yl-3H-imidazo[4,5-*b*]pyridine
2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-(4*H*-1,2,4-triazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-morpholin-4-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-piperidin-1-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-(4-methylpiperazin-1-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-[3-(trifluoromethyl)benzyl]-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-(2-phenylethyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-(2-pyridin-3-ylethyl)-3*H*-imidazo[4,5-*b*]pyridine
2-[1-(4-Chlorophenyl)ethyl]-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
4-{2-[6-(3-Fluoro-pyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]-ethyl}-benzoic acid
6-(3-Fluoropyridin-4-yl)-*N*,5-dipyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine
N-(4-Fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine
4-{[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]amino}benzoic acid
6-(3,5-Difluoropyridin-4-yl)-2-(4-fluorophenyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
4-[6-(3,5-Difluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoic acid
6-(3,5-Difluoropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

Of outstanding interest are:

5-(3-Fluoropyridin-4-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one
6-(3-Fluoropyridin-4-yl)-5-(1,3-oxazol-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one
4-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoic acid
6-(3-Fluoropyridin-4-yl)-2-(4-methoxyphenyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
N-(4-[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]phenyl)-*N*,*N*-dimethylamine
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine
2-(4-Fluorobenzyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
2-(3-Fluoro-4-methylphenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine.
2-(3-Fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2,5-dipyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-(1-methyl-1*H*-imidazol-5-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3,5-Difluoropyridin-4-yl)-2-(4-fluorophenyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
4-[6-(3,5-Difluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoic acid
6-(3,5-Difluoropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

Compounds of general formula (I) and in particular those wherein A, B are as defined in claim 1 and L represents a linking group selected from the group comprising direct bond, -$(CRR')_n$- or –CO- and G represents a group selected from the group comprising –H, -OH (general formula (XI)), C_{3-7} cycloalkyl; C_{1-4} alkyl, aryl, heteroaryl and nitrogen-containing saturated heterocyclic rings (general formula (XII)) may be prepared following the synthetic scheme depicted in scheme 1.

SCHEME 1



Step a

Halogenation of 6-chloro-3-nitropyridin-2-amine (II) using reagents such as I_2 or *N*-halosuccinimide in polar aprotic solvents such as DMF or mixtures of solvents DMSO:H_2O and at temperatures ranging from 0°C to 100°C yields dihalonitropyridin-2-amines (III).

Step b

Regioselective Suzuki or Stille-type coupling with the boronic acid or boronate derivative or the trialkyltin (preferably tributyltin) derivative of B using a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0), [1,1'-bis(diphenylphosphino)ferrocene] palladium(II)dichloride dichloromethane complex (1:1) or bis(triphenylphosphine) palladium(II)dichloride in solvents such as toluene, dioxane in the presence of an aqueous solution of a base such as sodium or caesium carbonate and at a temperature between 25°C to 110°C, or in solvents such as DMF using a copper catalyst and at a temperature between 25°C to 150°C provides compounds of general formula (IV).

Step c

A further Suzuki, Negishi or Stille-type coupling using the corresponding boronic acid or boronate derivative, the arylzinc derivative or the trialkyltin (preferably tributyltin) derivative of A under the standard procedures for Pd catalyzed reactions described above provides the 2-amino-3-nitropyridines (V).

Steps d and e

Alternatively, regioselective Suzuki, Stille or Negishy-type coupling of the corresponding derivative of A with 6-chloro-3-nitropyridin-2-amine (II), using the standard procedures for Pd catalyzed reactions described above, provides compounds of general formula (VI), which upon a halogenation step using the same protocols described above provides compounds of general formula (VII).

Steps f and g

Dihalopyridine derivatives (IX) are prepared by halogenation of 6-halopyridine derivatives (VIII) using reagents such as Br_2 or *N*-halosuccinimide in polar aprotic solvents such as DMF and at temperatures ranging from 0°C to 100°C, to yield dihaloaminopyridines (not shown). These products are in turn nitrated in a two step process involving nitration of the amino group in a mixture of sulphuric and nitric acid in a temperature range between –10°C to 0°C followed by a sulfuric acid promoted rearrangement of the nitro group to produce compounds of formula (IX). A further regioselective Suzuki, Negishi or Stille-type coupling with the corresponding derivative of A and using the standard procedures for Pd catalyzed reactions described above provides compounds of general formula (VII).

Steps h and i

A further Suzuki or Stille-type coupling with the corresponding derivative of B described above provides compounds of general formula (V). Reduction of the nitro group using standard hydrogenation conditions in the presence of hydrogen and using Pd on carbon as a catalyst provides the diamino derivatives (X). Alternatively, the reduction of the nitro group can also be accomplished by treatment with iron in the presence of hydrochloric acid in solvents such as ethanol.

Step j

Treatment of (X) with carbonylating agents such as carbonyldiimidazole in polar aprotic solvents such as DMF or THF in the presence or absence of a base such as sodium

hydride or triethylamine and heating at temperatures between 50°C and 200°C provides the imidazolone compounds (Ib).

Steps k and l

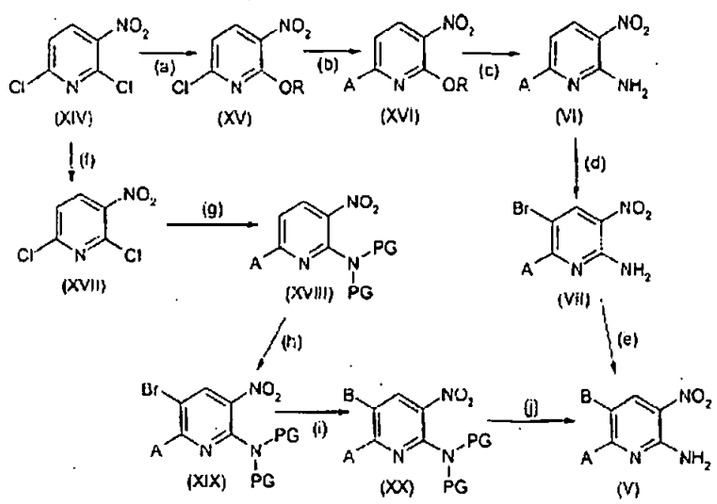
Treatment of compounds of formula (X) with acylating agents such as anhydrides, acid chlorides or acylcarbonates in apolar organic solvents such as THF and in the presence of a convenient organic base (such as triethylamine) or inorganic base, and eventually acylating with carboxylic acids using coupling agents such as diethylcarbodiimide, yields the compounds of formula (XIII), which can be converted into the compounds of formula (Ia) by acid (for example acetic acid) or base (for example sodium hydroxide) catalyzed cyclization at temperatures between 70°C and 200°C.

Step m

Alternatively, diamino derivatives (X) can be cyclized to the imidazopyridines (Ia) by heating in neat trialkylorthoacid or in an acetic acid solution of the orthoacid derivatives or by using an acyl chloride (Cl-CO-L-G) and a solvent such as pyridine and at temperatures between 70°C and 200°C.

By following another synthetic pathway (Scheme 2), intermediates (V) can also be accessed starting from 2,6-dichloro-3-nitropyridine (XIV)

SCHEME 2



Steps a to e

Displacement of the 2-chloro functionality of (XIV) with an alcohol, preferably methyl alcohol, in the presence of a base, preferably sodium hydride, in an organic solvent such as xylene leads to compounds of formula (XV). Reaction of (XV) under typical cross-coupling conditions with, for example, an aryl boronic acid or an aryl stannane, preferably a tributyl stannane, in the presence of a palladium catalyst such as such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene] palladium(II)dichloride dichloromethane complex (1:1) in solvents such as toluene or dioxane at temperatures ranging from 80°C -120°C gives rise to intermediates of type (XVI). Displacement of the alkoxy functionality of (XVI) by heating with concentrated aqueous ammonia at temperatures ranging from 80°C -120°C in a sealed vessel gives rise to intermediates of type (VI) which can be elaborated to intermediates (V) by using the protocols outlined in Scheme 1.

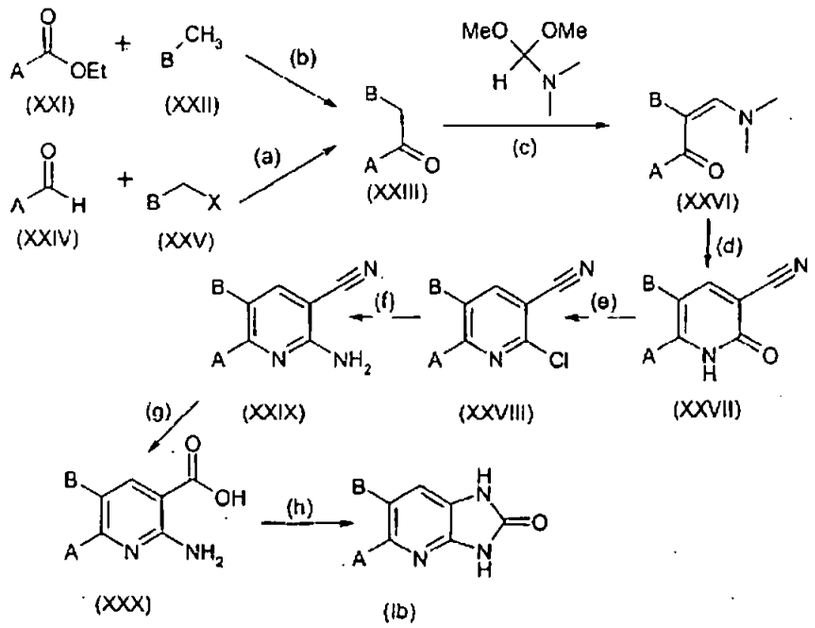
Steps f to i

Intermediates of type (V) can also be accessed via an alternative route (Scheme 2) starting from 2,6-dichloro-3-nitropyridine (XIV) Displacement of the 2-chloro functionality with a suitable secondary aliphatic amine, such as *N,N*-di(4-methoxy)benzylamine, in a suitable solvent such as chloroform in the presence of an organic base such as trietnylamine, at temperatures ranging from 0°C to 25°C gives to rise to intermediates of type (XVII), which may be considered a nitrogen protected version of compound (II). Reaction of (XVII)

under typical cross-coupling conditions with, for example, an aryl boronic acid or an aryl stannane in the presence of a palladium catalyst such as such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene] palladium(II)dichloride dichloromethane complex (1:1) in solvents such as toluene or dioxane at temperatures ranging from 80°C -120°C gives rise to intermediates of type (XVIII) which can be halogenated using reagents such as Br_2 or *N*-halosuccinimide in polar aprotic solvents such as DMF and at temperatures ranging from 0°C to 100°C, to yield compounds (XIX). A second palladium catalyzed cross coupling reaction give rise to intermediates (XX) which can be deprotected with, for example, trifluoroacetic acid in dichloromethane, to give the desired intermediates (V).

Compounds of general formula (Ib) corresponding to compounds of formula (I) wherein L is a direct bond, G is a hydroxy group and A and B as as defined in claim 1, may be prepared following the synthetic scheme depicted in scheme 3.

SCHEME 3



Step a

The aldehydes of formula (XXIV) are reacted with the halomethyl derivatives of formula (XXV) to yield the ketones of formula (XXIII) either *via* cyanohydrin intermediates or in a two step process involving addition of an organometallic derivative of (XXV), preferably magnesium or zinc derivative, followed by reoxidation of the resulting alcohol using oxidizing agents such as manganese (IV) oxide.

Step b

Alternatively the ketones of formula (XXIII) may be obtained by condensation of the ethyl esters of formula (XXI) with the compounds of formula (XXII). This reaction is conveniently carried out in the presence of an organic base such as lithium bis(trimethylsilyl)amide in a range of temperature about -10°C to about 50°C and in organic aprotic solvents, preferably tetrahydrofuran or diethyl ether.

Steps c to e

The ketones of formula (XXIII) are then reacted in neat *N,N*-dimethylformamide dialkyl acetal, such as dimethylacetal, at a temperature range between room temperature and 150°C to yield the dimethylamino α,β unsaturated ketone of formula (XXVI) which can be converted into the 2-oxo-1,2-dihydropyridine-3-carbonitriles of formula (XXVII) by cyclization in the presence of cyanoacetamide using alkoxides such as sodium methoxide in polar aprotic solvents such as dimethylformamide and at temperatures between 50°C to 150°C. These compounds may be converted into the 2-chloronicotinonitriles of formula (XXVIII) by treatment of the resulting pyridone (XXVII) with chlorinating agents such as $POCl_3$, PCl_5 and $PhPOCl_2$ or by using a combination of such reagents.

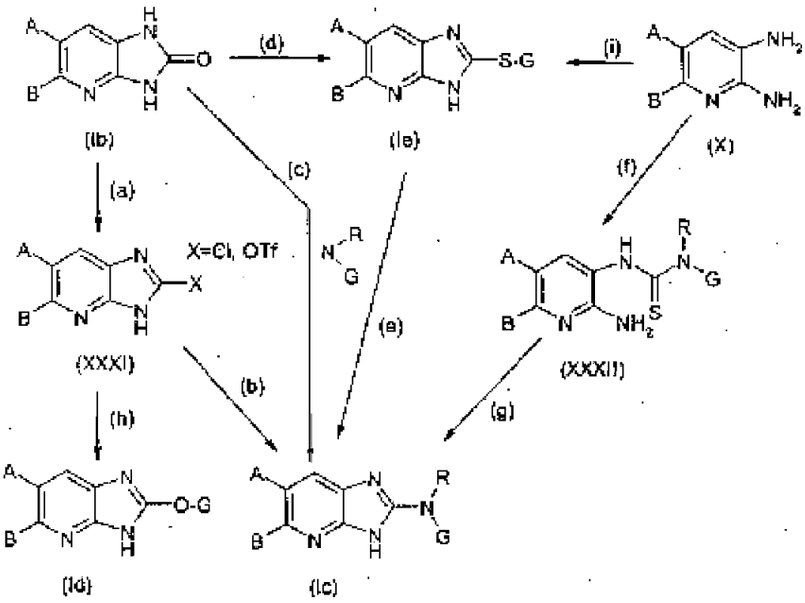
Steps f to h

2-Chloronicotinonitriles of formula (XXVIII) may be reacted with a saturated solution of ammonia in an organic solvent, preferably ethanol, at a temperature between 25°C to 150°C to yield the compounds of formula (XXIX). Hydrolysis of compounds (XXIX) to the carboxylic acid of formula (XXX) can be achieved with a base such as potassium hydroxide in aqueous or organic solvents such as ethylene glycol and at a temperature between 50°C to 200°C. Alternatively this conversion could be achieved under aqueous acidic media such as 6M sulphuric acid. These compounds may be subjected to Curtius rearrangement by formation and rearrangement of the acyl azide derivative which may be formed by reacting (XXX) with diphenylphosphoryl azide (or sodium azide with activated acid) in an organic solvent compatible with these reaction conditions (e.g. dioxane) and at a range of temperature between 0°C to 30°C followed by heating at a temperature ranging

between 50°C to 200°C, with *in situ* formation of the target pyridoimidazolone ring yielding compounds of formula (Ib).

Compounds of general formula (I) and in particular those wherein A, B are as defined in claim 1 and L represents a linking group selected from the group comprising -NR-, -S- or -O- and G represents a group selected from the group comprising C_{3-7} cycloalkyl; C_{1-4} alkyl, aryl, heteroaryl and nitrogen-containing saturated heterocyclic rings may be prepared following the synthetic scheme depicted in scheme 4.

SCHEME 4



Steps a to c

Compounds of general formula (XXXI) can be prepared from imidazolones (Ib) using reagents such as oxalyl chloride, phosphorus oxychloride, phosphorus pentachloride or a combination of them at a temperature ranging from 20° to 150°C in a solvent like

dichloromethane or acetonitrile. Alternatively, compounds (XXXI) may be prepared by treating imidazolones (Ib) with sodium hydride and then with trifluoromethansulfonyl chloride, trifluoromethansulphonyl anhydride or *N*-phenyl-bis(trifluoroethansulfonimide) in dimethylformamide at a range of temperatures between 20°C and 150°C. Compounds of general formula (XXXI) can be treated with primary or secondary amines at a range of temperatures between 40° and 170°C to give compounds of general formula (Ic). Alternatively, compounds of general formula (Ic) may be obtained by heating imidazolones (Ib) in the presence of a primary or secondary amine and a dehydrating agent like magnesium sulphate or molecular sieves.

Steps d, e and i

On the other hand, compounds of general formula (Ie) can be prepared from imidazolones (Ib) using reagents such as oxalyl chloride or phosporus chloride at a temperature ranging from 20° to 150°C and then with an aryl or alkyl thiol at a temperature between 60° to 150°C. Additionally, compounds of general formula (Ie) where G is an alkyl or cycloalkyl group can be prepared by reaction of diamines (X) with 1,1'-thiocarbonyldiimidazole followed by alkylation using the corresponding alkylhalides. Compounds (Ie) can then be heated up at a temperature between 60°C and 150°C in the presence of the primary or secondary amine to afford compounds of general formula (Ic). In some cases, oxidation to the corresponding sulfone or the use of catalytic Lewis acid such as zinc chloride may be needed.

Steps f and g

Diamines (X) may be treated with alkyl or aryl isothiocianates to give the thioureas of general formula (XXXII). Thioureas of formula (XXXII) can be treated with alkylcarbodiimides at room temperature or with the assistance of the microwaves to give compounds of general formula (Ic). Alternatively, thioureas of general formula (XXXII) may be treated under reductive conditions such as mercury oxide and sulphur to give compounds of general formula (Ic).

Step h

Compounds of general formula (Id) can be prepared by treating compounds of formula (XXXI) with aryloxy or alkyloxy nucleophiles such as sodium methoxide or lithium phenyl. Alternatively, compounds of general formula (Id) may be prepared from imidazolones (Ib) using sodium or potassium hydride and alkyl or arylalkyl halides or trifaltes in a solvent

such as dimethylformamide or tetrahydrofuran in a range of temperatures between -78° to 100°C.

EXPERIMENTAL

PHARMACOLOGICAL ACTIVITY

Adenosine 2B receptor subtype competition radioligand binding assay

A2B membranes were prepared from HEK293 cells stably expressing the human A2B receptor that were purchased from Euroscreen (ES-013-C). Competition assays were carried out incubating in polypropylene 96 well-plates (nº 267245, NUNC) containing 2 µl of either 1% DMSO solution, test compound or 100 µM 5`NECA (SIGMA E-2387) for non-specific binding, 100 µg of A2B-membranes (prepared in Tris-HCl 50 mM pH 6.5, $MgCl_2$ 10 mM, EDTA 1 mM, benzamidine 0.1 mM; buffer A) and 35 nM [^{3}H]-DPCPX (TRK1064, 128Ci/mmol, Amersham), in a total volume of 200 µl of buffer A + 2UI/ml adenosine deaminase, for 60 minutes at room temperature. At the end of the incubation, samples were transferred to a GF/C filter plates (Milipore MAFCN0B50) pretreated for 15 min. with 250 µl of Tris-HCl 50 mM pH 6.5 (Buffer B). Samples were then filtered 4 times with 250 µl of buffer B. Samples were counted using 30 µl of Hisafe II (Perkin Elmer) in a Trilux counter.

Table 1 shows the binding activitities of some of the compounds of the present invention determined using the adenosine 2B receptor subtype competition radioligand binding assay described above.

TABLE 1

Example	K_i
6	0.8
7	1.7
11	8
12	1.8
16	24
23	7

32	24
37	2.2
38	2.8
39	3.8
46	9.5
65	2.8
66	23
67	26

The compounds of formula (I) have been tested according to the assay described above and have shown to be potent inhibitors of the A_{2B} adenosine receptor subtype. Preferred imidazopyridine derivatives of the invention possess a K_i value for the antagonism of A_{2B} (determined as defined above) of less than 50 nM, preferably less than 10 nM and more preferably less than 5 nM.

The imidazopyridine derivatives of the invention are useful in the treatment or prevention of diseases known to be susceptible to improvement by treatment with an antagonist of the A_{2B} adenosine receptor. Such diseases include but are not limited to asthma, chronic obstructive pulmonary disorder, pulmonary fibrosis, emphysema, allergic diseases, inflammation, reperfusion injury, myocardial ischemia, atherosclerosis, hypertension, retinopathy, diabetes mellitus, inflammatory gastrointestinal tract disorders, and/or autoimmune diseases. Examples of autoimmune diseases which can be treated or prevented using the compounds of the invention are Addison's disease, autoimmune hemolytic anemia, Crohn's disease, Goodpasture's syndrome, Graves disease, Hashimoto's thyroiditis, idiopathic thrombocytopenic purpura, insulin-dependent diabetes mellitus, multiple sclerosis, myasthenia gravis, pemphigus vulgaris, pernicious anemia, poststreptococcal glomerulonephritis, psoriasis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, spontaneous infertility, and systemic lupus erythematosus.

Accordingly, the imidazopyridine derivatives of the invention and pharmaceutical compositions comprising such compounds and/or salts thereof may be used in a method of treatment of disorders of the human or animal body which comprises administering to a subject requiring such treatment an effective amount of imidazopyridine derivative of the invention or a pharmaceutically acceptable salt thereof.

When imidazopyridine derivatives of the invention are used for the treatment of respiratory diseases such as asthma, chronic obstructive pulmonary disorder, pulmonary fibrosis or emphysema it may be advantageous to use them in combination with other active compounds known to be useful in the treatment of respiratory diseases such as (1) antagonists of M3 muscarinic receptors, (2) β2-agonists, (3) PDE4 inhibitors, (4) cortiocosteroids, (5) leukotriene D4 antagonists, (6) inhibitors of egfr-kinase, (7) p38 kinase inhibitors, (8) NK1 receptor agonists, (9) CRTh2 antagonists, (10) syk kinase inhibitors, (11) CCR3 antagonists and (12) VLA-4 antagonists.

Thus, the present invention also provides pharmaceutical compositions comprising a imidazopyridine derivative of the invention and another active compound selected from the groups consisting of (1) antagonists of M3 muscarinic receptors, (2) β2-agonists, (3) PDE 4 inhibitors, (4) cortiocosteroids, (5) leukotriene D4 antagonists, (6) inhibitors of egfr-kinase, (7) p38 kinase inhibitors, (8) NK1 receptor agonists, (9) CRTh2 antagonists, (10) syk kinase inhibitors , (11) CCR3 antagonists and (12) VLA-4 antagonists.

The present invention also provides pharmaceutical compositions which comprise, as an active ingredient, at least a imidazopyridine derivative of formula (I) in association with a pharmaceutically acceptable excipient such as a carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight of the composition depending upon the nature of the formulation and whether further dilution is to be made prior to application. Preferably the compositions are made up in a form suitable for oral, topical, nasal, rectal, percutaneous, injectable administration or inhalation.

The pharmaceutically acceptable excipients which are admixed with the active compound or salts of such compound, to form the compositions of this invention are well-known *per se* and the actual excipients used depend *inter alia* on the intended method of administering the compositions.

Compositions of this invention are preferably adapted for inhaled, injectable or oral administration. The compositions for oral administration may take the form of tablets, retard tablets, sublingual tablets, capsules or liquid preparations, such as mixtures, elixirs, syrups or suspensions. The compositions for inhalation may take the form of inhalation

aerosols, inhalation solutions or dry powders for inhalation all containing the compound of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 2 and 500 mg of active ingredient or the equivalent amount of a salt thereof.

The liquid composition adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or a pharmaceutically acceptable salt thereof in association with water, together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in pyrogen free aqueous media or other appropriate parenteral injection fluid.

When the compositions are intended for inhalation they may be in the form of spray compositions for topical delivery to the lung by inhalation or in the form of dry powder compositions for topical delivery to the lung by inhalation.

The spray composition for inhalation may, for example, be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in different primary packaging systems (such as capsules and cartridges of for example gelatine or blisters of for example laminated aluminium foil), for use in an inhaler or insufflator. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi- dose delivery, the formulation can be pre-metered or metered in use. Dry powder inhalers are thus classified into three groups: (a) single dose, (b) multiple unit dose and (c) multi dose devices.

Dry powder formulations generally contain a powder mix for inhalation of the compounds of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 2µg and 400 µg of each therapeutically active ingredient. Alternatively, the active ingredient (s) may be presented without excipients.

Effective doses are normally in the range of 2-2000 mg of active ingredient per day. Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples (1 to 36) including Preparation Examples (Intermediates 1 to 13) which do not limit the scope of the invention in any way.

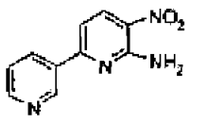
^{1}H Nuclear Magnetic Resonance Spectra were recorded on a Varian Mercury spectrometer operating at 200 MHz. Melting points were recorded using a Büchi B-540 apparatus. The chromatographic separations were obtained using a Waters 2795 system equipped with a Symmetry C18 (2.1 x 100 mm, 3.5 mm) column. As detectors a Micromass ZMD mass spectrometer using ES ionization and a Waters 996 Diode Array detector were used. The mobile phase was formic acid (0.46 ml), ammonia (0.115 ml) and water (1000 ml) (A) and formic acid (0.4 ml), ammonia (0.1 ml), methanol (500 ml) and acetonitrile (500 ml) (B): initially from 0% to 95% of B in 20 min, and then 4 min. with 95% of B. The reequilibration time between two injections was 5 min. The flow rate was 0.4 ml/min. The injection volume was 5 µl. Diode array chromatograms were processed at 210 nm.

PREPARATION EXAMPLES

Intermediate 1:

3''-Fluoro-3,2':3',4''-terpyridine-5',6'-diamine

Step a:



5-Nitro-2,3'-bipyridin-6-amine

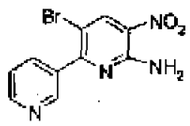
32

An oven dried resealable Schlenk tube was charged with 6-chloro-3-nitropyridin-2-amine (5 g, 28.81 mmol), 3-pyridineboronic acid (5.31 g, 43.2 mmol), dioxane (250 mL) and a 2M aqueous solution of cesium carbonate (43 mL, 86.4 mmol). The Schlenk tube was subjected to three cycles of evacuation-backfilling with argon, and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (2.3 g, 2.81 mmol) was added. After three new cycles of evacuation-backfilling with argon, the Schlenk tube was capped and placed in a 100°C oil bath. After 3h, the mixture was cooled, partitioned between water and ethyl acetate, the aqueous phase extracted twice with ethyl acetate, the organic layers washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel flash chromatography (95:5 dichloromethane/methanol) to give the title compound (4.8 g, 77%) as a solid.

δ ^{1}H-NMR ($CDCl_3$): 1.64 (s, 2H), 7.20-7.25 (d, 1H), 7.44-7.46 (m, 1H), 8.32-8.36 (d, 1H), 8.52-8.56 (d, 1H), 8.70-8.74 (m, 1H), 9.22-9.26 (m, 1H).

ESI/MS m/e: 217 ([M+H]$^+$, $C_{10}H_8N_4O_2$)

Step b:



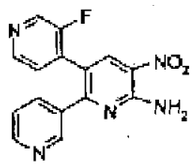
3-Bromo-5-nitro-2,3'-bipyridin-6-amine

To a 0°C cooled stirred solution of 5-nitro-2,3'-bipyridin-6-amine (4.8 g, 22.2 mmol) in DMF (50 mL), *N*-bromosuccinimide (4.75 g, 26.7 mmol) was added in portions. After stirring at room temperature for 16h, the solvent was removed under reduced pressure. The crude residue was solved with ethyl acetate and washed with saturated potassium carbonate aqueous solution. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel flash chromatography (95:5 dichloromethane/methanol) to give the title compound (6.6 g, 100%) as a solid.

δ ^{1}H-NMR ($CDCl_3$): 1.60 (s, 2H), 7.40-7.46 (dd, 1H), 8.03-8.09 (m, 1H), 8.67-8.77 (m, 2H), 8.93-9.02 (m, 1H).

ESI/MS m/e: 295, 297 ([M]$^+$, [M+2]$^+$,$C_{10}H_7BrN_4O_2$)

Step c:



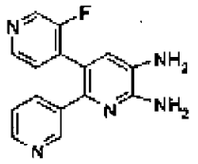
3''-Fluoro-5'-nitro-3,2':3',4''-terpyridin-6'-amine

An oven dried resealable Schlenk tube was charged with 3-bromo-5-nitro-2,3'-bipyridin-6-amine (4.51 g, 15.3 mmol), 3-fluoro-4-(tributylstannyl)pyridine (11.8 g, 30.6 mmol) and dimethylformamide (150 mL). The Schlenk tube was subjected to three cycles of evacuation-backfilling with argon, and bis(triphenylphosphino)-palladium (II) chloride (1.1 g, 1.53 mmol) and copper (I) iodide (291 mg, 1.53 mmol) were added. After three new cycles of evacuation-backfilling with argon, the Schlenk tube was capped and placed in a 160°C oil bath. After 3h, the solvent was evaporated and the crude residue was treated with 2N hydrogen chloride (130 mL) aqueous solution for 45 minutes. The aqueous solution was washed with ethyl acetate and then neutralised with 6N sodium hydroxide aqueous solution. The solution was extracted with ethyl acetate, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel flash chromatography (95:5 dichloromethane/methanol) to give the title compound (2.39 g, 51%) as a solid.

δ ^{1}H-NMR ($CDCl_3$): 7.32-7.39 (m, 1H), 7.47-7.53 (dd, 1H), 7.66-7.72 (m, 1H), 8.43-8.45 (m, 2H), 8.48-8.50 (dd, 1H), 8.52-8.57 (m, 2H).

ESI/MS m/e: 312 ($[M+H]^+$, $C_{15}H_{10}FN_5O_2$)

Step d:



3''-Fluoro-3,2':3',4''-terpyridine-5',6'-diamine

A suspension of 3''-fluoro-5'-nitro-3,2':3',4''-terpyridin-6'-amine (2.25 g, 7.23 mmol) and 10% palladium on carbon (0.4 g) in a mixture of THF/ ethanol 40:60 (100 mL) was stirred under hydrogen atmosphere. After 3h, the mixture was filtered through Celite® and the filter cake was washed with ethanol. The combined filtrate and washings were evaporated to give the title compound as a solid (2.01 g, 99%).

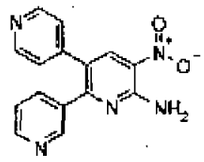
δ ^{1}H-NMR ($CDCl_3$): 5.10 (s, 2H), 5.95 (s, 2H), 6.75 (s, 1H), 7.18-7.30 (m, 2H), 7.49-7.55 (m, 1H), 8.29-8.31 (m, 1H), 8.32-8.34 (m, 1H), 8.35-8.38 (m, 1H), 8.40 (m, 1H).

ESI/MS m/e: 281 ($[M+H]^+$, $C_{15}H_{12}FN_5$)

Intermediate 2:

3,2':3',4''-Terpyridine-5',6'-diamine

Step a:



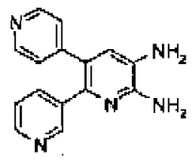
5'-Nitro-3,2':3',4''-terpyridin-6'-amine

Obtained (220 mg, 22%) from 3-bromo-5-nitro-2,3'-bipyridin-6-amine (**Intermediate 1-Step b**, 1.0 g, 3.4 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (764 mg, 3.73 mmol) following the same procedure described in Intermediate 1, step a.

δ ^{1}H NMR (DMSO-d_6): 7.17 (d, 1H), 7.35 (dd, 1H), 7.68-7.40 (m, 3H), 7.82 (d, 1H), 8.22 (broad s, 1H), 8.50-8.40 (m, 2H), 8.53 (broad d, 1H), 8.69 (broad s, 1H).

ESI/MS m/e: 294 ([M+H]$^+$, $C_{15}H_{11}N_5O_2$).

Step b:



3,2':3',4''-Terpyridine-5',6'-diamine

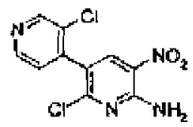
Obtained (148 mg, 75%) from 5'-nitro-3,2':3',4''-terpyridin-6'-amine (220 mg, 0.75 mmol) following the same protocol described in Intermediate 1, step d.

ESI/MS m/e: 264 ([M+H]$^+$, $C_{15}H_{13}N_5$).

Intermediate 3:

3''-Chloro-3,2':3',4''-terpyridine-5',6'-diamine

Step a:



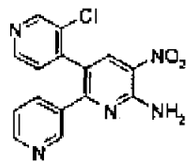
2,3'-Dichloro-5-nitro-3,4'-bipyridin-6-amine

Following the same procedure as in Intermediate 1 (step a), but using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-chloropyridine, 6-chloro-5-iodo-3-nitropyridin-2-amine (**Intermediate 5 - step a**) was transformed into the title compound as a white solid (205 mg, 22%).

δ ^{1}H NMR ($CDCl_3$): 7.28 (d, 1H), 8.39 (s, 1H), 8.61 (d, 1H), 8.75 (s, 1H).

ESI/MS m/e: 286 ([M+H]$^+$, $C_{10}H_6Cl_2N_4O_2$).

Step b:

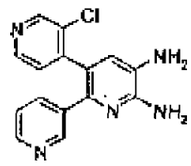


3"-Chloro-5'-nitro-3,2':3',4"-terpyridin-6'-amine

Following the same procedure as in Intermediate 1 (step a), 2,3'-dichloro-5-nitro-3,4'-bipyridin-6-amine afforded the title compound as a brownish solid (127 mg, 54%).

ESI/MS m/e: 328 ($[M+H]^+$, $C_{15}H_{10}ClN_5O_2$).

Step c:



3"-Chloro-3,2':3',4"-terpyridine-5',6'-diamine

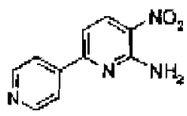
3"-chloro-5'-nitro-3,2':3',4"-terpyridin-6'-amine (127 mg, 0.39 mmol) was dissolved in EtOH (4.0 mL) and conc. HCl (245 µL). Iron metal (109 mg, 1.09 mmol) was added to the suspension and the mixture was heated to 70 °C for 1 h. The suspension was then filtered through Celite® and the solvent removed *in vacuo*. $NaHCO_3$ (20 mL of a 4% w/w aqueous solution) was added to the residue and the aqueous phase was extracted with AcOEt (3 x 20 mL). The organic layer was dried, filtered and concentrated to dryness to yield the title compound (52 mg, 45%), which was used without further purification.

ESI/MS m/e: 298 ($[M+H]^+$, $C_{15}H_{12}ClN_5$).

Intermediate 4:

4,2':3',4"-Terpyridine-5',6'-diamine

Step a:



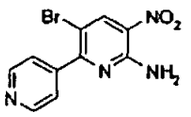
5-Nitro-2,4'-bipyridin-6-amine

Obtained (0.240g, 96% of yield) from 6-chloro-3-nitropyridin-2-amine (0.2 g, 1.15 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (0.308 g, 1.50 mmol) following the procedure described in Intermediate 1, step a.

δ ^{1}H-NMR ($CDCl_3$): 7.23-7.27 (d, 1H), 7.87-7.90 (m, 2H), 8.54-8.58 (d, 1H), 8.76-8.79 (m, 2H).

ESI/MS m/e: 217 ([M+H]$^+$, $C_{10}H_8N_4O_2$)

Step b:

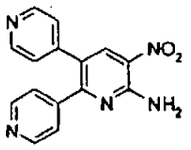


3-Bromo-5-nitro-2,4'-bipyridin-6-amine

Obtained (0.246 g, 76% of yield) from 5-nitro-2,4'-bipyridin-6-amine (0.240 g, 1.11 mmol) following the procedure described in Intermediate 1, step b.

ESI/MS m/e: 295, 297 ([M]$^+$, [M+2]$^+$, $C_{10}H_7BrN_4O_2$)

Step c:

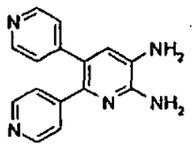


5'-Nitro-4,2':3',4''-terpyridin-6'-amine

Obtained (0.144 g, 60% of yield) from 3-bromo-5-nitro-2,4'-bipyridin-6-amine (0.240 g, 0.813 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (0.250 g, 1.220 mmol) following the procedure described in Intermediate 1, step c.

ESI/MS m/e: 294 ([M+H]$^+$, $C_{15}H_{11}N_5O_2$)

Step d:



4,2':3',4''-Terpyridine-5',6'-diamine

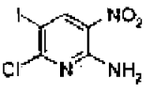
To a solution of 5'-nitro-4,2':3',4''-terpyridin-6'-amine (0.144 g, 0.490 mmol) in ethanol (5 mL), 0.300 mL of hydrogen chloride and 0.140 g (2.45 mmol) of iron were added. The mixture was heated at 90°C for 2h and the solvent was evaporated. The crude mixture was extracted between ethyl acetate and water. The organic layer was dried ($MgSO_4$) and the solvent evaporated to give the title compound (0.120 g, 93% of yield).

ESI/MS m/e: 264 ([M+H]$^+$, $C_{15}H_{13}N_5$)

Intermediate 5:

3-Fluoro-4,2':3',4"-terpyridine-5',6'-diamine

Step a:



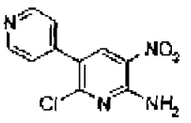
6-Chloro-5-iodo-3-nitropyridin-2-amine

To a suspension of 6-chloro-3-nitropyridin-2-amine (6.3 g, 36.3 mmol)in ethanol (110 mL), 9.2 g (36.3 mmol) of iodine and 11.32 g (36.3 mmol) of silver sulphate were added. The crude mixture was stirred at room temperature overnight and the precipitate formed was filtered off. The solid isolated was purified by flash chromatography (1:1 hexane/ethyl acetate) to give the title compound (9.74 g, 88% of yield).

δ ^{1}H-NMR ($CDCl_3$): 1.56 (s, 2H), 8.76 (s, 1H).

ESI/MS m/e: 300 ([M+H]$^+$, $C_5H_3ClIN_3O_2$)

Step b:

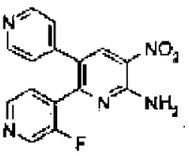


2-Chloro-5-nitro-3,4'-bipyridin-6-amine

Obtained (0.666 g, 80% of yield) from 6-chloro-5-iodo-3-nitropyridin-2-amine (1 g, 3.34 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (0.754 g, 3.67 mmol) following the procedure described in Intermediate 1, step a.

ESI/MS m/e: 251 ([M+H]$^+$, $C_{10}H_7ClN_4O_2$)

Step c:



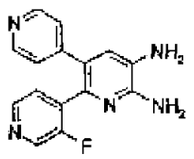
3-Fluoro-5'-nitro-4,2':3',4"-terpyridin-6'-amine

Obtained (0.214 g, 69% of yield) from 2-chloro-5-nitro-3,4'-bipyridin-6-amine (0.250 g, 1 mmol) and 3-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (0.445 g, 2 mmol) following the procedure described in Intermediate 1, step a.

δ ^{1}H-NMR ($CDCl_3$): 1.24 (s, 2H), 7.04-7.07 (m, 2H), 7.39-7.45 (m, 2H), 8.37 (s, 1H), 8.51-8.57 (m, 3H).

ESI/MS m/e: 312 ([M+H]$^+$, $C_{15}H_{10}FN_5O_2$)

Step d:



3-Fluoro-4,2':3',4"-terpyridine-5',6'-diamine

Obtained (0.183 g, 94% of yield) from 3-fluoro-5'-nitro-4,2':3',4"-terpyridin-6'-amine (0.215 g, 0.69 mmol) following the procedure described in Intermediate 1, step d.

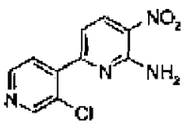
δ ^{1}H-NMR ($CDCl_3$): 1.26 (s, 4H), 7.00-7.05 (m, 3H), 7.37-7.43 (m, 1H), 8.27 (s, 1H), 8.40-8.48 (m, 3H).

ESI/MS m/e: 282 ([M+H]$^+$, $C_{15}H_{12}FN_5$)

Intermediate 6:

3-Chloro-4,2':3',4"-terpyridine-5',6'-diamine

Step a:



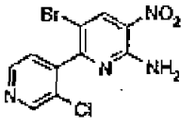
3'-Chloro-5-nitro-2,4'-bipyridin-6-amine

Following the same procedure as in Intermediate 1 (step a), but using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-chloropyridine, 6-chloro-3-nitropyridin-2-amine was transformed into the title compound as a white solid (2.14 g, 99%).

δ ^{1}H NMR ($CDCl_3$): 7.15 (d, 1H), 7.52 (d, 1H), 8.55 (d, 1H), 8.62 (d, 1H), 8.73 (s, 1H).

ESI/MS m/e: 251 ([M+H]$^+$, $C_{10}H_7ClN_4O_2$).

Step b:



3-Bromo-3'-chloro-5-nitro-2,4'-bipyridin-6-amine

Following the same procedure as in Intermediate 1 (step b) 3'-chloro-5-nitro-2,4'-bipyridin-6-amine afforded the title compound as a brownish solid (2.04 g, 93%).

δ ^{1}H NMR ($CDCl_3$): 7.25 (d, 1H), 8.64 (d, 1H), 8.73 (s, 1H), 8.74 (d, 1H).

ESI/MS m/e: 328,330 ([M]$^+$, [M+2]$^+$, $C_{10}H_6BrClN_4O_2$).

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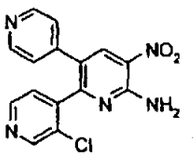
Step c:



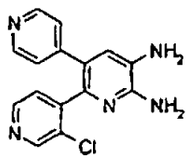
3-Chloro-5'-nitro-4,2':3',4''-terpyridin-6'-amine

Following the same procedure as in Intermediate 1 (step a), but using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 3-bromo-3'-chloro-5-nitro-2,4'-bipyridin-6-amine was converted to the title compound as yellowish solid (0.84 g, 85%).

δ ^{1}H NMR ($CDCl_3$): 7.03 (broad d, 2H), 7.25 (d, 1H), 8.51 (broad d, 2H), 8.55 (d, 1H), 8.57 (s, 1H), 8.59 (s, 1H).

ESI/MS m/e: 328 ($[M+H]^+$, $C_{15}H_{10}ClN_5O_2$).

Step d:



3-Chloro-4,2':3',4''-terpyridine-5',6'-diamine

Following the same procedure as in Intermediate 1 (step d), 3-chloro-5'-nitro-4,2':3',4''-terpyridin-6'-amine gave the title compound as white solid (0.78 g, >99%).

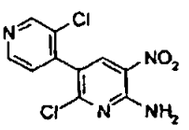
δ ^{1}H NMR (DMSO): 5.14 (broad s, 2H), 5.94 (broad s, 2H), 6.83 (s, 1H), 6.95 (broad d, 2H), 7.32 (d, 1H), 8.33 (broad d, 2H), 8.42 (d, 1H), 8.46 (s, 1H).

ESI/MS m/e: 298 ($[M+H]^+$, $C_{15}H_{12}ClN_5$).

Intermediate 7:

3''-Chloro-4,2':3',4''-terpyridine-5',6'-diamine

Step a:

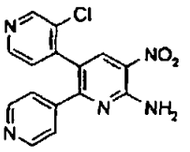


2,3'-Dichloro-5-nitro-3,4'-bipyridin-6-amine

Obtained (0.118 g, 41% of yield) from 6-chloro-5-iodo-3-nitropyridin-2-amine (0.3 g, 1 mmol) and 3-chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (0.311 g, 1.3 mmol) following the procedure described in Intermediate 3, step a.

ESI/MS m/e: 285 ($[M+H]^+$, $C_{10}H_6Cl_2N_4O_2$)

Step b:



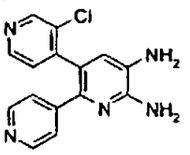
3''-Chloro-5'-nitro-4,2':3',4''-terpyridin-6'-amine

Obtained (0.130 g, 99% of yield) from 2,3'-dichloro-5-nitro-3,4'-bipyridin-6-amine (0.120 g, 0.42 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (0.130 g, 0.63 mmol) following the procedure described in Intermediate 1, step a.

δ ^{1}H-NMR ($CDCl_3$): 1.24 (s, 2H), 7.12-7.23 (m, 3H), 7.40-7.64 (m, 1H), 8.48-8.57 (m, 2H), 8.61 (s, 1H).

ESI/MS m/e: 328 ($[M+H]^+$, $C_{15}H_{10}ClN_5O_2$)

Step c:

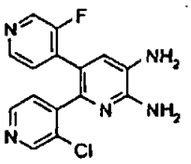


3''-Chloro-4,2':3',4''-terpyridine-5',6'-diamine

Obtained (0.082 g, 62% of yield) from 3''-chloro-5'-nitro-4,2':3',4''-terpyridin-6'-amine (0.145 g, 0.443 mmol) following the procedure described in Intermediate 4, step d.

ESI/MS m/e: 298 ($[M+H]^+$, $C_{15}H_{12}ClN_5$)

Intermediate 8:



3-Chloro-3''-fluoro-4,2':3',4''-terpyridine-5',6'-diamine

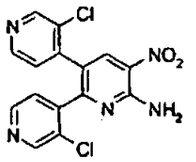
Obtained as a white solid (24%) from 3-bromo-3'-chloro-5-nitro-2,4'-bipyridin-6-amine (**Intermediate 6-step b**) and 3-fluoro-4-(tributylstannyl)pyridine, following the same procedure as in Intermediate1 (step c).

ESI/MS m/e: 316 ($[M+H]^+$, $C_{15}H_{11}ClFN_5$).

Intermediate 9:

3,3''-Dichloro-4,2':3',4''-terpyridine-5',6'-diamine

Step a:

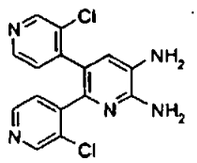


3,3''-Dichloro-5'-nitro-4,2':3',4''-terpyridin-6'-amine

Obtained (0.034 g, 10% of yield) from 6-chloro-5-iodo-3-nitropyridin-2-amine (0.3 g, 1 mmol) and 3-chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (0.311 g, 1.3 mmol) following the procedure described in Intermediate 1, step a.

ESI/MS m/e: 362 ([M+H]$^+$, $C_{15}H_9Cl_2N_5O_2$)

Step b:



3,3''-Dichloro-4,2':3',4''-terpyridine-5',6'-diamine

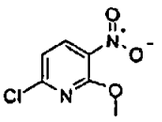
Obtained (0.029 g, 72% of yield) from 3,3''-dichloro-5'-nitro-4,2':3',4''-terpyridin-6'-amine (0.045 g, 0.123 mmol) following the procedure described in Intermediate 4, step d.

ESI/MS m/e: 332 ([M+H]$^+$, $C_{15}H_{11}Cl_2N_5$)

Intermediate 10:

2-(1,3-Oxazol-2-yl)-3,4'-bipyridine-5,6-diamine

Step a:



6-Chloro-2-methoxy-3-nitropyridine

Methanol (3.3 g, 103 mmol) in xylene (100 mL) was added dropwise to a stirred suspension of sodium hydride (60% in mineral oil, 2.72 g, 113 mmol) in xylene (300 mL) at 0 °C under an argon atmosphere. After 20 minutes, 2,6-dichloro-3-nitropyridine (20.0 g, 103 mmol) in xylene (300 mL) was added dropwise then the reaction was warmed to ambient temperature and stirred overnight. Water (200 mL) was then added and the two phases were separated. The organic layer was washed with water and brine, dried

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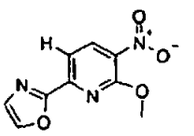
($MgSO_4$) and evaporated. The residue was purified by flash chromatography (10:1 hexanes/ethyl acetate) to give the title compound (15.3 g, 78%) as a white solid.

δ ^{1}H-NMR ($CDCl_3$): 4.10 (s, 3H), 7.05 (d, 1H), 8.28 (d, 1H).

Step b:



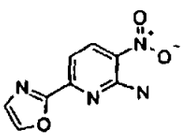
2-Methoxy-3-nitro-6-(1,3-oxazol-2-yl)pyridine

An oven-dried resealable Schlenk tube was charged with 6-chloro-2-methoxy-3-nitropyridine (0.50 g, 2.6 mmol), 2-tributylstannanyloxazole (1.20 g, 3.4 mmol) and 1,4-dioxane (10 mL) and then subjected to several cycles of evacuation-backfilling with argon. Tetrakis(triphenylphosphine)palladium (0.18 g, 0.16 mmol) was then added and, after three new cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred and heated in an oil bath to 110 °C. After stirring overnight, water and ethyl acetate were added and the organic layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (2:1 hexanes/ethyl acetate) to give the title compound (0.38 g, 67%) as a yellow solid.

δ ^{1}H-NMR ($CDCl_3$): 4.24 (s, 3H), 7.38 (s, 1H), 7.84 (d, 1H), 7.87 (s, 1H), 8.40 (d, 1H).

ESI/MS m/e: 222 ([M+H]+, $C_9H_7N_3O_4$)

Step c:



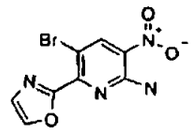
3-Nitro-6-(1,3-oxazol-2-yl)pyridin-2-amine

A suspension of 2-methoxy-3-nitro-6-(1,3-oxazol-2-yl)pyridine (0.187 g, 0.85 mmol) in aqueous ammonia (32%, 5 mL) was heated in a sealed tube to 100 °C with stirring. After 2.5 hours the mixture was cooled and the precipitate was filtered and washed with water and then dried in vacuo to give the title compound (0.134 g, 77%) as a yellow solid.

δ ^{1}H-NMR (DMSO-d_6): 7.41 (d, 1H), 7.53 (s, 1H), 8.14 (s, 2H), 8.38 (s, 1H), 8.53 (d, 1H).

ESI/MS m/e: 207 ([M+H]+, $C_6H_6N_4O_3$)

Step d:



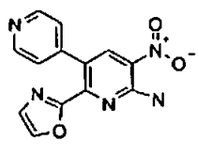
5-Bromo-3-nitro-6-(1,3-oxazol-2-yl)pyridin-2-amine

To a stirred solution of 3-nitro-6-(1,3-oxazol-2-yl)pyridin-2-amine (0.127 g, 0.62 mmol) in dimethylformamide (3 mL) at 0 °C was added *N*-bromosuccinimide (0.115 g, 0.65 mmol) and the mixture was warmed to room temperature. After 3 days, further N-bromosuccinimide (0.058 g, 0.33 mmol) was added and stirring was continued for 3 hours. The solution was poured into water and the precipitate was filtered, washed with water and dried to give the title compound (0.18 g, 70%) as a yellow solid.

δ ^{1}H NMR (DMSO-d_6): 7.56 (s, 1H), 8.19 (s, 2H), 8.41 (s, 1H), 8.68 (s, 1H).

ESI/MS m/e: 285/287 ([M+H]+, $C_8H_5BrN_4O_3$)

Step e:



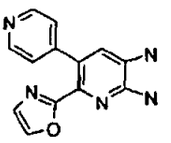
5-Nitro-2-(1,3-oxazol-2-yl)-3,4'-bipyridin-6-amine

An oven-dried resealable Schlenk tube was charged with 5-bromo-3-nitro-6-(1,3-oxazol-2-yl)pyridin-2-amine (0.141 g, 0.49 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.203 g, 0.99 mmol), dioxane (5 mL) and a 2M aqueous solution of cesium carbonate (0.74 mL, 1.48 mmol). The Schlenk tube was subjected to three cycles of evacuation-backfilling with argon, and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex [$PdCl_2$dppf.DCM] (0.024 g, 0.03 mmol) was added. After three new cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred and heated in an oil bath to 95 °C. After 20 hours, the mixture was cooled and partitioned between 2M aqueous hydrochloric acid and ethyl acetate. The aqueous phase was filtered through Celite® and the pH was adjusted to 5-6 with solid sodium hydroxide. The suspension was cooled in an ice bath and the precipitate was filtered, washed with water and dried to give the title compound (0.090 g, 65%) as a yellow solid.

δ ^{1}H-NMR (DMSO-d_6): 7.24 (d, 2H), 7.33 (s, 1H), 8.24 (s, 1H), 8.29 (s, 2H), 8.43 (s, 1H), 8.52 (d, 2H).

ESI/MS m/e: 284 ([M+H]+, $C_{13}H_9N_5O_3$)

Step f:



2-(1,3-Oxazol-2-yl)-3,4'-bipyridine-5,6-diamine

A suspension of 5-nitro-2-(1,3-oxazol-2-yl)-3,4'-bipyridin-6-amine (0.089 g, 0.31 mmol) and palladium on carbon (10%, 20 mg) in ethanol (15 mL) was placed under a hydrogen atmosphere (balloon) and stirred at room temperature. After 3 hours, the mixture was filtered through Celite® and the filtrate was evaporated. Trituration with diethyl ether gave the title compound (0.077 g, 97%) as a pale orange solid.

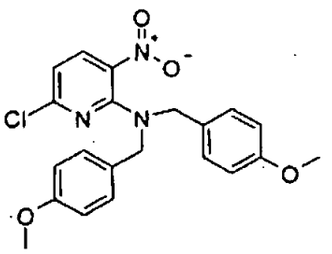
δ ^{1}H-NMR ($CDCl_3$): 6.87 (s, 1H), 7.13 (m, 3H), 7.49 (s, 1H), 8.56 (d, 2H).

ESI/MS m/e: 254 ([M+H]+, $C_{13}H_{11}N_5O$)

Intermediate 11:

3'-Fluoro-2-(1,3-oxazol-2-yl)-3,4'-bipyridine-5,6-diamine

Step a:



6-Chloro-*N*,*N*-bis(4-methoxybenzyl)-3-nitropyridin-2-amine

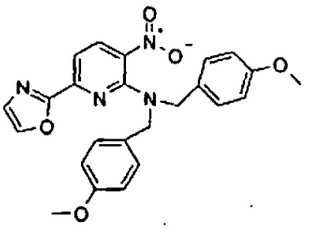
A solution of N,N-bis(4-methoxybenzyl)amine (7.79 g, 30.3 mmol) and triethylamine (2.89 g, 28.6 mmol) in chloroform (20 mL) was added dropwise over 20 minutes to a cold (ice-bath), stirred solution of 2,6-dichloro-3-nitropyridine (5.0 g, 26.0 mmol) in chloroform (25 mL). The mixture was warmed to room temperature and stirred overnight. The solvent was evaporated and the mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give an oil. The mixture was taken up in dichloromethane (120 mL) and polymer-supported isocyanate resin (1.6 mmol/g, 8.0 g) was added and the mixture was shaken at room temperature for

2 days. The mixture was filtered and the filtrate was evaporated to give the title compound (10.7 g, 100%) as a bright yellow oil.

δ ^{1}H-NMR ($CDCl_3$): 3.78 (s, 6H), 4.51 (s, 4H), 6.68 (d, 2H), 6.80 (d, 4H), 8.23 (d, 4H), 8.02 (d, 1H).

ESI/MS m/e: 414 ([M+H]+, $C_{21}H_{20}ClN_3O_4$)

Step b:



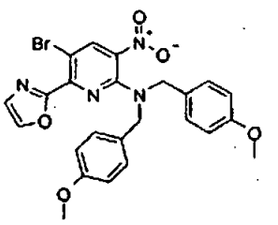
2-*N*,*N*-bis(4-methoxybenzyl)-3-nitro-6-(1,3-oxazol-2-yl)pyridine

Obtained (79%) from 6-chloro-N,N-bis(4-methoxybenzyl)-3-nitropyridin-2-amine and 2-tributylstannanyloxazole, following the procedure described in Preparation 10, step b.

δ ^{1}H-NMR ($CDCl_3$): 3.79 (s, 6H), 4.60 (s, 4H), 6.80 (d, 4H), 7.10 (d, 4H), 7.34 (d, 1H), 7.55 (d, 1H), 7.82 (s, 1H), 8.20 (d, 1H).

ESI/MS m/e: 447 ([M+H]+, $C_{24}H_{22}N_4O_5$)

Step c:



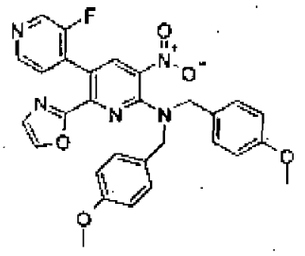
4-Bromo-2-*N*,*N*-bis(4-methoxybenzyl)-3-nitro-6-(1,3-oxazol-2-yl)pyridine

Obtained (52%) from 2-N,N-bis(4-methoxybenzyl)-3-nitro-6-(1,3-oxazol-2-yl)pyridine and *N*-bromosuccinimide, following the procedure described in Preparation 10, step d.

δ ^{1}H-NMR (DMSO-d_6): 3.69 (s, 6H), 4.59 (s, 4H), 6.83 (d, 4H), 7.12 (d, 4H), 7.58 (s, 1H), 8.42 (s, 1H), 8.51 (s, 1H).

ESI/MS m/e: 525/527 ([M+H]+, $C_{24}H_{21}BrN_4O_5$)

Step d:

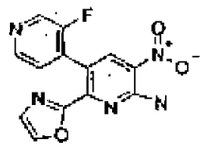


2-*N*,*N*-bis(4-methoxybenzyl)-4-(3-fluoropyridin-4-yl)-3-nitro-6-(1,3-oxazol-2-yl)pyridine

An oven-dried resealable Schlenk tube was charged with 4-Bromo-2-N,N-bis(4-methoxybenzyl)-3-nitro-6-(1,3-oxazol-2-yl)pyridine (5.47 g, 10.4 mmol), 3-fluoro-4-(tributylstannyl)pyridine (5.22 g, 13.5 mmol) and dimethylformamide (82 mL). The Schlenk tube was subjected to three cycles of evacuation-backfilling with argon, and bis(triphenylphosphino)-palladium (II) chloride (0.365 g, 0.52 mmol) and copper (I) iodide (0.198 g, 1.04 mmol) were added. After three new cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred and heated to 160 °C in an oil bath. After 20 hours, the mixture was cooled and the solvent evaporated. The residue was taken up in a mixture of methanol and ethyl acetate, filtered through a plug of Celite® and evaporated. Purification by flash chromatography (6:1 hexanes/ethyl acetate to hexanes/ethyl acetate) provided the title compound (4.07 g, 72%) as a solid.

ESI/MS m/e: 542 ([M+H]+, $C_{29}H_{24}FN_5O_5$)

Step e:



3'-Fluoro-5-nitro-2-(1,3-oxazol-2-yl)-3,4'-bipyridin-6-amine

A solution of 2-N,N-bis(4-methoxybenzyl)-4-(3-fluoropyridin-4-yl)-3-nitro-6-(1,3-oxazol-2-yl)pyridine (0.15 g, 0.37 mmol) in dichloromethane (2 mL) and trifluoroacetic acid (2 mL) was stirred at ambient temperature overnight. The solvent was evaporated and then the mixture was neutralized with 4% aqueous sodium hydrogen carbonate solution. The solid that formed was extracted with ethyl acetate and the organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated to give the title compound (0.11 g, 67%) as a yellow solid.

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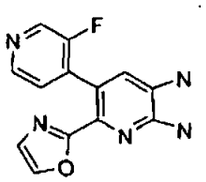
δ ^{1}H-NMR ($CDCl_3$): 7.21 (s, 1H), 7.30 (m, 1H), 7.71 (s, 1H), 8.51 (m, 3H).
ESI/MS m/e: 302 ([M+H]+, $C_{13}H_8FN_5O_3$)

Step f:



3'-Fluoro-2-(1,3-oxazol-2-yl)-3,4'-bipyridine-5,6-diamine

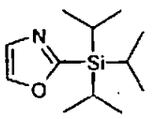
Obtained (93%) from 3'-fluoro-5-nitro-2-(1,3-oxazol-2-yl)-3,4'-bipyridin-6-amine by hydrogenation over palladium on carbon following the procedure described in Preparation 10, step f.

δ ^{1}H-NMR (DMSO-d_6): 5.42 (s, 2H), 6.07 (s, 2H), 6.65 (s, 1H), 7.05 (s, 2H), 7.30 (m, 1H), 7.96 (s, 1H), 8.39 (m, 2H).
ESI/MS m/e: 272 ([M+H]+, $C_{13}H_{10}FN_5O$)

Intermediate 12

2-(1,3-Oxazol-5-yl)-3,4'-bipyridine-5,6-diamine

Step a:



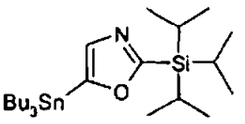
2-Triisopropylsilyloxazole

n-BuLi (1.6M in hexanes, 76 mL, 190 mmol) was added dropwise over 30 minutes to a stirred solution of oxazole (12.0 g, 174 mmol) in diethyl ether (400 mL) at –78 °C under argon. The solution was allowed to stir for 60 minutes at –78 °C and then triisopropylsilyl triflate (46.3 mL, 172 mmol) was added dropwise over 30 minutes. The reaction mixture was slowly warmed up to room temperature and stirred overnight. The mixture was concentrated in vacuo and the residue was taken up in hexanes and filtered through a pad of silica gel eluting with 8:1 hexanes/ethyl acetate. Concentration gave the title compound (36.0 g, 93%) as a colourless oil.

δ ^{1}H-NMR ($CDCl_3$): 1.12 (d, 18H), 1.37 (m, 3H), 7.20 (m, 1H), 7.81 (d, 1H).

Step b:

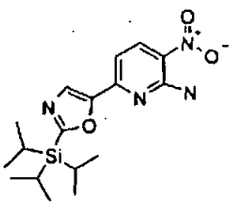
5-Tributylstannanyl-2-triisopropylsilanyl-oxazole



tert-BuLi (1.7M in *n*-pentane, 8.4 mL, 14.3 mmol) was added dropwise over (approximately) 30 minutes to a stirred solution of 2-triisopropylsilyloxazole (3g, 13 mmol) in tetrahydrofuran (75 mL) at –78 °C under argon. The solution was allowed to stir for 20 minutes at –78 °C and tributyltin chloride (5.2 mL, 19.5 mmol) was then added over 20 minutes. The reaction mixture was warmed to room temperature and stirred for an additional 16 hours. The reaction was diluted with ethyl acetate, washed with water and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was dissolved in n-pentane, filtered through Celite® and the solvent evaporated to give the title compound in quantitative yield as a pale-yellow oily residue, which was used without further purification in the next step.

δ ^{1}H-NMR ($CDCl_3$): 1.12 (d, 18H), 1.38 (m, 3H), 1.42 (d, 9H), 1.52-1.95 (m, 18H) 7.22 (s, 1H).

Step c:



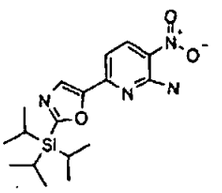
3-Nitro-6-(2-triisopropylsilanyl-1,3-oxazol-5-yl)pyridin-2-amine

Obtained (80%) from 6-bromo-3-nitropyridin-2-amine and 5-tributylstannanyl-2-triisopropylsilanyloxazole, following the procedure described in Preparation 10, step b.

δ ^{1}H-NMR ($CDCl_3$): 1.17 (d, 18H), 1.43 (m, 3H), 7.11 (d, 1H), 7.85 (s, 1H), 8.48 (d, 1H).

ESI/MS m/e: 363 ([M+H]+, $C_{17}H_{26}N_4O_3Si$)

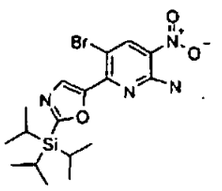
Step c: (alternative method)



3-Nitro-6-(2-triisopropylsilanyl-1,3-oxazol-5-yl)pyridin-2-amine

Obtained (67%) from 6-chloro-3-nitropyridin-2-amine and 5-tributylstannanyl-2-triisopropylsilanyloxazole, following the procedure described in Preparation 10, step b.

Step d:



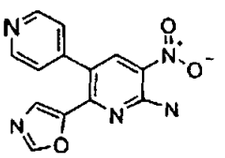
5-Bromo-3-nitro-6-(2-triisopropylsilanyl-1,3-oxazol-5-yl)pyridin-2-amine

Obtained (88%) from 3-nitro-6-(2-triisopropylsilanyl-1,3-oxazol-5-yl)pyridin-2-amine and *N*-bromosuccinimide, following the procedure described in Preparation 10, step d.

δ ^{1}H-NMR ($CDCl_3$): 1.17 (d, 18H), 1.45 (m, 3H), 8.15 (s, 1H), 8.68 (s, 1H).

ESI/MS m/e: 441/443 ([M+H]+, $C_{17}H_{26}BrN_4O_3Si$)

Step e:



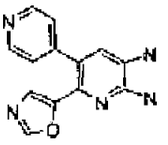
5-Nitro-2-(1,3-oxazol-5-yl)-3,4'-bipyridin-6-amine

Obtained (74%) from 5-bromo-3-nitro-6-(2-triisopropylsilanyl-1,3-oxazol-5-yl)pyridin-2-amine and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine following the procedure described in Preparation 10, step e.

δ ^{1}H-NMR ($CDCl_3$): 7.15 (s, 1H), 7.38 (d, 2H), 8.20 (s, 1H), 8.32 (s, 1H), 8.45 (s, 1H), 8.62 (d, 2H).

ESI/MS m/e: 284 ([M+H]+, $C_{13}H_9N_5O_3$)

Step f:



2-(1,3-Oxazol-5-yl)-3,4'-bipyridine-5,6-diamine.

Obtained (82%) from 5-nitro-2-(1,3-oxazol-5-yl)-3,4'-bipyridin-6-amine by hydrogenation over palladium on carbon following the procedure described in Preparation 10, step f.

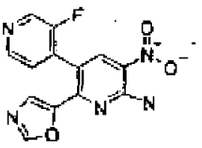
δ ^{1}H-NMR (DMSO-d_6): 5.26 (s, 2H), 5.94 (s, 2H), 6.67 (s, 1H), 6.79 (s, 1H), 7.16 (d, 2H), 8.12 (s, 1H), 8.52 (m, 2H).

ESI/MS *m/e*: 254 ([M+H]+, $C_{13}H_{11}N_5O$)

Intermediate 13

3'-Fluoro-2-(1,3-oxazol-5-yl)-3,4'-bipyridine-5,6-diamine

Step a:



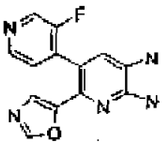
3'-Fluoro-5-nitro-2-(1,3-oxazol-5-yl)-3,4'-bipyridin-6-amine

Obtained (18%) *from 5-bromo-3-nitro-6-(2-triisopropylsilanyl-1,3-oxazol-5-yl)pyridin-2-amine* and 3-fluoro-4-(tributylstannyl)pyridine following the procedure described in Preparation 11, step d.

δ ^{1}H-NMR ($CDCl_3$): 7.30 (m, 1H), 7.38 (s, 1H), 7.81 (s, 1H), 8.40 (s, 1H), 8.52 (m, 2H).

ESI/MS *m/e*: 302 ([M+H]+, $C_{13}H_8FN_5O_3$)

Step b:



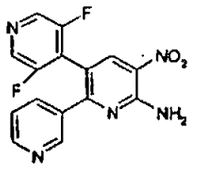
3'-Fluoro-2-(1,3-oxazol-5-yl)-3,4'-bipyridine-5,6-diamine

Obtained (89%) from 3'-fluoro-5-nitro-2-(1,3-oxazol-5-yl)-3,4'-bipyridin-6-amine by hydrogenation over palladium on carbon following the procedure described in Preparation 10, step f.

ESI/MS m/e: 272 ([M+H]+, $C_{13}H_{10}FN_5O$)

Intermediate 14

Step a:



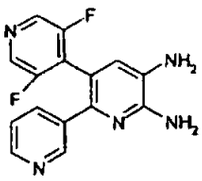
3",5"-difluoro-5'-nitro-3,2':3',4"-terpyridin-6'-amine

A mixture of 3-bromo-5-nitro-2,3'-bipyridin-6-amine (**Intermediate 1, step b**, 1 g, 3.39 mmol), 3,5-difluoro-4-tributylstannanylpyridine (1.5 g, 3.71 mmol), bis(triphenylphosphino) palladium (II) chloride (0.24 g, 0.34 mmol) and copper (I) iodide (0.13 g, 0.68 mmol) in dioxane (15 mL) was heated at 150 °C for 6 hours in Biotage Initiator Microwave Synthesizer.

The mixture was filtered through Celite® and the filter cake was washed with dioxane. The solvent was evaporated and the crude residue was purified by silica gel flash chromatography (95:5 dichloromethane/methanol) to give the title compound (1.07 g, 95%) as a yellow solid.

ESI/MS m/e: 330 ([M+H]$^+$, $C_{15}H_9F_2N_5O_2$).

Step b:



3",5"-difluoro-3,2':3',4"-terpyridine-5',6'-diamine

A suspension of 3",5"-difluoro-5'-nitro-3,2':3',4"-terpyridin-6'-amine (0.2 g, 0.608 mmol) and 10% palladium on carbon (0.04 g) in a mixture of THF/ ethanol 40:60 (8 mL) was stirred under hydrogen atmosphere at 2.76 bar. After 12h, the mixture was filtered through Celite® and the filter cake was washed with ethanol and THF. The combined filtrate and washings were evaporated to give the title compound as a solid (0.180 g, 99%).

ESI/MS m/e: 300 ([M+H]$^+$, $C_{15}H_{11}F_2N_5$).

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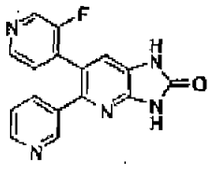
EXAMPLES

Example 1



6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

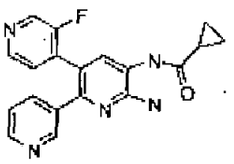
To a solution of 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 158 mg, 0.56 mmol) in THF (5 mL) Et_3N (156 µL, 1.12 mmol) and carbonyldiimidazole (182 mg, 1.12 mmol) were added sequentially. The reaction mixture was heated to reflux for 4 h and then the solvent was removed under reduced pressure. Flash chromatography of the resulting crude oil (CH_2Cl_2/EtOH/aq NH_3 60:8:1 to 40:8:1) followed by reverse phase chromatography (0% CH_3CN in H_2O to 25% CH_3CN in H_2O) gave the title compound as a white solid (29 mg, 17%).

δ ^{1}H-NMR (DMSO-d_6): 7.27 (dd, 1H), 7.33 (s, 1H), 7.44 (dd, 1H), 7.59 (dt, 1H), 8.37 (d, 1H), 8.42 (m, 3H), 11.18 (s, 1H), 11.70 (s, 1H),

ESI/MS m/e: 308 ($[M+H]^+$, $C_{16}H_{10}FN_5O$).

Example 2

Step a:

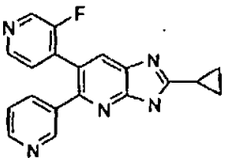


***N*-(6'-amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)cyclopropanecarboxamide**

To a solution of 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.2 g, 0.71 mmol) in pyridine (2 mL), 0.071 mL (0.78 mmol) of cyclopropanoylcarbonyl chloride were added. The mixture was heated at 80°C for 4h and the solvent was evaporated. The crude mixture was extracted between ethyl acetate and water, the organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by silica gel flash chromatography (90:10 dichloromethane/methanol) to give the title compound (0.202 g, 82% of yield).

ESI/MS m/e: 350 ($[M+H]^+$, $C_{19}H_{16}FN_5O$)

Step b:

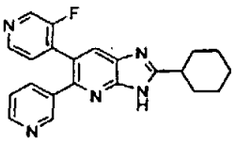


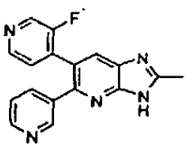
2-Cyclopropyl-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

A solution of *N*-(6'-amino-3"-fluoro-3,2':3',4"-terpyridin-5'-yl)cyclopropanecarboxamide (0.2 g, 0.58 mmol) in acetic acid (2.5 mL) was heated in a sealed tube at 130°C for 16h. The solvent was evaporated and water (1 mL) was added and the solution was neutralised with 4% sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel flash chromatography (100:8:1 dichloromethane/methanol/NH_3) to give the title compound (0.024g, 12% of yield).

ESI/MS *m/e*: 332 ($[M+H]^+$, $C_{18}H_{14}FN_5$)

Example 3 and **Example 4**

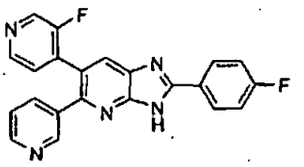




2-Cyclohexyl-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine and **6-(3-fluoropyridin-4-yl)-2-methyl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine**

The same procedure as in Example 2, but using cyclohexanecarbonyl chloride was followed. Final purification of the residue by flash chromatography (CH_2Cl_2/^{i}PrOH 98:2 to 65:35) afforded 2-cyclohexyl-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3H-imidazo[4,5-b]pyridine (**Example 3**) as a yellowish solid (134 mg, 51%): δ ^{1}H-NMR ($CDCl_3$): 1.28-1.66 (m, 4H), 1.71-1.98 (m, 4H), 2.15 (broad d, 2H), 7.36 (ddd, 1H), 7.52 (dd, 1H), 7.82 (dt, 1H), 8.01 (s, 1H), 8.36 (d, 1H), 8.42 (dd, 1H), 8.46 (dd, 1H), 8.51 (broad d, 1H), ESI/MS m/e: 374 ($[M+H]^+$; $C_{22}H_{20}FN_5$), and 6-(3-fluoropyridin-4-yl)-2-methyl-5-pyridin-3-yl-3H-imidazo[4,5-b]pyridine (**Example 4**) as a white solid (90 mg, 42%) δ ^{1}H-NMR ($CDCl_3$): 2.69 (s, 3H), 7.36 (ddd, 1H), 7.52 (dd, 1H), 7.82 (dt, 1H), 8.02 (s, 1H), 8.36 (d, 1H), 8.41 (dd, 1H), 8.46 (dd, 1H), 8.50 (broad d, 1H). ESI/MS m/e: 306 ($[M+H]^+$, $C_{17}H_{12}FN_5$).

Example 5



2-(4-Fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

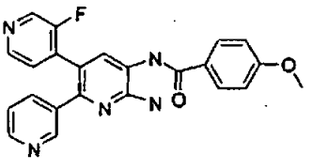
3''-Fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 158 mg, 0.56 mmol), 4-fluorobenzoyl chloride (73.0 µL, 0.62 mmol) and pyridine (ca. 4 mL) were placed in a sealed tube. The solution was initially heated at 140 °C for 48 h and afterwards, at 160 °C for another 48 h. Then, the reaction mixture was cooled to room temperature, the pyridine was removed *in vacuo*, and the crude oil was purified by flash column chromatography (CH_2Cl_2/EtOH, 95:5) affording the title compound as a white solid (141 mg, 65%).

δ ^{1}H-NMR (DMSO-d_6): 6.89 (t, 1H), 7.06 (t, 2H), 7.26 (dd, 1H), 7.56 (dt, 1H), 7.77 (dd, 1H), 7.82 (s, 1H), 7.96 (dd, 2H), 8.14 (dd, 1H), 8.18 (broad d, 1H), 8.25 (broad s, 1H).

ESI/MS *m/e*: 386 ([M+H]$^+$, $C_{22}H_{13}F_2N_5$).

Example 6

Step a:

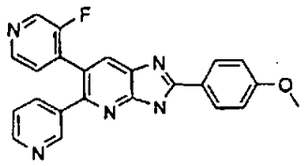


***N*-(6'-Amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)-4-methoxybenzamide**

To a solution of 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.36 mmol) in pyridine (2 mL), 4-methoxybenzoyl chloride (0.066 g, 0.39 mmol) was added. The mixture was stirred at room temperature overnight and the solvent was evaporated. Dichloromethane (1.6 mL) and tris-(2-aminoethyl)amine polystyrene (0.180 g, 0.72 mmol) were added and the mixture was stirred at room temperature for 1h. The resin was filtrated and washed twice with dichloromethane. The filtrates were combined and the solvent was evaporated to give the title compound (0.172 g) which was used in the next step without further purification.

ESI/MS *m/e*: 416 ([M+H]$^+$, $C_{23}H_{18}FN_5O_2$)

Step b:



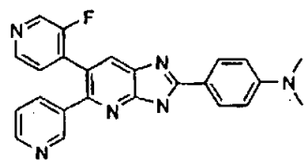
6-(3-Fluoropyridin-4-yl)-2-(4-methoxyphenyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.039 g, 28% of yield) from *N*-(6'-amino-3"-fluoro-3,2':3',4"-terpyridin-5'-yl)-4-methoxybenzamide following the procedure described in Example 2, step b.

δ ^{1}H-NMR ($CDCl_3$): 3.93 (s, 3H), 7.09-7.14 (d, 2H), 7.08-7.36 (m, 4H), 7.48-7.52 (s, 1H), 8.09 (s, 1H), 8.21-8.25 (d, 2H), 8.42-8.48 (m, 1H), 8.54-8.62 (m, 1H), 9.42-9.46 (m, 1H).

ESI/MS m/e: 398 ($[M+H]^+$, $C_{23}H_{16}FN_5O$)

Example 7



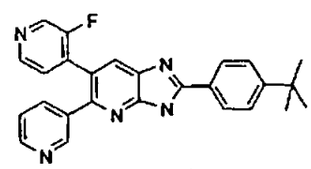
***N*-{4-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]phenyl}-*N*,*N*-dimethylamine**

Obtained (0.020 g, 14% of yield) from 3"-fluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and 4-(dimethylamino)benzoyl chloride (0.072 g, 0.391 mmol) following the procedure described in Example 6.

δ ^{1}H-NMR ($CDCl_3$): 3.10 (s, 6H), 6.81-6.85 (d, 2H), 7.21-7.30 (m, 4H), 7.62-7.66 (m, 1H), 7.99 (s, 1H), 8.04-8.09 (d, 2H), 8.37-8.42 (m, 1H), 8.53-8.55 (m, 1H), 8.65-8.70 (m, 1H).

ESI/MS m/e: 411 ($[M+H]^+$, $C_{24}H_{19}FN_6$)

Example 8



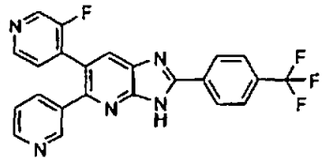
6-(3-Fluoropyridin-4-yl)-2-(4-*tert*-butylphenyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.050 g, 33% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and 4-tert-butylbenzoyl chloride (0.072 mL, 0.391 mmol) following the procedure described in Example 6.

δ ^{1}H-NMR ($CDCl_3$): 1.41 (s, 9H), 7.16-7.37 (m, 2H), 7.46-7.50 (m, 2H), 7.61-7.65 (d, 2H), 8.15 (s, 1H), 8.24-8.28 (d, 2H), 8.43-8.49 (m, 2H), 8.66-8.68 (m, 1H), 9.54 (bs, 1H).

ESI/MS m/e: 424 ($[M+H]^+$, $C_{26}H_{22}FN_5$)

Example 9



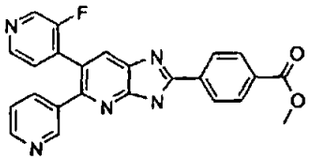
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-[4-(trifluoromethyl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine

Following the same procedure as in **Example 2**, but using 4-(trifluoromethyl)benzoyl chloride, the title compound was obtained as a white solid (172 mg, 57%).

δ ^{1}H-NMR ($CDCl_3$): 7.21 (dd, 1H), 7.39 (t, 1H), 7.46 (broad d, 1H), 7.89 (d, 2H), 8.19 (s, 1H), 8.47 (d, 2H), 8.52 (broad s, 2H), 8.67 (broad d, 1H), 8.68 (s, 1H), 9,80 (broad s, 1H).

ESI/MS m/e: 436 ($[M+H]^+$, $C_{23}H_{13}F_4N_5$).

Example 10



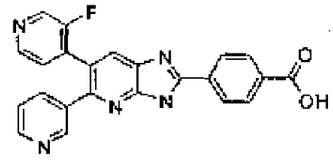
Methyl 4-[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoate

Obtained (0.047 g, 31% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and methyl 4-(chlorocarbonyl)benzoate (0.078 g, 0.391 mmol) following the procedure described in Example 6.

δ ^{1}H-NMR (DMSO-d_6): 3.90 (s, 3H), 7.30-7.37 (m, 2H), 7.55-7.60 (m, 2H), 7.68-7.74 (m, 2H), 8.14-8.24 (m, 3H), 8.40-8.51 (m, 4H).

ESI/MS m/e: 426 ($[M+H]^+$, $C_{24}H_{16}FN_5O_2$)

Example 11



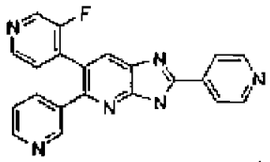
4-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoic acid

To a solution of methyl 4-[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3H-imidazo[4,5-b]pyridin-2-yl]benzoate (**Example 10**, 0.041 g, 0.097 mmol) in a mixture of THF/ethanol 1:1 (1.2 mL), 2N sodium hydroxide aqueous solution (0.1 mL) was added. The mixture was heated at 60°C for 3h and then neutralised with 2N hydrogen chloride aqueous solution. The solvent was evaporated and the crude mixture was purified by silica gel flash chromatography (78:10:10:2 dichloromethane/ethanol/ethyl acetate/acetic acid) to give the title compound (0.013g, 31% of yield).

δ ^{1}H-NMR (DMSO-d_6): 7.31-7.37 (m, 2H), 7.55-7.60 (m, 2H), 7.68-7.74 (m, 2H), 8.09-8.13 (m, 1H), 8.21 (s, 1H), 8.30-8.35 (d, 2H), 8.47-8.51 (m, 3H).

ESI/MS m/e: 412 ($[M+H]^+$, $C_{23}H_{14}FN_5O_2$)

Example 12



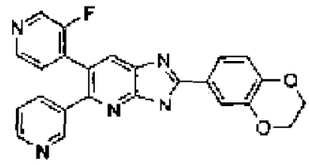
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.070 g, 53% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and isonicotinoyl chloride (0.070 g, 0.391 mmol) following the procedure described in Example 6.

δ ^{1}H-NMR ($CDCl_3$): 7.24-7.34 (m, 3H), 7.65-7.69 (m, 1H), 8.12-8.20 (m, 3H), 8.38-8.44 (m, 2H), 8.53-8.55 (m, 1H), 8.68-8.70 (m, 1H), 8.79-8.82 (m, 2H)

ESI/MS m/e: 369 ($[M+H]^+$, $C_{21}H_{13}FN_6$)

Example 13



2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

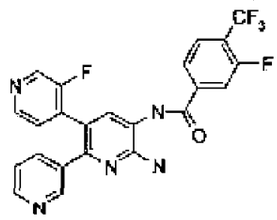
Obtained (0.027 g, 18% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and 2,3-dihydro-1,4-benzodioxine-6-carbonyl chloride (0.078 g, 0.391 mmol) following the procedure described in Example 6.

δ ^{1}H-NMR ($CDCl_3$): 4.37 (s, 4H), 7.05-7.34 (m, 4H), 7.36-7.43 (d, 1H), 7.82-7.87 (m, 2H), 8.10 (s, 1H), 8.42-8.49 (m, 2H), 8.66-8.69 (m, 1H), 9.64 (s, 1H).

ESI/MS m/e: 426 ($[M+H]^+$, $C_{24}H_{16}FN_5O_2$)

Example 14

Step a:

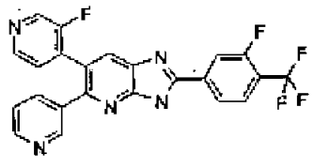


***N*-(6'-Amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)-3-fluoro-4-methylbenzamide**

To a solution of 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**intermediate 1**, 0.2 g, 0.71 mmol) in pyridine (2 mL), 0.071 mL (0.78 mmol) of 3-fluoro-4-methylbenzoyl chloride were added. The mixture was heated at 40°C for 4h and the solvent was evaporated. The crude mixture was extracted between ethyl acetate and water, the organic layer was dried ($MgSO_4$) and evaporated to give the title compound (0.295 g, 88% of yield) which was used in the next step without further purification.

ESI/MS m/e: 418 ($[M+H]^+$, $C_{23}H_{17}F_2N_5O$)

Step b:



59

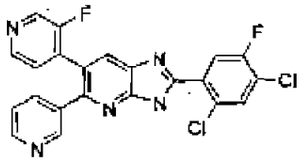
6-(3-Fluoropyridin-4-yl)-2-[3-fluoro-4-(trifluoromethyl)phenyl]-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.043 g, 15% of yield) from *N*-(6'-amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)-3-fluoro-4-methylbenzamide following the procedure described in Example 2, step b.

δ ^{1}H-NMR ($CDCl_3$): 7.19-7.24 (m, 2H), 7.38-7.46 (m, 2H), 7.83-7.91 (t, 1H), 8.21 (s, 1H), 8.22-8.29 (m, 2H), 8.45 (s, 1H), 8.52-8.55 (d, 1H), 8.69-8.71 (d, 1H), 9.89 (s, 1H).

ESI/MS m/e: 454 ([M+H]$^+$, $C_{23}H_{12}F_6N_5$)

Example 15

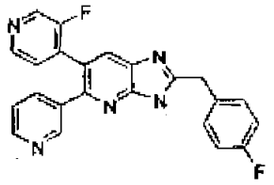


2-(2,4-Dichloro-5-fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.075 g, 47% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and 2,4-dichloro-5-fluorobenzoyl chloride (0.070 g, 0.391 mmol) following the procedure described in Example 6.

ESI/MS m/e: 454 ([M+H]$^+$, $C_{22}H_{11}Cl_2F_2N_5$)

Example 16



2-(4-Fluorobenzyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.035 g, 25% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and (4-fluorophenyl)acetyl chloride (0.054 mL, 0.391 mmol) following the procedure described in Example 6.

δ ^{1}H-NMR ($CDCl_3$): 4.33 (s, 2H), 7.01-7.09 (m, 2H), 7.25-7.38 (m, 4H), 7.55-7.59 (d, 1H), 8.02 (s, 1H), 8.36-8.42 (m, 3H), 8.46-8.49 (d, 1H), 8.70 (s, 1H).

ESI/MS m/e: 400 ([M+H]$^+$, $C_{23}H_{16}F_2N_5$)

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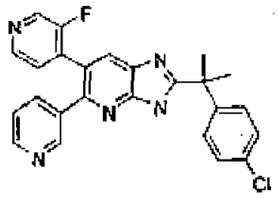
Example 17



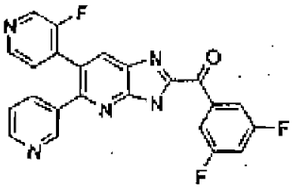
2-[1-(4-Chlorophenyl)-1-methylethyl]-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.040 g, 49% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and 2-(4-chlorophenyl)-2-methylpropanoyl chloride (0.14 g, 0.651 mmol) following the procedure described in Example 6.

δ ^{1}H-NMR ($CDCl_3$): 1.61 (s, 6H), 7.00-7.06 (m, 2H), 7.26-7.38 (m, 4H), 8.08-8.14 (m, 3H), 8.42-8.44 (m, 1H), 8.46-8.48 (d, 2H), 9.30 (s, 1H).

ESI/MS m/e: 444 ($[M+H]^+$, $C_{25}H_{19}ClFN_5$)

Example 18



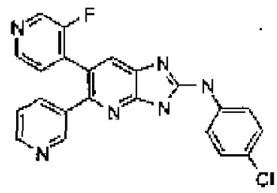
(3,5-Difluorophenyl)[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone

To a solution of 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.79 mmol) in pyridine (2 mL), 0.071 mL (0.78 mmol) of 3,5-difluorobenzoyl chloride were added. The mixture was stirred at room temperature for 16h and the solvent was evaporated. The crude mixture was purified by flash chromatography (95:5 dichloromethane/methanol) to give the title compound (0.015g, 10% of yield).

δ ^{1}H-NMR ($CDCl_3$): 6.96-7.08 (m, 1H), 7.22-7.35 (m, 3H), 7.75 (s, 1H), 7.82-7.87 (m, 1H), 8.18-8.24 (m, 2H), 8.45-8.47 (m, 2H), 8.56-8.58 (m, 2H).

ESI/MS m/e: 432 ($[M+H]^+$, $C_{23}H_{12}F_3N_5O$)

Example 19



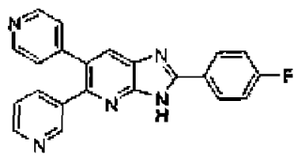
***N*-(4-Chlorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine**

To a solution of 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.050 g, 0.179 mmol) and 1-chloro-4-isothiocyanatobenzene (0.045 g, 0.267 mmol) in ethanol (1 mL), 1,3-diisopropylcarbodiimide (0.042 mL, 0.267 mmol) was added. The mixture was heated at 50°C for 2h. After cooling at room temperature, the solid precipitated was filtered off to give the title compound (0.035 g, 47% of yield).

δ ^{1}H-NMR (MeOD): 7.34-7.38 (m, 3H), 7.44-7.49 (dd, 1H), 7.67-7.70 (m, 2H), 7.73 (s, 1H), 7.77-7.84 (m, 1H), 8.34-8.48 (m, 5H).

ESI/MS m/e: 417 ([M+H]$^+$, $C_{22}H_{14}ClFN_6$)

Example 20



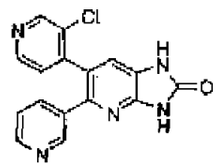
2-(4-Fluorophenyl)-5-pyridin-3-yl-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

A sealed tube containing 3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 2**, 148 mg, 0.56 mmol), 4-fluorobenzaldehyde (57.0 µL, 0.53 mmol) and dioxane (3 mL) was filled with air and heated to 100 °C for 6 days. Then, the solvent was removed and CH_3CN (2 mL) followed by $Yb(OTf)_3$ were added, and the reaction mixture was stirred for 4 days at room temperature. Afterwards, the solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (CH_2Cl_2/EtOH/aq NH_3 100:8:1) to afford the title compound as a white solid (27 mg, 13%).

δ ^{1}H-NMR ($CDCl_3$): 7.14-7.34 (m, 6H), 7.40-7.48 (m, 1H), 8.12 (s, 1H), 8.32 (dd, 2H), 8.60 (d, 2H), 8.62 (s, 1H), 9.58 (broad s, 1H).

ESI/MS m/e: 368 ([M+H]$^+$, $C_{22}H_{14}FN_5$).

Example 21



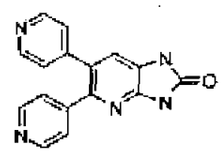
6-(3-Chloropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

Following the same protocol as in Example 1, but using 3''-chloro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 3**), the title compound was obtained as a white solid (29 mg, 17%).

δ ^{1}H-NMR ($CDCl_3$): 7.10-7.16 (m, 4H), 7.50 (dt, 1H), 7.80 (broad s, 1H), 8.44 (d, 1H), 8.49 (dd, 1H), 8.61 (s, 1H), 8.80 (d, 1H).

ESI/MS m/e: 324 ($[M+H]^+$, $C_{16}H_{10}ClN_5O$).

Example 22

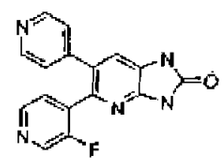


5,6-Dipyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

Obtained (0.012 g, 23% of yield) from 4,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 4**, 0.048 g, 0.18 mmol) following the procedure described in Example 1.

ESI/MS m/e: 290 ($[M+H]^+$, $C_{16}H_{11}N_5O$)

Example 23

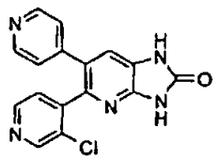


5-(3-Fluoropyridin-4-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

Obtained (0.024 g, 15% of yield) from 3-fluoro-4,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 5**, 0.173 g, 1.06 mmol) following the procedure described in Example 1.

ESI/MS m/e: 308 ($[M+H]^+$, $C_{16}H_{10}FN_5O$)

Example 24



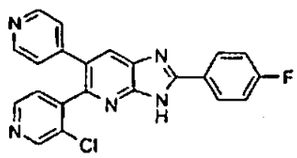
5-(3-Chloropyridin-4-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

Following the same protocol as in Example 1, but using 3-chloro-4,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 6**), the title compound was obtained as a white solid (74 mg, 65%).

δ ^{1}H-NMR (DMSO-d_6): 7.11 (broad d, 2H), 7.35 (s, 1H), 7.41 (d, 1H), 8.41 (broad d, 2H), 8.47 (d, 1H), 8.54 (s, 1H), 11.24 (broad s, 1H), 11.69 (broad s, 1H).

ESI/MS m/e: 324 ([M+H]$^+$, $C_{16}H_{10}ClN_5O$).

Example 25



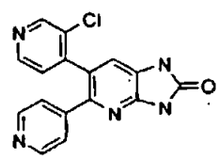
5-(3-Chloropyridin-4-yl)-2-(4-fluorophenyl)-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

Following the same protocol as in Example 5, but using 3-chloro-4,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 6**), the title compound was obtained as a white solid (68 mg, 34%).

δ ^{1}H-NMR ($CDCl_3$): 7.15 (d, 2H), 7.23-7.32 (m, 3H), 8.14-8.25 (m, 2H), 8.21 (dd, 1H), 8.49 (m, 1H), 8.51 (d, 2H), 8.58 (s, 1H).

ESI/MS m/e: 402 ([M+H]$^+$, $C_{22}H_{13}ClFN_5$).

Example 26



6-(3-Chloropyridin-4-yl)-5-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

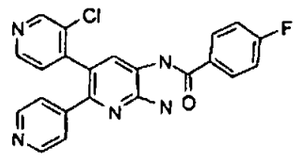
Obtained (0.021 g, 23% of yield) from 3"-chloro-4,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 7**, 0.082 g, 0.275 mmol) following the procedure described in Example 1.

δ ^{1}H-NMR (DMSO-d_6): 7.13-7.16 (m, 2H), 7.26 (s, 1H), 7.41-7.43 (m, 1H), 8.41-8.43 (m, 2H), 8.48-8.51 (m, 1H), 8.62 (s, 1H).

ESI/MS m/e: 324 ([M+H]$^+$, $C_{16}H_{10}ClN_5O$)

Example 27

Step a:

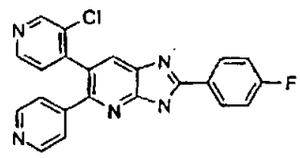


***N*-(6'-Amino-3"-chloro-4,2':3',4"-terpyridin-5'-yl)-4-fluorobenzamide**

Obtained (0.335 g, 95% of yield) from 3"-chloro-4,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 7**, 0.250 g, 0.84 mmol) and 4-fluorobenzoyl chloride (0.120 mL, 1.01 mmol) following the procedure described in Example 2, step a. The crude mixture was used in the next step without further purification.

ESI/MS m/e: 420 ([M+H]$^+$, $C_{22}H_{15}ClFN_5O$)

Step b:



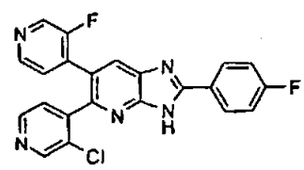
6-(3-Chloropyridin-4-yl)-2-(4-fluorophenyl)-5-pyridin-4-yl-3H-imidazo[4,5-b]pyridine

Obtained (0.099 g, 31% of yield) from *N*-(6'-amino-3"-chloro-4,2':3',4"-terpyridin-5'-yl)-4-fluorobenzamide (0.005 g, 0.8 mmol) following the procedure described in Example 2, step b.

δ ^{1}H-NMR (DMSO-d_6): 7.25-7.28 (m, 2H), 7.41-7-54 (m, 3H), 8.08 (s, 1H), 8.30-8.37 (m, 2H), 8.46-8.49 (m, 2H), 8.54-8.56 (d, 1H), 8.64 (s, 1H).

ESI/MS m/e: 402 ([M+H]$^+$, $C_{22}H_{13}ClFN_5$)

Example 28

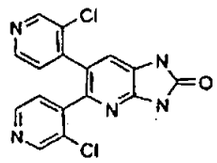


5-(3-Chloropyridin-4-yl)-2-(4-fluorophenyl)-6-(3-fluoropyridin-4-yl)-3*H*-imidazo[4,5-*b*]pyridine

Following the same protocol as in Example 2, but using 4-fluorobenzoylchloride and 3-chloro-3"-fluoro-4,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 8**), the title compound was obtained as a white solid (13 mg, 12%).

ESI/MS m/e: 420 ([M+H]$^+$, $C_{22}H_{12}ClF_2N_5$).

Example 29

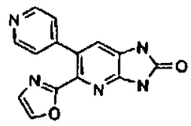


5,6-Bis(3-chloropyridin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

Obtained (0.026 g, 84% of yield) from 3,3"-dichloro-4,2':3',4"-terpyridine-5';6'-diamine (**Intermediate 9**, 0.029 g, 0.09 mmol) following the procedure described in Example 1.

ESI/MS m/e: 358 ([M+H]$^+$, $C_{16}H_9Cl_2N_5O$)

Example 30



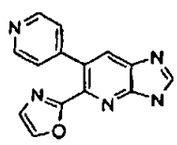
5-(1,3-Oxazol-2-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

A solution of 2-(1,3-oxazol-2-yl)-3,4'-bipyridine-5,6-diamine (**Intermediate 10**, 0.077g, 0.3 mmol), *N,N'*-carbonyldiimidazole (0.146 g, 0.9 mmol) and triethylamine (91 mg, 0.9 mmol) in *N,N*-dimethylformamide (1 mL) was heated to 100 °C in a sealed tube. After 4 hours, the mixture was cooled and concentrated in vacuo. Water was added to the residue and the solid that separated was washed with water and dried to give the title compound (0.038 g, 45%) as a white solid.

δ ^{1}H-NMR (DMSO-d_6): 7.21 (d, 2H), 7.29 (s, 1H), 8.08 (s, 1H), 8.51 (d, 2H), 11.39 (s, 1H), 11.78 (s, 1H).

ESI/MS m/e: 280 ([M+H]+, $C_{14}H_9N_5O_2$)

Example 31



66

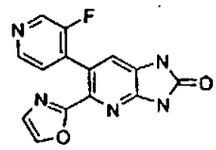
5-(1,3-Oxazol-2-yl)-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

A mixture of 2-(1,3-oxazol-2-yl)-3,4'-bipyridine-5,6-diamine (Intermediate 10, 0.100 g, 0.39 mmol) and triethylorthoformate (0.117 g, 0.79 mmol) in glacial acetic acid (2 mL) was heated in a sealed tube to 140 °C. After stirring for 2 hours, the mixture was cooled and taken to pH 7 with 6N aqueous sodium hydroxide solution. Ethyl acetate was added to the mixture and, after stirring for 30 minutes, the separated solid was filtered, washed with diethyl ether and dried in vacuo to give the title compound (0.047 g, 49%) as an off-white solid.

δ ^{1}H-NMR (DMSO-d_6): 7.20 (m, 3H), 8.06 (m, 2H), 8.50 (d, 2H), 8.60 (s, 1H).

ESI/MS m/e: 264 ([M+H]+, $C_{14}H_9N_5O$)

Example 32



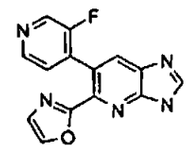
6-(3-Fluoropyridin-4-yl)-5-(1,3-oxazol-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

Obtained (37%) from 3'-fluoro-2-(1,3-oxazol-2-yl)-3,4'-bipyridine-5,6-diamine (**Intermediate 11**) and *N,N'*-carbonyldiimidazole following the procedure described for preparation of example 30.

δ ^{1}H-NMR (DMSO-d_6): 7.18 (s, 1H), 7.31 (s, 1H), 7.47 (dd, 1H), 8.12 (s, 1H), 8.49 (m, 2H), 11.36 (s, 1H), 11.85 (s, 1H).

ESI/MS m/e: 298 ([M+H]+, $C_{14}H_8FN_5O_2$)

Example 33



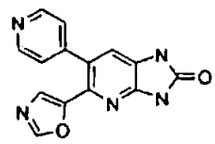
6-(3-Fluoropyridin-4-yl)-5-(1,3-oxazol-2-yl)-3*H*-imidazo[4,5-*b*]pyridine

Obtained (26%) from 3'-fluoro-2-(1,3-oxazol-2-yl)-3,4'-bipyridine-5,6-diamine (**Intermediate 11**) and triethylorthoformate following the procedure described for preparation of example 31.

δ ^{1}H-NMR (DMSO-d_6): 7.21 (s, 1H), 7.53 (dd, 1H), 8.18 (m, 2H), 8.50 (m, 2H), 8.71 (s, 1H).

ESI/MS m/e: 282 ([M+H]+, $C_{14}H_8FN_5O$)

Example 34



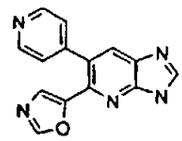
5-(1,3-Oxazol-5-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

Obtained (58%) from 2-(1,3-oxazol-5-yl)-3,4'-bipyridine-5,6-diamine (**Intermediate 12**) and N,N'-carbonyldiimidazole following the procedure described for preparation of example 30.

δ ^{1}H-NMR (DMSO-d_6): 6.92 (s, 1H), 7.20 (s, 1H), 7.30 (d, 2H), 8.24 (s, 1H), 8.58 (d, 2H), 11.21 (s, 1H), 11.69 (s, 1H).

ESI/MS m/e: 278 ([M-H]+, $C_{14}H_9N_5O_2$)

Example 35



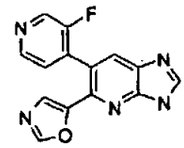
5-(1,3-oxazol-5-yl)-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (66%) from 2-(1,3-oxazol-5-yl)-3,4'-bipyridine-5,6-diamine (**Intermediate 12**) and triethylorthoformate following the procedure described for preparation of example 31.

δ ^{1}H-NMR (DMSO-d_6): 7.00 (m, 1H), 7.36 (m, 2H), 8.00 (m, 1H), 8.31 (s, 1H), 8.62 (m ,3H), 13.0 (s, 1H).

ESI/MS m/e: 264 ([M+H]+, $C_{14}H_9N_5O$)

Example 36



6-(3-Fluoropyridin-4-yl)-5-(1,3-oxazol-5-yl)-3*H*-imidazo[4,5-*b*]pyridine

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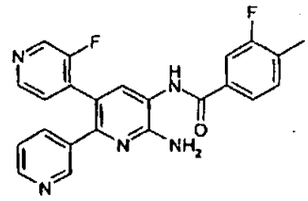
Obtained (25%) from 3'-fluoro-2-(1,3-oxazol-5-yl)-3,4'-bipyridine-5,6-diamine (**Intermediate 13**) and triethylorthoformate following the procedure described for preparation of example 31.

δ ^{1}H-NMR (DMSO-d_6): 7.17 (s, 1H), 7.58 (dd, 1H), 8.15 (s, 1H), 8.32 (s, 1H), 8.55 (dd, 1H), 8.65 (m, 2H).

ESI/MS m/e: 282 ([M+H]+, $C_{14}H_8FN_5O$)

Example 37

Step a:

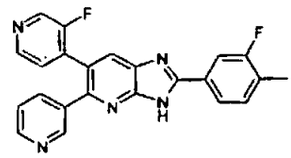


N-(6'-Amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)-3-fluoro-4-methylbenzamide

To a solution of 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) in pyridine (2 mL), 0.15 g (0.89 mmol) of 3-fluoro-4-methylbenzoyl chloride were added. The mixture was stirred at room temperature overnight and the solvent was evaporated. The crude mixture (0.33 g) was purified by silica gel flash chromatography (95:5 dichloromethane/methanol) to give the title compound (0.12 g, 81% of yield).

ESI/MS m/e: 418 ([M+H]$^+$, $C_{23}H_{17}F_2N_5O$)

Step b:



2-(3-Fluoro-4-methylphenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

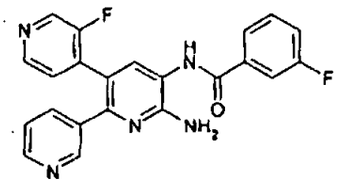
A solution of *N*-(6'-amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)-3-fluoro-4-methylbenzamide (0.12 g, 0.288 mmol) in acetic acid (2 mL) was heated in a sealed tube at 118°C for 16h. The solvent was evaporated and 4% sodium bicarbonate aqueous solution was added and extracted with ethyl acetate. The organic layer was dried and evaporated. The residue was purified by silica gel flash chromatography (95:5 dichloromethane/methanol) to give the title compound (0.03 g, 26% of yield).

δ ^{1}H-NMR ($CDCl_3$): 2.41 (s, 3H), 7.17-7.50 (m, 4H), 7.96 (m, 1H), 8.01 (s, 1H), 8.14 (s, 1H), 8.43 (d, 1H), 8.49 (dd, 1H), 8.65 (dd, 1H), 9.57 (m, 1H).

ESI/MS m/e: 400 ($[M+H]^+$, $C_{23}H_{15}F_2N_5$).

Example 38

Step a:

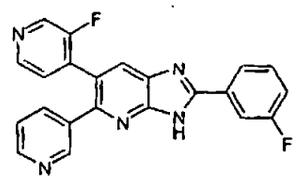


***N*-(6'-Amino-3"-fluoro-3,2':3',4"-terpyridin-5'-yl)-3-fluorobenzamide**

Obtained (0.180 g) from 3"-fluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and 3-fluorobenzoyl chloride (0.048 mL, 0.392 mmol) following the procedure described in Example 6, step a.

ESI/MS m/e: 404 ($[M+H]^+$, $C_{22}H_{15}F_2N_5O$)

Step b:



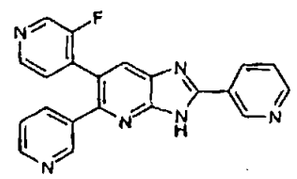
2-(3-Fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.035 g, 26% of yield) from *N*-(6'-amino-3"-fluoro-3,2':3',4"-terpyridin-5'-yl)-3-fluorobenzamide following the procedure described in Example 37, step b.

δ ^{1}H-NMR ($CDCl_3$): 7.20 (m, 1H), 7.39 (m, 3H), 7.60 (td, 1H), 8.09 (m, 2H), 8.16 (s, 1H), 8.44 (s, 1H), 8.50 (d, 1H), 8.68 (dd, 1H), 9.73 (s, 1H).

ESI/MS m/e: 386 ($[M+H]^+$, $C_{22}H_{13}F_2N_5$).

Example 39



6-(3-Fluoropyridin-4-yl)-2,5-dipyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

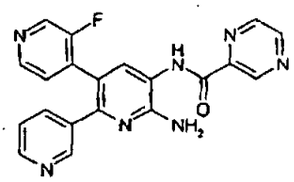
Obtained (0.025 g, 24% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and nicotinoyl chloride hydrochloride (0.070 g, 0.392 mmol) following the procedure described in Example 38.

δ ^{1}H-NMR ($CDCl_3$): 7.21 (m, 1H), 7.41 (m, 2H), 7.59 (m, 1H), 8.20 (s, 1H), 8.45 (s, 1H), 8.52 (m, 1H), 8.69 (s, 1H), 8.72 (s, 1H), 8.82 (m, 1H), 9.61 (m, 1H), 9.82 (m, 1H).

ESI/MS m/e: 369 ([M+H]$^+$, $C_{21}H_{13}FN_6$).

Example 40

Step a:

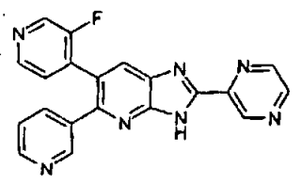


***N*-(6'-Amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)pyrazine-2-carboxamide**

A solution of pyrazine-2-carboxylic acid (0.114 g, 0.924 mmol), *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (0.178 g, 0.924 mmol) and 1*H*-1,2,3-benzotriazol-1-ol (0.096 g, 0.712 mmol) in DMF (6mL) was heated at 40ºC for 15 minutes. Finally, 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) in DMF (1 mL) was added and the mixture was stirred at room temperature overnight. The crude mixture was extracted between ethyl acetate and water. The organic layer was washed with 4% sodium bicarbonate aqueous solution and water, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel flash chromatography (90:10 dichloromethane/methanol) to give the title compound (0.057 g, 41% of yield).

ESI/MS m/e: 388 ([M+H]$^+$, $C_{20}H_{14}FN_7O$).

Step b:



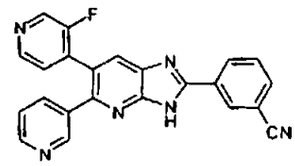
6-(3-Fluoropyridin-4-yl)-2-pyrazin-2-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.016 g, 28% of yield) from *N*-(6'-amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)pyrazine-2-carboxamide following the procedure described in Example 37, step b.

δ ^{1}H-NMR ($CDCl_3$): 7.20-7.35 (m, 3H), 7.57 (m, 1H), 8.22 (s, 1H), 8.43 (m, 1H), 8.48 (d, 1H), 8.72-8.77 (m, 3H), 9.24 (m, 1H), 9.75 (d, 1H).

ESI/MS m/e: 370 ([M+H]$^+$, $C_{20}H_{12}FN_7$).

Example 41



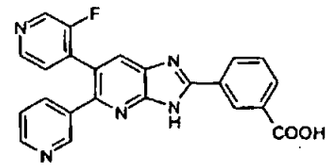
3-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzonitrile

Obtained (0.11 g, 53% of yield) from 3"-fluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 1**, 0.15 g, 0.534 mmol) and 3-cyanobenzoyl chloride (0.133 g, 0.803 mmol) following the procedure described in Example 38.

δ ^{1}H-NMR ($CDCl_3$): 7.22 (m, 1H), 7.37-7.45 (m, 2H), 7.72-7.88 (m, 2H), 8.19 (s, 1H), 8.46 (d, 1H), 8.54 (d, 1H), 8.64 (d, 1H), 8.71 (m, 1H), 8.73 (m, 1H), 9.92 (m, 1H).

ESI/MS m/e: 393 ([M+H]$^+$, $C_{23}H_{13}FN_6$).

Example 42



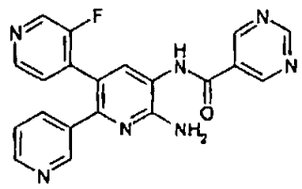
3-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoic acid

To a solution of 3-[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzonitrile (**Example 41**, 0.1 g, 0.255 mmol) in a mixture of THF/water 1:2.5 (0.83 mL), 37 % hydrogen chloride aqueous solution (1.07 mL) was added. The mixture was heated at 70°C for 4 days. After cooling at room temperature, the solid precipitated was filtered off to give the title compound (0.070 g, 67% of yield).

ESI/MS m/e: 412 ([M+H]$^+$, $C_{23}H_{14}FN_5O_2$).

Example 43

Step a:

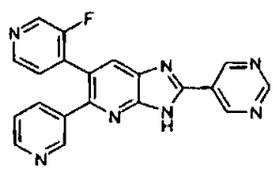


N-(6'-Amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)pyrimidine-5-carboxamide

A solution of pyrimidine-5-carboxylic acid (0.088 g, 0.709 mmol), *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (0.136 g, 0.709 mmol) and 1H-1,2,3-benzotriazol-1-ol (0.072 g, 0.534 mmol) in DMF (4 mL) was heated at 40ºC for 15 minutes. Finally, 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.15 g, 0.534 mmol) in DMF (4 mL) was added and the mixture was stirred at room temperature overnight. The crude mixture was extracted between ethyl acetate and water. The organic layer was washed with 4% sodium bicarbonate aqueous solution and water, dried ($MgSO_4$) and evaporated. The residue (0.2 g) was used in the next step without further purification.

ESI/MS m/e: 388 ($[M+H]^+$, $C_{20}H_{14}FN_7O$).

Step b:

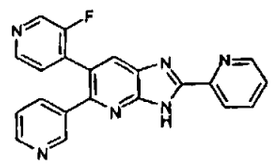


6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-pyrimidin-5-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.024 g, 12% of yield) from *N*-(6'-amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)pyrimidine-5-carboxamide following the procedure described in Example 37, step b.

ESI/MS m/e: 370 ($[M+H]^+$, $C_{20}H_{12}FN_7$).

Example 44



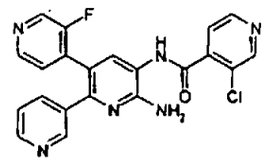
6-(3-Fluoropyridin-4-yl)-2-pyridin-2-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.006 g, 18% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and pyridine-2-carbonyl chloride (0.131 g, 0.926 mmol) following the procedure described in Example 37.

ESI/MS m/e: 369 ([M+H]$^+$, $C_{21}H_{13}FN_6$).

Example 45

Step a:

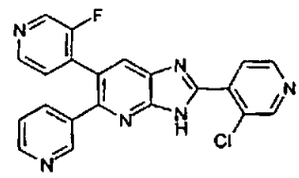


***N*-(6'-Amino-3"-fluoro-3,2':3',4"-terpyridin-5'-yl)-3-chloroisonicotinamide**

A solution of 3-chloroisonicotinic acid (0.075 g, 0.48 mmol), *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate (0.178 g, 0.47 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.15 mL, 0.86 mmol) in DMF (1mL) was stirred 15 minutes. Finally, 3"-fluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 1**, 0.11 g, 0.39 mmol) in DMF (2.9 mL) was added and the mixture was stirred at room temperature 3.5 hours. The crude mixture was extracted between ethyl acetate and water. The organic layer was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue (0.195 g) was used in the next step without further purification.

ESI/MS m/e: 421 ([M+H]$^+$, $C_{21}H_{14}ClFN_6O$).

Step b:



2-(3-Chloropyridin-4-yl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.030 g, 16% of yield) from *N*-(6'-amino-3"-fluoro-3,2':3',4"-terpyridin-5'-yl)-3-chloroisonicotinamide following the procedure described in Example 37, step b.

δ ^{1}H-NMR ($CDCl_3$): 7.19 (dd, 1H), 7.31 (t, 1H), 7.57 (d, 1H), 8.25 (m, 2H), 8.42 (s, 1H), 8.47 (d, 1H), 8.57 (dt, 1H), 8.73 (d, 1H), 8.82 (s, 1H), 9.11 (s, 1H).

ESI/MS m/e: 403 ([M+H]$^+$, $C_{21}H_{12}ClFN_6$).

Example 46

Step a:

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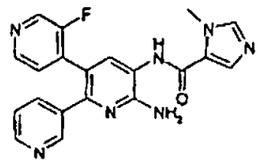
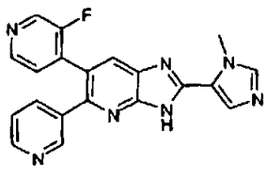


N-(6'-amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)-1-methyl-1*H*-imidazole-5-carboxamide

Obtained (0.040 g, 19% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.15 g, 0.534 mmol) and 1-methyl-1*H*-imidazole-5-carboxylic acid (0.088 g, 0.694 mmol) following the procedure described in Example 41, step a.

ESI/MS m/e: 390 ($[M+H]^+$, $C_{20}H_{16}FN_7O$).

Step b:



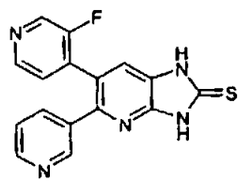
6-(3-Fluoropyridin-4-yl)-2-(1-methyl-1*H*-imidazol-5-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

A solution of *N*-(6'-amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)-1-methyl-1*H*-imidazole-5-carboxamide (0.040 g, 0.103 mmol) in acetic acid (1 mL) was heated in a sealed tube at 118°C for 16h. The solvent was evaporated and 4% sodium bicarbonate aqueous solution was added and extracted with ethyl acetate. The organic layer was dried and evaporated to give the title compound (0.022g, 58% of yield).

ESI/MS m/e: 372 ($[M+H]^+$, $C_{20}H_{14}FN_7$).

Example 47

Step a:



6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridine-2-thione

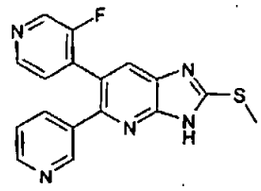
A solution of 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 2 g, 7.11 mmol), 1,1'-thiocarbonyldiimidazole (2.54 g, 14.22 mmol) and triethylamine (2 mL, 14.22 mmol) in

THF (30 mL) was heated at 80 °C in a sealed tube. After 6 hours, the mixture was cooled and the solid was filtrered, washed with NH_4Cl aq. and water and dried to give the title compound (2.03 g, 88%) as a white solid.

δ ^{1}H-NMR (DMSO-d_6): 7.31 (dd, 1H), 7.49 (dd, 1H), 7.58 (s, 1H), 7.64 (dt, 1H), 8.39-8.48 (m, 4H).

ESI/MS m/e: 324 ([M+H]+, $C_{16}H_{10}FN_5S$).

Step b:



6-(3-Fluoropyridin-4-yl)-2-(methylthio)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

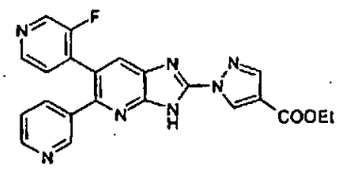
To a suspension of sodium hydride 60% (0.098 g, 2.45 mmols) in DMF (5 mL) a suspension of 6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridine-2-thione (0.6 g, 1.86 mmols) in DMF (15 mL) was added dropwise, at 0 °C, under argon. The solution was allowed to stir for 30 minutes at 0°C and then iodomethane (0.116 mL, 1.86 mmol) in DMF (1mL) was added dropwise. The reaction mixture was warmed up to room temperature and stirred for 2.5 hours. The mixture was concentrated and purified by silica gel flash chromatography (150:40:5 dichloromethane/methanol/ammonia) to give the title compound (0.34 g, 54% of yield).

δ ^{1}H-NMR (DMSO-d_6): 2.74 (s, 3H), 7.309 (dd, 1H), 7.51 (t, 1H), 7.66 (dt, 2H), 7.98 (s, 1H), 8.43-8.47 (m, 4H).

ESI/MS m/e: 338 ([M+H]+, $C_{17}H_{12}FN_5S$).

Example 48

Step a:

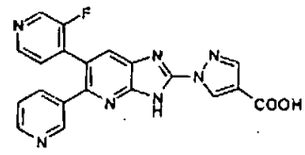


Ethyl 1-[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]-1*H*-pyrazole-4-carboxylate

A solution of 6-(3-fluoropyridin-4-yl)-2-(methylthio)-5-pyridin-3-yl-3H-imidazo[4,5-b]pyridine (**Example 47**, 0.1 g, 0.3 mmol), ethyl 1*H*-pyrazole-4-carboxylate (0.125 g, 0.88 mmol) and potassium carbonate (0.164 mg, 1.18 mmol) in DMF (2 mL) was heated at 120°C in a sealed tube. After 2 days, the solvent was evaporated and the crude mixture was purified by silica gel flash chromatography (100:8:1 dichloromethane/methanol/ammonia) to give the title compound (0.034 g, 27% of yield).

ESI/MS m/e: 430 ([M+H]+, $C_{22}H_{16}FN_7O_2$).

Step b:

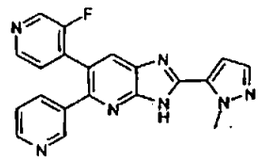


1-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]-1*H*-pyrazole-4-carboxylic acid

To a solution of ethyl 1-[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]-1*H*-pyrazole-4-carboxylate (0.022 g, 0.05 mmol) in a mixture of THF/ethanol 1:1 (1 mL), 2N sodium hydroxide aqueous solution (0.05 mL) was added. The mixture was heated at 60°C for 2 hours and then neutralised with 2N hydrogen chloride aqueous solution. The solvent was evaporated and the crude mixture was purified by solid phase extraction, SCX, it was washed with water and eluted with methanol/amonnia (9:1) to give the title compound (0.007g, 29% of yield).

ESI/MS m/e: 402 ([M+H]$^+$, $C_{20}H_{12}FN_7O_2$).

Example 49

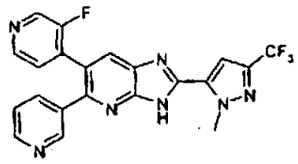


6-(3-Fluoropyridin-4-yl)-2-(1-methyl-1*H*-pyrazol-5-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.012 g, 24% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.2 g, 0.71 mmol), *N*,*N*'-dicyclohexylcarbodiimide (0.19 g, 0.92 mmol), 1*H*-1,2,3-benzotriazol-1-ol (0.099 g, 0.73 mmol) and 1-methyl-1H-pyrazole-5-carboxylic acid (0.116 g, 0.92 mmol) following the procedure described in Example 41.

ESI/MS m/e: 372 ([M+H]$^+$, $C_{20}H_{14}FN_7$).

Example 50



6-(3-Fluoropyridin-4-yl)-2-[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

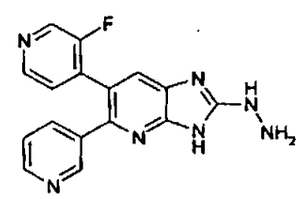
Obtained (0.017 g, 24% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.085 g, 0.30 mmol), *N*,*N*'-dicyclohexylcarbodiimide (0.074 g, 0.36 mmol), 1*H*-1,2,3-benzotriazol-1-ol (0.042 g, 0.31 mmol) and 1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (0.071 g, 0.36 mmol) following the procedure described in Example 41.

δ ^{1}H-NMR (DMSO-d_6): 4.45 (s, 3H), 7.33 (dd, 1H), 7.55-7.59 (m, 2H), 7.71 (dt, 1H), 8.31 (s, 1H), 8.48-8.50 (m, 4H).

ESI/MS m/e: 440 ([M+H]$^+$, $C_{21}H_{13}F_4N_7$).

Example 51

Step a:

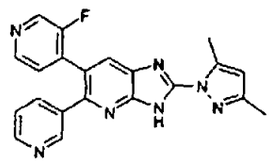


6-(3-luoropyridin-4-yl)-2-hydrazino-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

A solution of 6-(3-fluoropyridin-4-yl)-2-(methylthio)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine (**Example 47**, 0.05 g, 0.15 mmol) in hydrazine (0.5 mL) was heated in a sealed tube at 100°C for 30 hours. The solvent was evaporated and the residue (0.05 g) was used in the next step without further purification.

ESI/MS m/e: 322 ([M+H]+, $C_{16}H_{12}FN_7$).

Step b:



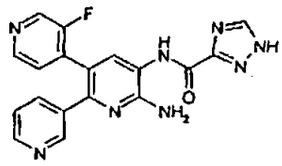
2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

A solution of 6-(3-fluoropyridin-4-yl)-2-hydrazino-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine (0.05 g, 0.15 mmol), pentane-2,4-dione (0.016 mL, 0.16 mmol) and hydrogen chloride aqueous solution in ethanol (1 mL) was heated in a sealed tube at 80ºC for 16 hours. The acidic pH was neutralized and then the solvent was evaporated and the crude mixture was purified by reverse phase chromatography (water/acetonitrile) to give the title compound (0.015 g, 25% of yield).

ESI/MS m/e: 386 ($[M+H]^+$, $C_{21}H_{16}FN_7$).

Example 52

Step a:

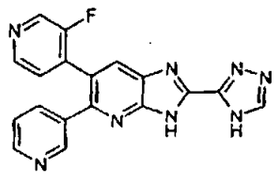


***N*-(6'-Amino-3''-fluoro-3,2':3',4''-terpyridin-5'-yl)-1*H*-1,2,4-triazole-3-carboxamide**

A solution of 1*H*-1,2,4-triazole-3-carboxylic acid (0.072 g, 0.64 mmol), *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate (0.243 g, 0.64 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.205 mL, 1.17 mmol) in DMF (1.5 mL) was stirred for 15 minutes under argon. Finally, 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.15 g, 0.53 mmol) in DMF (3 mL) was added and the mixture was stirred at room temperature for 20 hours. The solvent was evaporated and the crude mixture was purified by silica gel flash chromatography (90:10 dichloromethane/methanol) to give the title compound (0.070 g, 35% of yield).

ESI/MS m/e: 377 ([M+H]+, $C_{18}H_{13}FN_8O$).

Step b:



6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-(4H-1,2,4-triazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine

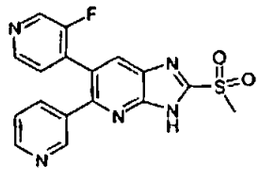
A solution of *N*-(6'-amino-3"-fluoro-3,2':3',4"-terpyridin-5'-yl)-1*H*-1,2,4-triazole-3-carboxamide (0.070 g, 0.19 mmol) in acetic acid (2.5 mL) was heated in a sealed tube at 120°C for 18h. The solvent was evaporated and the residue was suspended in ethyl acetate and 4% sodium bicarbonate aqueous solution. The solid formed was filtrered and dried *in vacuo* to give the title compound (0.039g, 59% of yield).

δ ^{1}H-NMR (DMSO-d_6): 7.33 (m, 1H), 7.56 (m, 1H), 7.69 (m, 1H), 8.13 (m, 1H), 8.47 (m, 4H), 8.69 (m, 1H).

ESI/MS m/e: 359 ([M+H]$^+$, $C_{18}H_{11}FN_8$).

Example 53

Step a:

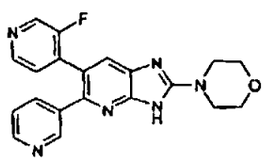


6-(3-Fluoropyridin-4-yl)-2-(methylsulfonyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

To a solution of 6-(3-fluoropyridin-4-yl)-2-(methylthio)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine (**Example 47**, 0.096 g, 0.285 mmol) in DCM (6 mL) was added 3-chlorobenzenecarboperoxoic acid (0.128 g, 77% purity, 0.570 mmol) at 0°C. The reaction mixture was warmed up to room temperature and stirred for 16 h. The mixture was concentrated and purified by reverse phase chromatography (water/acetonitrile) to give the title compound (0.040 g, 38% of yield).

ESI/MS m/e: 370 ([M+H]+, $C_{17}H_{12}FN_5O_2S$).

Step b:



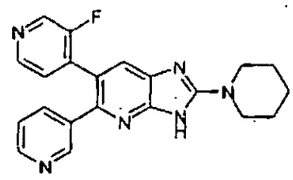
80

6-(3-Fluoropyridin-4-yl)-2-morpholin-4-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

A solution of 6-(3-fluoropyridin-4-yl)-2-(methylsulfonyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine (0.025 g, 0.068 mmol), morpholine (0.024 mL, 0.268 mmol) in dioxane (0.5 mL) was heated in a sealed tube at 120°C overnight. The solvent was evaporated and the residue was purified by silica gel flash chromatography (95:5 dichloromethane/methanol) to give the title compound (0.011g, 44% of yield).

ESI/MS m/e: 377 ([M+H]$^+$, $C_{20}H_{17}FN_6O$).

Example 54

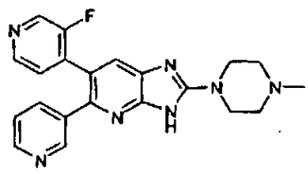


6-(3-Fluoropyridin-4-yl)-2-piperidin-1-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

A solution of 6-(3-fluoropyridin-4-yl)-2-(methylthio)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine (**Example 47**, 0.05 g, 0.15 mmol), piperidine (0.052 mL, 0.45 mmol) and acetic acid in xylene (1 mL) was heated at 120°C in a sealed tube. After 2 days, the solvent was evaporated and the crude mixture was purified by silica gel flash chromatography (95:5 dichloromethane/methanol) to give the title compound (0.03 g, 54% of yield).

ESI/MS m/e: 430 ([M+H]+, $C_{21}H_{19}FN_6$).

Example 55



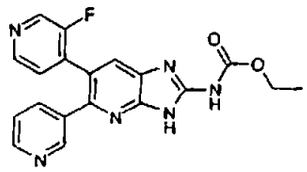
6-(3-Fluoropyridin-4-yl)-2-(4-methylpiperazin-1-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.045 g, 55% of yield) from 6-(3-fluoropyridin-4-yl)-2-(methylthio)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine (**Example 47**, 0.1 g, 0.3 mmol) and 1-methylpiperazine (0.117 mL, 1.05 mmol) following the procedure described in Example 57.

ESI/MS m/e: 390 ([M+H]$^+$, $C_{21}H_{20}FN_7$).

Example 56

Step a:



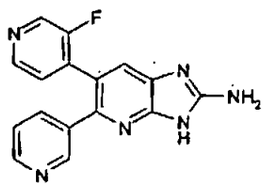
Ethyl [6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]carbamate

Obtained (0.175 g, 87% of yield) from 3"-fluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 1**, 0.15 g, 0.53 mmol) and ethyl isothiocyanatidocarbonate (0.094 mL, 0.8 mmol) following the procedure described in Example 19 (reaction time:20 h).

δ ^{1}H-NMR ($CDCl_3$): 1.37 (t, 3H), 4.37 (q, 2H), 7.23 (m, 2H), 7.70 (d, 1H), 7.81 (s, 1H), 8.39 (m, 2H), 8.51 (d, 1H), 8.57 (m, 1H).

ESI/MS m/e: 379 ($[M+H]^+$, $C_{19}H_{15}FN_6O_2$).

<u>Step b:</u>



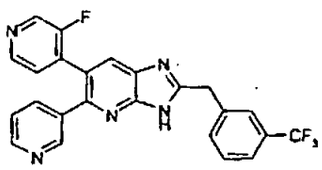
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine

A solution of ethyl [6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]carbamate (0.175 g, 0.46 mmol), potassium hydroxide (0.17 g, 3.01 mmol) in propan-2-ol (2 mL) was heated at 110°C for 24h. The solvent was evaporated and the crude mixture (0.38 g) was purified by reverse phase chromatography (water/acetonitrile) to give the title compound (0.08 g, 57% of yield).

δ ^{1}H-NMR (DMSO-d_6): 6.98 (s, 1H), 7.26 (dd, 1H), 7.42 (m, 2H), 7.62 (dt, 1H), 8.36-8.41 (m, 3H).

ESI/MS m/e: 307 ($[M+H]^+$, $C_{16}H_{11}FN_6$).

Example 57



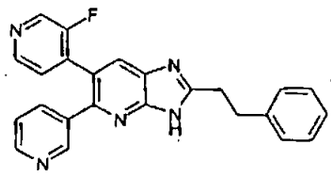
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-[3-(trifluoromethyl)benzyl]-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.026 g, 42% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and [3-(trifluoromethyl)phenyl]acetyl chloride (0.075 g, 0.337 mmol) following the procedure described in Example 37.

δ ^{1}H-NMR ($CDCl_3$): 4.47 (s, 2H), 7.04-7.11 (m, 1H), 7.25-7.60 (m, 6H), 7.66 (s, 1H), 8.04 (s, 1H), 8.26 (d, 1H), 8.40 (m, 1H), 8.46 (d, 1H), 9.31 (s, 1H).

ESI/MS m/e: 450 ($[M+H]^+$, $C_{24}H_{15}F_4N_5$).

Example 58



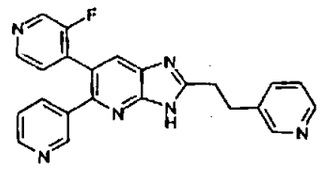
6-(3-Fluoropyridin-4-yl)-2-(2-phenylethyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.060 g, 49% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and 3-phenylpropanoyl chloride (0.080 mL, 0.534 mmol) following the procedure described in Example 37.

δ ^{1}H-NMR ($CDCl_3$): 3.24 (m, 4H), 7.11 (dd, 1H), 7.20-7.33 (m, 6H), 7.46 (d, 1H), 8.04 (s, 1H), 8.40 (d, 1H), 8.45 (d, 1H), 8.49 (dd, 1H), 9.23 (s, 1H), 12.76 (s, 1H).

ESI/MS m/e: 396 ($[M+H]^+$, $C_{24}H_{18}FN_5$).

Example 59



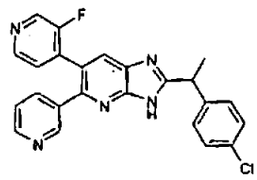
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-(2-pyridin-3-ylethyl)-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.02 g, 59% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and 3-pyridin-3-ylpropanoic acid (0.070 g, 0.463 mmol) following the procedure described in Example 41.

δ ^{1}H-NMR ($CDCl_3$): 3.29 (s, 4H), 7.23 (m, 3H), 7.61 (d, 2H), 8.00 (s, 1H), 8.37 (d, 1H), 8.40 (d, 1H), 8.45 (m, 1H), 8.52 (d, 1H), 8.54 (d, 1H), 8.65 (d, 1H).

ESI/MS m/e: 397 ($[M+H]^+$, $C_{23}H_{17}FN_6$).

Example 60



2-[1-(4-Chlorophenyl)ethyl]-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

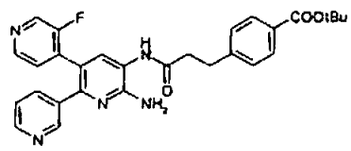
Obtained (0.035 g, 52% of yield) from 3"-fluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 1**, 0.15 g, 0.534 mmol) and 2-(4-chlorophenyl)propanoic acid (0.128 g, 0.694 mmol) following the procedure described in Example 41.

δ ^{1}H-NMR ($CDCl_3$): 1.91 (d, 3H), 4.51 (q, 1H), 7.08 (m, 1H), 7.30 (m, 5H), 7.39 (m, 1H), 8.07 (s, 1H), 8.28 (dd, 1H), 8.41 (d, 1H), 8.47 (d, 1H), 9.24 (d, 1H), 12.58 (s, 1H).

ESI/MS m/e: 430 ($[M+H]^+$, $C_{24}H_{17}ClFN_5$).

Example 61

Step a:

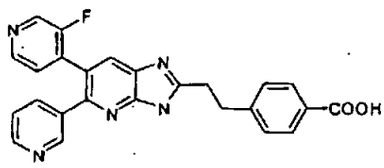


4-[2-(6'-Amino-3"-fluoro-[3,2';3',4"]terpyridin-5'-ylcarbamoyl)-ethyl]-benzoic acid *tert*-butyl ester

Obtained (0.135 g, 49% of yield) from 3"-fluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 1**, 0.15 g, 0.534 mmol) and 3-[4-(tert-butoxycarbonyl)phenyl]propanoic acid (0.174 g, 0.694 mmol) following the procedure described in Example 41, step a.

ESI/MS m/e: 514 ($[M+H]^+$, $C_{29}H_{28}FN_5O_3$).

Step b:

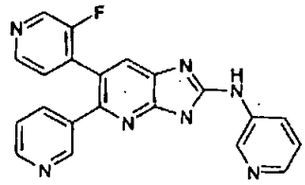


4-{2-[6-(3-Fluoro-pyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]-ethyl}-benzoic acid

A solution of 4-[2-(6'-Amino-3"-fluoro-[3,2';3',4"]terpyridin-5'-ylcarbamoyl)-ethyl]-benzoic acid *tert*-butyl ester (0.135 g, 0.263 mmol) in acetic acid (2 mL) was heated in a sealed tube at 118°C for 16h. The solvent was evaporated and ethyl acetate was added. The solid formed was filtrered and washed with 4% sodium bicarbonate aqueous solution, water and dried to give the title compound (0.08g, 69% of yield).

ESI/MS m/e: 440 ($[M+H]^+$, $C_{25}H_{18}FN_5O_2$).

Example 62

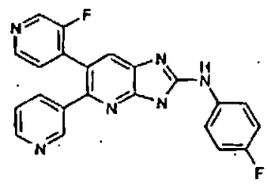


6-(3-Fluoropyridin-4-yl)-*N*,5-dipyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine

To a solution of 3"-fluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 1**, 0.1 g, 0.356 mmol) and 3-isothiocyanatopyridine (0.06 mL, 0.534 mmol) in ethanol (2 mL), 1,3-diisopropylcarbodiimide (0.083 mL, 0.534 mmol) was added. The mixture was heated at 50°C for 2h. After cooling at room temperature, the solvent was evaporated. The crude mixture was purified by silica gel flash chromatography (95:5 dichloromethane/methanol) to give the title compound (0.045 g, 33% of yield).

ESI/MS m/e: 384 ($[M+H]^+$, $C_{21}H_{14}FN_7$).

Example 63



***N*-(4-Fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine**

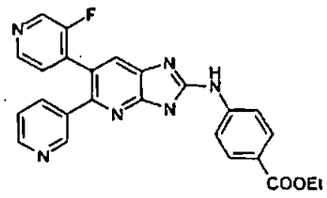
Obtained (0.048 g, 49% of yield) from 3"-fluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 1**, 0.15 g, 0.534 mmol) and 1-fluoro-4-isothiocyanatobenzene (0.082 g, 0.534 mmol) following the procedure described in Example 62.

δ ^{1}H-NMR (DMSO-d_6): 7.19 (t, 2H), 7.30 (dd, 1H), 7.47 (dd, 1H), 7.63-7.69 (m, 2H), 7.80-7.87 (m, 2H), 8.43 (m, 4H).

ESI/MS m/e: 401 ($[M+H]^+$, $C_{22}H_{14}F_2N_6$).

Example 64

Step a:

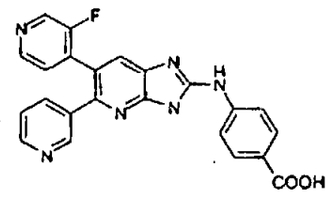


4-[6-(3-Fluoro-pyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-ylamino]-benzoic acid ethyl ester

Obtained (0.120 g, 74% of yield) from 3''-fluoro-3,2':3',4''-terpyridine-5',6'-diamine (**Intermediate 1**, 0.10 g, 0.356 mmol) and ethyl 4-isothiocyanatobenzoate (0.111 g, 0.534 mmol) following the procedure described in Example 62.

ESI/MS m/e: 455 ($[M+H]^+$, $C_{25}H_{19}FN_6O_2$).

Step b:

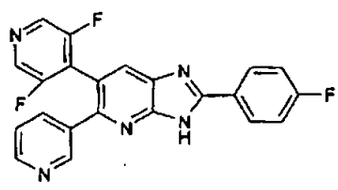


4-{[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]amino}benzoic acid

To a solution of 4-[6-(3-fluoro-pyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-ylamino]-benzoic acid ethyl ester (0.120 g, 0.264 mmol) in ethanol (3.5 mL), 2N sodium hydroxide aqueous solution (0.53 mL) was added. The mixture was stirred at room temperature overnight and then neutralised with 2N hydrogen chloride aqueous solution. The solvent was evaporated and the crude mixture (0.18 g) was purified by reverse phase chromatography (water/acetonitrile) to give the title compound (0.02g, 18% of yield).

ESI/MS m/e: 427 ($[M+H]^+$, $C_{23}H_{15}FN_6O_2$).

Example 65



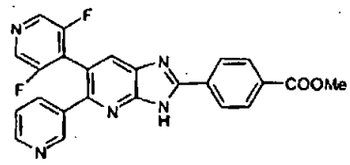
6-(3,5-Difluoropyridin-4-yl)-2-(4-fluorophenyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

Obtained (0.037 g, 20% of yield) from 3",5"-difluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 14**, 0.10 g, 0.33 mmol) and 4-fluorobenzoyl chloride (0.059 mL, 0.5 mmol) following the procedure described in Example 37.

ESI/MS m/e: 404 ($[M+H]^+$, $C_{22}H_{12}F_3N_5$).

Example 66

Step a:

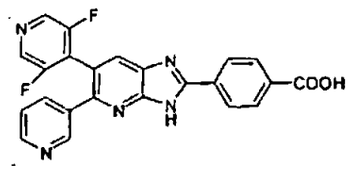


Methyl 4-[6-(3,5-difluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoate

Obtained (0.050 g, 70% of yield) from 3",5"-difluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 14**, 0.10 g, 0.33 mmol) and 4-(methoxycarbonyl)benzoic acid (0.078 g, 0.43 mmol) following the procedure described in Example 41.

ESI/MS m/e: 404 ($[M+H]^+$, $C_{22}H_{12}F_3N_5$).

Step b:



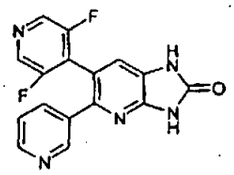
4-[6-(3,5-Difluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoic acid

To a solution of methyl 4-[6-(3,5-difluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoate (0.05 g, 0.11 mmol) in ethanol (1.1 mL), 2N sodium hydroxide aqueous solution (0.11 mL) was added. The mixture was heated at 60°C for 5.5 h and then neutralised with 2N hydrogen chloride aqueous solution. The solvent was evaporated and the crude mixture was suspended in water, the solid formed was filtrered and dried to give the title compound (0.04 g, 76% of yield).

δ ^{1}H-NMR (MeOD): 7.41 (m, 1H), 7.86 (m, 1H), 8.22-8.33 (m, 5H), 8.42 (s, 2H), 8.50 (s, 1H), 8.57 (s, 1H).

ESI/MS m/e: 430 ([M+H]$^+$, $C_{23}H_{13}F_2N_5O_2$).

Example 67



6-(3,5-Difluoropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

A solution of 3",5"-difluoro-3,2':3',4"-terpyridine-5',6'-diamine (**Intermediate 14**, 0.045 g, 0.15 mmol), *N,N'*-carbonyldiimidazole (0.1 g, 0.6 mmol) and triethylamine (0.084 mL, 0.6 mmol) in THF (1.5 mL) was heated at 80 °C in a sealed tube. After 72 hours, the mixture was cooled and the solid was separated, washed with THF and dried to give the title compound (0.029 g, 59% of yield).

δ ^{1}H-NMR (DMSO-d_6): 7.30 (dd, 1H), 7.44 (s, 1H), 7.61 (d, 1H), 8.38 (d, 1H), 8.46 (dd, 1H), 8.50 (s, 2H).

ESI/MS m/e: 326 ([M+H]+, $C_{16}H_9F_2N_5O$).

COMPOSITION EXAMPLE 1

50,000 capsules, each containing 100 mg 5-(3-Fluoropyridin-4-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (active ingredient), were prepared according to the following formulation:

Active ingredient	5 Kg
Lactose monohydrate	10 Kg
Colloidal silicon dioxide	0.1 Kg
Corn starch	1 Kg
Magnesium stearate	0.2 Kg

Procedure

The above ingredients were sieved through a 60 mesh sieve, and were loaded into a suitable mixer and filled into 50,000 gelatine capsules.

COMPOSITION EXAMPLE 2

50,000 tablets, each containing 50 mg of 5-(3-Fluoropyridin-4-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (active ingredient), were prepared from the following formulation:

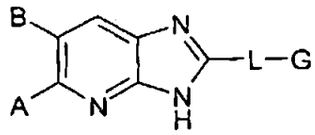
Active ingredient	2.5 Kg
Microcrystalline cellulose	1.95 Kg
Spray dried lactose	9.95 Kg
Carboxymethyl starch	0.4 Kg
Sodium stearyl fumarate	0.1 Kg
Colloidal silicon dioxide	0.1 Kg

Procedure

All the powders were passed through a screen with an aperture of 0.6 mm, then mixed in a suitable mixer for 20 minutes and compressed into 300 mg tablets using 9 mm disc and flat bevelled punches. The disintegration time of the tablets was about 3 minutes.

CLAIMS

1. A compound of formula (I)



wherein:

A represents a monocyclic nitrogen-containing heteroaryl group optionally substituted by one or more substituents independently selected from the group comprising halogen atoms, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl- C_{1-4}alkyl, C_{1-4}alkoxy, aryl-C_{1-4}alkoxy, C_{1-4}alkylthio, mono or di-C_{1-4}alkylamino, trifluoromethyl, hydroxy and cyano groups;

B represents a monocyclic nitrogen-containing heteroaryl group optionally substituted by one or more substituents independently selected from the group comprising halogen atoms, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl- C_{1-4}alkyl, C_{1-4}alkoxy, aryl-C_{1-4}alkoxy, C_{1-4}alkylthio, mono or di-C_{1-4}alkylamino, trifluoromethyl, hydroxy and cyano groups;

L represents a linking group selected from the group comprising direct bond, $-(CRR')_n-$, -NR-, -S-, -O- and -CO-; wherein n is an integer from 0 to 2;

G represent a group selected from the group comprising –H, -OH, C_{3-7} cycloalkyl; C_{1-6} alkyl, aryl, heteroaryl and nitrogen-containing saturated heterocyclic rings, wherein the aryl, heteroaryl and nitrogen-containing saturated heterocyclic groups are unsubstituted or substituted by one or more groups selected from halogen atoms, C_{1-4} alkyl, C_{1-4} alkylthio, C_{1-4} alkoxy, mono- or di-C_{1-4} alkylamino, cyano, trifluoromethyl, –COOH and -CO-O-C_{1-4} alkyl groups;

R and R' are independently selected from hydrogen atoms and C_{1-4} alkyl groups;

and the pharmaceutically acceptable salts and N-oxides thereof.

2. A compound according to claim 1 wherein A represents an optionally substituted pyridine or an optionally substituted oxazole group.

3. A compound according to any preceding claim wherein the group A represents a pyridine ring either unsubstituted or substituted with one halogen atom.

4. A compound according to any preceding claim wherein B represents an optionally substituted pyridine or pyrimidine group.

5. A compound according to claim 4 wherein B represents a pyridine group which is unsubstituted or substituted by one or more halogen atoms.

6. A compound according to any preceding claim wherein –L-G represents a moeity selected from the group comprising of hydrogen atoms, hydroxyl groups, optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzyl, optionally substituted benzoyl, C_{3-7} cycloalkyl; C_{1-6} alkyl, optionally substituted morpholino, optionally substituted piperidino and optionally substituted piperazine groups wherein optionally substituted groups may carry from 0 to 2 substituents selected from the group consisting of halogen atoms, C_{1-4}alkyl, C_{1-4}alkylthio, C_{1-4}alkoxy, mono or di-C_{1-4}alkylamino, cyano, -(CO)OH, -(CO)O-C_{1-4}alkyl, trifluoromethyl, piperidinylmethyl, pyridinylmethyl, phenylamino and piperidinylamino.

7. A compound according to claim 1 which is one of:

6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one
2-Cyclopropyl-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
2-Cyclohexyl-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-methyl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
2-(4-Fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-(4-methoxyphenyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
N-{4-[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3H-imidazo[4,5-b]pyridin-2-yl]phenyl}-*N*,*N*-dimethylamine
6-(3-Fluoropyridin-4-yl)-2-(4-*tert*-butylphenyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-[4-(trifluoromethyl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine
Methyl 4-[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoate
4-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoic acid
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Fluoropyridin-4-yl)-2-[3-fluoro-4-(trifluoromethyl)phenyl]-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

2-(2,4-Dichloro-5-fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

2-(4-Fluorobenzyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

2-[1-(4-Chlorophenyl)-1-methylethyl]-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

(3,5-Difluorophenyl)[6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone

N-(4-chlorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine

2-(4-Fluorophenyl)-5-pyridin-3-yl-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Chloropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5,6-Dipyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(3-Fluoropyridin-4-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(3-Chloropyridin-4-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(3-Chloropyridin-4-yl)-2-(4-fluorophenyl)-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Chloropyridin-4-yl)-5-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

6-(3-Chloropyridin-4-yl)-2-(4-fluorophenyl)-5-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

5-(3-Chloropyridin-4-yl)-2-(4-fluorophenyl)-6-(3-fluoropyridin-4-yl)-3*H*-imidazo[4,5-*b*]pyridine

5,6-Bis(3-chloropyridin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(1,3-Oxazol-2-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(1,3-Oxazol-2-yl)-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Fluoropyridin-4-yl)-5-(1,3-oxazol-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

6-(3-Fluoropyridin-4-yl)-5-(1,3-oxazol-2-yl)-3*H*-imidazo[4,5-*b*]pyridine

5-(1,3-Oxazol-5-yl)-6-pyridin-4-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

5-(1,3-Oxazol-5-yl)-6-pyridin-4-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Fluoropyridin-4-yl)-5-(1,3-oxazol-5-yl)-3*H*-imidazo[4,5-*b*]pyridine

2-(3-Fluoro-4-methylphenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine.

2-(3-Fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Fluoropyridin-4-yl)-2,5-dipyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

6-(3-Fluoropyridin-4-yl)-2-pyrazin-2-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine

3-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzonitrile
3-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoic acid;
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-pyrimidin-5-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-pyridin-2-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
2-(3-Chloropyridin-4-yl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-(1-methyl-1*H*-imidazol-5-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-(methylthio)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
1-[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]-1*H*-pyrazole-4-carboxylic acid
6-(3-Fluoropyridin-4-yl)-2-(1-methyl-1*H*-pyrazol-5-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-5-pyridin-3-yl-3H-imidazo[4,5-*b*]pyridine
2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-(4*H*-1,2,4-triazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-morpholin-4-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-piperidin-1-yl-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-(4-methylpiperazin-1-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-[3-(trifluoromethyl)benzyl]-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-2-(2-phenylethyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-2-(2-pyridin-3-ylethyl)-3*H*-imidazo[4,5-*b*]pyridine
2-[1-(4-Chlorophenyl)ethyl]-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
4-{2-[6-(3-Fluoro-pyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]-ethyl}-benzoic acid
6-(3-Fluoropyridin-4-yl)-*N*,5-dipyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine
N-(4-Fluorophenyl)-6-(3-fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-amine
4-{[6-(3-Fluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]amino}benzoic acid
6-(3,5-Difluoropyridin-4-yl)-2-(4-fluorophenyl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridine
4-[6-(3,5-Difluoropyridin-4-yl)-5-pyridin-3-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl]benzoic acid
6-(3,5-Difluoropyridin-4-yl)-5-pyridin-3-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

8. A compound according to any one of claims 1 to 7 for use in the treatment of a pathological condition or disease susceptible to amelioration by antagonism of the adenosine A_{2B} receptor.

9. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 7 in association with a pharmaceutically acceptable diluent or carrier.

10. Use of a compound as defined in any one of claims 1 to 7 in the manufacture of a medicament for the treatment of a pathological condition or disease susceptible of being improved by antagonism of the A_{2B} adenosine receptor.

11. Use according to claim 10, wherein the pathological condition or disease is asthma, bronchoconstriction, allergic diseases, hypertension, atherosclerosis, reperfusion injury, myocardial ischemia, retinopathy, inflammation, gastrointestinal tract disorders, cell proliferation disorders, diabetes mellitus, and/or autoimmune diseases.

12. A method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by antagonism of the A_{2B} adenosine receptor, which comprises administering to said subject an effective amount of a compound as defined in any one of claims 1 to 7.

13. A method according to claim 12, wherein the pathological condition or disease is asthma, bronchoconstriction, allergic diseases, hypertension, atherosclerosis, reperfusion injury, myocardial ischemia, retinopathy, inflammation, gastrointestinal tract disorders, cell proliferation disorders, diabetes mellitus, and/or autoimmune diseases.

14. A combination product comprising:

(i) a compound according to any one of claims 1 to 7; and

(ii) another compound selected from (1) antagonists of M3 muscarinic receptors, (2) β2-agonists, (3) PDE4 inhibitors, (4) cortiocosteroids, (5) leukotriene D4 antagonists, (6) inhibitors of egfr-kinase, (7) p38 kinase inhibitors, (8) NK1 receptor agonists, (9) CRTh2 antagonists, (10) syk kinase inhibitors, (11) CCR3 antagonists and (12) VLA-4 antagonists

for simultaneous, separate or sequential use in the treatment of the human or animal body.

NUEVOS DERIVADOS IMIDAZOPIRIDINA

La presente invención se refiere a nuevos antagonistas del receptor de adenosina A_{2B}. Estos compuestos son útiles en el tratamiento, prevención o supresión de enfermedades y trastornos conocidos por ser susceptibles de mejora por acción antagonista del receptor de adenosina A_{2B}, tales como asma, enfermedad pulmonar obstructiva crónica, fibrosis pulmonar, enfisema, enfermedades alérgicas, inflamación, lesión por reperfusión, isquemia de miocardio, aterosclerosis, hipertensión, retinopatía, diabetes mellitus, trastornos inflamatorios del tracto gastrointestinal y/o enfermedades autoinmunes.

La adenosina regula diversas funciones fisiológicas a través de receptores específicos de la membrana celular que son miembros de la familia de receptores acoplados a la proteína G. Se han identificado y clasificado cuatro receptores diferenciados de adenosina: A_1, A_{2A}, A_{2B} y A_3.

El subtipo de receptor de adenosina A_{2B} (véase Feoktistov, I., Biaggioni, I. *Pharmacol. Rev.* 1997, *49*, 381-402) se ha identificado en una diversidad de tejidos humanos y murinos y está implicado en la regulación del tono vascular, crecimiento del músculo liso, angiogénesis, producción de glucosa hepática, movimiento del intestino, secreción intestinal y desgranulación de mastocitos.

A la vista de los efectos fisiológicos mediados por la activación del receptor de adenosina, se han descrito recientemente varios antagonistas del receptor A_{2B} para el tratamiento o prevención de asma, broncoconstricción, enfermedades alérgicas, hipertensión, aterosclerosis, lesión por reperfusión, isquemia de miocardio, retinopatía, inflamación, trastornos del tracto gastrointestinal, enfermedades de proliferación celular y/o diabetes mellitus. Véanse por ejemplo los documentos WO2005070926, WO2005042534, WO2005021548, WO2004106337, US2004176399, US2003229106, WO03002566, WO03/063800, WO03/042214, WO 03/035639, WO02/42298, EP 1283056, WO 01/16134, WO 01/02400, WO01/60350, WO 00/73307 o *Br. J. Pharmacol.* **2005**, *145*, 1009-1015.

Se ha descubierto ahora que ciertos derivados de imidazopiridina son nuevos potentes antagonistas del receptor de adenosina A_{2B} y, por tanto, se pueden usar en el tratamiento o prevención de estas enfermedades.

nitrógeno no sustituidos o sustituidos con uno o más grupos seleccionados de átomos de halógeno, grupos alquilo C_{1-4}, alquil C_{1-4} tio, alcoxi C_{1-4}, mono- o di-alquil C_{1-4}amino, ciano, trifluorometilo, –COOH y -CO-O-alquilo C_{1-4};

R y R' se seleccionan independientemente de entre átomos de hidrógeno y grupos alquilo C_{1-4};

y sus sales y N-óxidos farmacéuticamente aceptables.

Tal y como se usan en la presente memoria los términos alquilo y alquilo inferior incluyen radicales hidrocarbonados lineales o ramificados opcionalmente sustituidos que tienen de 1 a 8, con preferencia de 1 a 6 y, más preferiblemente, de 1 a 4 átomos de carbono. Sustituyentes preferidos en los grupos alquilo son átomos de halógeno y grupos hidroxi.

Ejemplos incluyen radicales metilo, etilo, *n*-propilo, *i*-propilo, *n*-butilo, *sec*-butilo y *terc*-butilo, *n*-pentilo, 1-metilbutilo, 2-metilbutilo, isopentilo, 1-etilpropilo, 1,1-dimetilpropilo, 1,2-dimetilpropilo, *n*-hexilo, 1-etilbutilo, 2-etilbutilo, 1,1-dimetilbutilo, 1,2-dimetilbutilo, 1,3-dimetilbutilo, 2,2-dimetilbutilo, 2,3-dimetilbutilo, 2-metilpentilo, 3-metilpentilo e iso-hexilo.

Tal y como se usa en la presente memoria, el término cicloalquilo incluye radicales carbocíclicos saturados y, a no ser que se indique de otro modo, un radical cicloalquilo tiene de forma típica de 3 a 7 átomos de carbono.

Ejemplos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo. Cuando un radical cicloalquilo tiene 2 o más sustituyentes, los sustituyentes pueden ser iguales o distintos. Sustituyentes preferidos en los grupos cicloalquilo son átomos de halógeno y grupos hidroxi.

Tal y como se usa en la presente memoria, a no ser que se indique de otro modo, el término radical arilo incluye de forma típica un radical arilo monocíclico o policíclico C_5-C_{14} tal como fenilo o naftilo, antranilo o fenantrilo. Se prefiere fenilo opcionalmente sustituido. Cuando un radical arilo tiene 2 o más sustituyentes, los sustituyentes pueden ser iguales o distintos. Sustituyentes preferidos en los radicales arilo son átomos de halógeno y grupos alquilo C_{1-4}, alquil C_{1-4}tio, alcoxi C_{1-4}, mono- o di-alquil C_{1-4}amino, ciano,

trifluorometilo, –COOH y -CO-O-alquilo C_{1-4}. Se prefieren de forma particular los átomos de halógeno.

Tal y como se usa en la presente memoria, a no ser que se indique de otro modo, el término heteroarilo incluye de forma típica un sistema de anillo de 5 a 14 miembros que comprende al menos un anillo heteroaromático y que contiene al menos un heteroátomo seleccionado de O, S y N. El término heteroarilo que contiene nitrógeno se usa para designar grupos heteroarilo que comprenden al menos un átomo de nitrógeno que forma parte del sistema de anillo. Un radical heteroarilo puede ser un único anillo o más anillos condensados en los que al menos un anillo contiene un heteroátomo.

Ejemplos de radicales heteroarilo monocíclicos incluyen radicales piridilo, pirazinilo, pirimidinilo, piridazinilo, furilo, oxadiazolilo, oxazolilo, imidazolilo, tiazolilo, tiadiazolilo, tienilo, pirrolilo, piridinilo, triazolilo, imidazolidinilo y pirazolilo. Se prefieren los radicales piridilo, tienilo, furilo, piridazinilo y pirimidinilo. Los más preferidos son piridilo y pirimidinilo.

Cuando un radical heteroarilo tiene 2 o más sustituyentes, los sustituyentes pueden ser iguales o distintos. Sustituyentes preferidos en los radicales heteroarilo son átomos de halógeno y grupos alquilo C_{1-4}, cicloalquilo C_{3-7}, cicloalquil C_{3-7}- alquilo C_{1-4}, alcoxi C_{1-4}, aril-alcoxi C_{1-4}, alquil C_{1-4}tio, mono o di-alquil C_{1-4}amino, trifluorometilo, hidroxi –COOH, -CO-O-alquilo C_{1-4} y ciano.

Tal y como se usa en la presente memoria, el término grupo heterociclico incluye de forma típica un anillo carbocíclico C_3-C_{10} saturado o no saturado no aromático tal como un radical de 5, 6 ó 7 miembros en el que uno o más, por ejemplo, 1, 2, 3 ó 4 de los átomos de carbono, con preferencia 1 ó 2, de los átomos de carbono están reemplazados por un heteroátomo seleccionado de N, O y S. El término anillo heterocíclico saturado que contiene nitrógeno se usa para designar grupos heterocíclicos saturados que comprenden al menos un átomo de nitrógeno que forma parte del sistema de anillo. Un radical heterocíclico puede ser un único anillo o dos o más anillos condensados en los que al menos un anillo contiene un heteroátomo. Cuando un radical heterociclilo tiene 2 o más sustituyentes, los sustituyentes pueden ser iguales o distintos. Sustituyentes preferidos en los radicales heterocíclicos son átomos de halógeno y grupos alquilo C_{1-4},

alquil C_{1-4}tio, alcoxi C_{1-4}, mono- o di-alquil C_{1-4}amino, ciano, trifluorometilo –COOH y -CO-O-alquilo C_{1-4}.

Ejemplos de radicales heterocíclicos monocíclicos que contienen nitrógeno incluyen piperidilo, pirrolidilo, pirrolinilo, piperazinilo, morfolinilo, tiomorfolinilo, pirrolilo, pirazolinilo, pirazolidinilo, quinuclidinilo, pirazolilo. Se prefieren los radicales piperidilo, piperazinilo y morfolinilo.

Tal y como se usa en la presente memoria, algunos de los átomos, radicales, restos, cadenas o ciclos presentes en las estructuras generales de la invención están "opcionalmente sustituidos". Esto significa que estos átomos, radicales, restos, cadenas o ciclos pueden estar no sustituidos o estar sustituidos en cualquier posición con uno o más, por ejemplo 1, 2, 3 ó 4, sustituyentes, por lo que los átomos de hidrógeno unidos a los átomos, radicales, restos, cadenas o ciclos no sustituidos están reemplazados por átomos, radicales, restos, cadenas o ciclos químicamente aceptables. Cuando están presentes dos o más sustituyentes, cada sustituyente puede ser igual o distinto.

Tal y como se usa en la presente memoria, el término átomo de halógeno incluye un átomo de cloro, flúor, bromo o yodo, de forma típica un átomo de flúor, cloro o bromo, lo más preferible cloro o flúor. El término halo cuando se usa como prefijo tiene el mismo significado.

Tal y como se usa en la presente memoria, el término sal farmacéuticamente aceptable incluye sales con un ácido o base farmacéuticamente aceptable. Ácidos farmacéuticamente aceptables incluyen ácidos inorgánicos, por ejemplo, ácido clorhídrico, sulfúrico, fosfórico, difosfórico, bromhídrico, yodhídrico y nítrico, y ácidos orgánicos, por ejemplo, ácidos cítrico, fumárico, maleico, málico, mandélico, ascórbico, oxálico, succínico, tartárico, benzoico, acético, metanosulfónico, etanosulfónico, bencenosulfónico o *p*-toluenosulfónico. Bases farmacéuticamente aceptables incluyen hidróxidos de metales alcalinos (por ejemplo, sodio o potasio) y alcalinotérreos (por ejemplo, calcio o magnesio) y bases orgánicas, por ejemplo alquilaminas, arilalquilaminas y aminas heterocíclicas.

Otras sales preferidas conforme a la invención son compuestos de amonio cuaternario en los que un equivalente de un anión (X-) está asociado con la carga positiva del átomo de

N. X- puede ser un anión de diversos ácidos minerales tales como, por ejemplo, cloruro, bromuro, yoduro, sulfato, nitrato, fosfato, o un anión de un ácido orgánico, tal como, por ejemplo, acetato, maleato, fumarato, citrato, oxalato, succinato, tartrato, malato, mandelato, trifluoroacetato, metanosulfonato y *p*-toluenosulfonato. X- es preferiblemente un anión seleccionado de cloruro, bromuro, yoduro, sulfato, nitrato, acetato, maleato, oxalato, succinato o trifluoroacetato. Más preferiblemente X- es cloruro, bromuro, trifluoroacetato o metanosulfonato.

Tal y como se usa en la presente memoria, un N-óxido se forma a partir de las aminas o iminas básicas terciarias presentes en la molécula, usando un agente oxidante conveniente.

Compuestos preferidos de la invención son aquellos en los que A representa un grupo piridina opcionalmente sustituido o un grupo oxazol opcionalmente sustituido. Se prefiere además que A represente un anillo piridina, ya sea no sustituido o sustituido con un átomo de halógeno.

En otra realización de la presente invención, el grupo B representa un grupo piridina o pirimidina opcionalmente sustituidos. Se prefiere además que B represente un grupo piridina que no está sustituido o está sustituido con uno o más átomos de halógeno.

En una realización alternativa de la presente invención, -LG representa un resto seleccionado del grupo consistente en átomos de hidrógeno, grupos hidroxilo, fenilo opcionalmente sustituido, piridilo opcionalmente sustituido, bencilo opcionalmente sustituido, benzoilo opcionalmente sustituido, cicloalquilo C_{3-7}; alquilo C_{1-6}, morfolino opcionalmente sustituido, piperidino opcionalmente sustituido y grupos piperazina opcionalmente sustituidos, pudiendo tener los grupos opcionalmente sustituidos de 0 a 2 sustituyentes seleccionados del grupo consistente en átomos de halógeno, alquilo C_{1-4}, alquil C_{1-4}tio, alcoxi C_{1-4}, mono o di-alquil C_{1-4}amino, ciano, -(CO)OH, -(CO)O-alquilo C_{1-4}, trifluorometilo, piperidinilmetilo, piridinilmetilo, fenilamino y piperidinilamino.

Compuestos individuales particulares de la invención para su uso en la fabricación de un medicamento para el tratamiento de un estado patológico o enfermedad que puede mejorar por efecto antagonista del receptor de adenosina A_{2B} incluyen:

6-(3-Fluoropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

2-Ciclopropil-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-Ciclohexil-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-metil-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-(4-Fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-(4-metoxifenil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

N-{4-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3H-imidazo[4,5-b]piridin-2-il]fenil}-*N*,*N*-dimetilamina

6-(3-Fluoropiridin-4-il)-2-(4-*terc*-butilfenil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-[4-(trifluorometil)fenil]-3*H*-imidazo[4,5-*b*]piridina

4-[6-(3-Fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoato de metilo

Ácido 4-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoico

6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

2-(2,3-Dihidro-1,4-benzodioxin-6-il)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-[3-fluoro-4-(trifluorometil)fenil]-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-(2,4-Dicloro-5-fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-(4-Fluorobencil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-[1-(4-Clorofenil)-1-metiletil]-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

(3,5-Difluorofenil)[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]metanona

N-(4-clorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina

2-(4-Fluorofenil)-5-piridin-3-il-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Cloropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5,6-Dipiridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(3-Fluoropiridin-4-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(3-Cloropiridin-4-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Cloropiridin-4-il)-5-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

6-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-5-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

5-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-6-(3-fluoropiridin-4-il)-3*H*-imidazo[4,5-*b*]piridina

5,6-Bis(3-cloropiridin-4-il)-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(1,3-Oxazol-2-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(1,3-Oxazol-2-il)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-5-(1,3-oxazol-2-il)-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

6-(3-Fluoropiridin-4-il)-5-(1,3-oxazol-2-il)-3*H*-imidazo[4,5-*b*]piridina

5-(1,3-Oxazol-5-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(1,3-Oxazol-5-il)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-5-(1,3-oxazol-5-il)-3*H*-imidazo[4,5-*b*]piridina

2-(3-Fluoro-4-metilfenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina.

2-(3-Fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2,5-dipiridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-pirazin-2-il-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

3-[6-(3-Fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzonitrilo

Ácido 3-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoico;

6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-pirimidin-5-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-piridin-2-il-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-(3-Cloropiridin-4-il)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-(1-metil-1*H*-imidazol-5-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-(metiltio)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Ácido 1-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]-1*H*-pirazol-4-carboxílico

6-(3-Fluoropiridin-4-il)-2-(1-metil-1*H*-pirazol-5-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-[1-metil-3-(trifluorometil)-1*H*-pirazol-5-il]-5-piridin-3-il-3H-imidazo[4,5-*b*]piridina

2-(3,5-Dimetil-1*H*-pirazol-1-il)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-(4*H*-1,2,4-triazol-3-il)-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-morfolin-4-il-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-piperidin-1-il-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-(4-metilpiperazin-1-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina

6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-[3-(trifluorometil)bencil]-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-(2-feniletil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-(2-piridin-3-iletil)-3*H*-imidazo[4,5-*b*]piridina

2-[1-(4-Clorofenil)etil]-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Ácido 4-{2-[6-(3-fluoro-piridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]-etil}-benzoico

6-(3-Fluoropiridin-4-il)-*N*,5-dipiridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina

N-(4-Fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina

Ácido 4-{[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]amino}benzoico

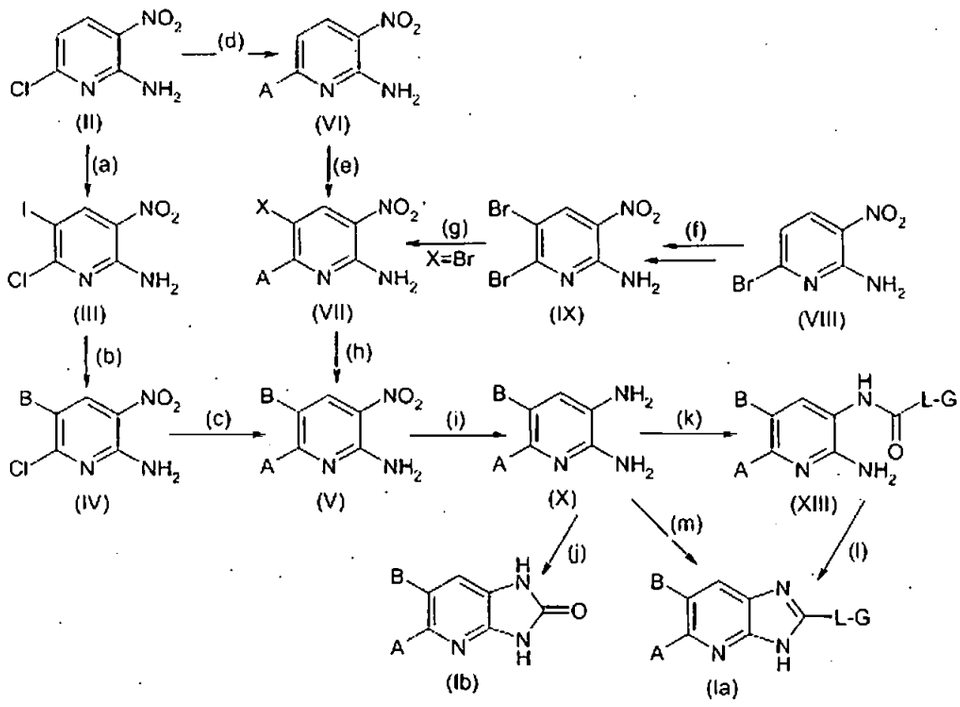
6-(3,5-Difluoropiridin-4-il)-2-(4-fluorofenil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
Ácido 4-[6-(3,5-difluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoico
6-(3,5-Difluoropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

Son de particular interés:

5-(3-Fluoropiridin-4-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona
6-(3-Fluoropiridin-4-il)-5-(1,3-oxazol-2-il)-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona
Ácido 4-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoico
6-(3-Fluoropiridin-4-il)-2-(4-metoxifenil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
N-{4-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]fenil}-*N*,*N*-dimetilamina
6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina
2-(4-Fluorobencil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
2-(3-Fluoro-4-metilfenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina.
2-(3-Fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
6-(3-Fluoropiridin-4-il)-2,5-dipiridin-3-il-3*H*-imidazo[4,5-*b*]piridina
6-(3-Fluoropiridin-4-il)-2-(1-metil-1*H*-imidazol-5-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
6-(3,5-Difluoropiridin-4-il)-2-(4-fluorofenil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
Ácido 4-[6-(3,5-difluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoico
6-(3,5-Difluoropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

Los compuestos de fórmula general (I) y en particular aquellos en los que A, B son como se definen en la reivindicación 1 y L representa un grupo de unión seleccionado del grupo consistente en un enlace directo, $-(CRR')_n-$ o –CO- y G representa un grupo seleccionado del grupo consistente en –H, -OH (fórmula general (XI)), cicloalquilo C_{3-7}; alquilo C_{1-4}, arilo, heteroarilo y anillos heterocíclicos saturados que contienen nitrógeno (fórmula general (XII)) se pueden preparar siguiendo el esquema de síntesis representado en el esquema 1.

Esquema 1



Etapa a

La halogenación de 6-cloro-3-nitropiridin-2-amina (II) usando reactivos tales como I_2 o *N*-halosuccinimida en disolventes apróticos polares tales como DMF o mezclas de disolventes DMSO:H_2O y a temperaturas que varian de 0ºC a 100ºC proporciona dihalonitropiridin-2-aminas (III).

Etapa b

El acoplamiento regioselectivo de Suzuki o de Stille con el ácido borónico o derivado de boronato o el derivado de trialquilestaño (con preferencia tributilestaño) de B usando un catalizador de paladio tal como tetrakis(trifenilfosfina)paladio(0), complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno] paladio(II)- diclorometano (1:1) o dicloruro de bis(trifenilfosfina) paladio(II) en disolventes tales como tolueno, dioxano en presencia de una solución acuosa de una base tal como carbonato de sodio o de cesio y a una temperatura de 25ºC a 110ºC, o en disolventes tales como DMF usando un catalizador de cobre y a una temperatura de 25ºC a 150ºC proporciona compuestos de fórmula general (IV).

Etapa c

Otro acoplamiento de tipo Suzuki, Negishi o Stille usando el derivado de ácido borónico o boronato correspondiente, el derivado de arilzinc o el derivado de trialquilestaño (preferiblemente tributilestaño) de A en los procedimientos convencionales para reacciones catalizadas con Pd descritas antes proporciona las 2-amino-3-nitropiridinas (V).

Etapas d y e

Como alternativa, el acoplamiento regioselectivo de tipo Suzuki, Stille o Negishy del derivado correspondiente de A con 6-cloro-3-nitropiridin-2-amina (II), usando los procedimientos convencionales para reacciones catalizadas con Pd descritas antes, proporciona compuestos de fórmula general (VI), que, tras una etapa de halogenación usando los mismos protocolos descritos antes proporciona compuestos de fórmula general (VII).

Etapas f y g

Se preparan derivados dihalopiridina (IX) por halogenación de derivados de 6-halopiridina (VIII) usando reaccionantes tales como Br_2 o *N*-halosuccinimida en disolventes apróticos polares tales como DMF y a temperaturas que varían de 0°C a 100°C, proporcionando dihaloaminopiridinas (no mostradas). Se nitran estos productos a su vez en un procedimiento en dos etapas que requiere la nitración del grupo amina en una mezcla de ácido sulfúrico y ácido nítrico en un intervalo de temperatura que varía de –10°C a 0°C seguido por una transposición promovida por ácido sulfúrico del grupo nitro produciendo compuestos de formula (IX). Un acoplamiento regioselectivo de tipo Suzuki, Negishi o Stille con el derivado correspondiente de A y usando los procedimientos convencionales para reacciones catalizadas con Pd descritos antes proporciona compuestos de fórmula general (VII).

Etapas h e i

Un acoplamiento adicional del tipo Suzuki o Still con el derivado correspondiente de B descrito antes proporciona compuestos de fórmula general (V). La reducción del grupo nitro usando condiciones convencionales de hidrogenación en presencia de hidrógeno y usando Pd sobre carbón como catalizador proporciona los derivados diamino (X). De forma alternativa, también se puede llevar a cabo la reducción del grupo nitro por tratamiento con hierro en presencia de ácido clorhídrico en disolventes tales como etanol.

Etapa j

El tratamiento de (X) con agentes de carbonilación tales como carbonildiimidazol en disolventes apróticos polares como DMF o THF en presencia o no de una base tal como hidruro de sodio o trietilamina y calentando a temperaturas que varían de 50°C a 200°C proporciona los compuestos imidazolona (Ib).

Etapas k y l

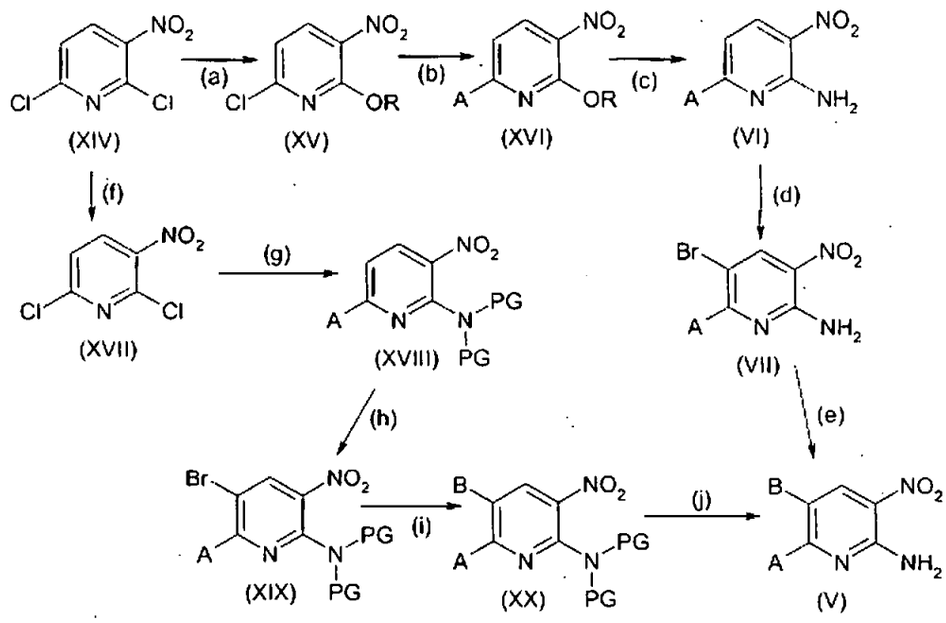
El tratamiento de compuestos de fórmula (X) con agentes de acilación tales como anhídridos, cloruros de ácido o carbonatos de acilo en disolventes orgánicos apolares como THF y en presencia de una base orgánica conveniente (como trietilamina) o base inorgánica, y finalmente acilación con ácidos carboxílicos usando agentes de acoplamiento como dietilcarbodiimida, proporciona los compuestos de fórmula (XIII), que se pueden convertir en los compuestos de fórmula (Ia) por ciclación catalizada por ácido (por ejemplo, ácido acético) o base (por ejemplo, hidróxido sódico) a temperaturas que varían de 70°C a 200°C.

Etapa m

De forma alternativa, se pueden ciclar los derivados diamino (X) a las imidazopiridinas (Ia) calentando en trialquilortoácido puro o en una solución de ácido acético de los derivados ortoácido o usando un cloruro de acilo y un disolvente tal como piridina y a temperaturas que varían de 70°C a 200°C.

Siguiendo otra ruta de síntesis (Esquema 2), también se puede llegar a los intermedios (V) partiendo de 2,6-dicloro-3-nitropiridina (XIV)

Esquema 2



Etapas a a e

El desplazamiento de la funcionalidad 2-cloro de (XIV) con un alcohol, con preferencia alcohol metílico, en presencia de una base, con preferencia hidruro sódico, en un disolvente orgánico como xileno conduce a compuestos defórmula (XV). La reacción de (XV) en las condiciones típicas de acoplamiento cruzado con, por ejemplo, un ácido arilborónico o un arilestannato, con preferencia un tributilestannato, en presencia de un catalizador de paladio tal como tetrakis(trifenilfosfina)paladio(0) o complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno] paladio(II) - diclorometano (1:1) en disolventes tales como tolueno o dioxano a temperaturas que varían de 80°C -120°C produce los intermedios de tipo (XVI). El desplazamiento de la funcionalidad alcoxi de (XVI) calentando con amoníaco acuoso concentrado a temperaturas que varían de 80°C - 120°C en un recipiente sellado da lugar a los intermedios de tipo (VI) que se pueden elaborar hasta intermedios (V) usando los protocolos representados en el Esquema 1.

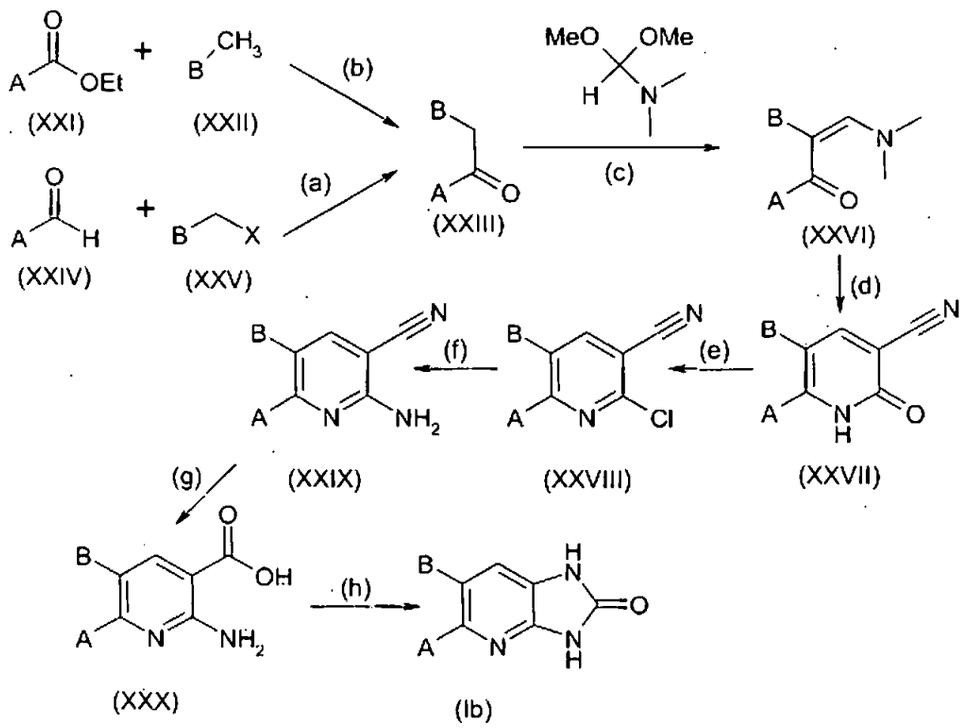
Etapas f a j

También se puede acceder a los intermedios de tipo (V) a través de una ruta alternativa (Esquema 2) partiendo de 2,6-dicloro-3-nitropiridina (XIV). El desplazamiento de la funcionalidad 2-cloro con una amina alifática secundaria adecuada, tal como *N,N*-di(4-metoxi)bencilamina, en un disolvente adecuado tal como cloroformo en presencia de una base orgánica como trietilamina, a temperaturas que varían de 0°C a 25°C da lugar a

intermedios de tipo (XVII), que se pueden considerar una versión del compuesto (II) con el nitrógeno protegido. La reacción de (XVII) en condiciones típicas de acoplamiento cruzado con, por ejemplo un ácido aril borónico o un arilestannato en presencia de un catalizador de paladio tal como tetrakis(trifenilfosfina)paladio(0) o complejo de dicloruro de [1,1'-bis(difenilfosfino)ferroceno] paladio(II) - diclorometano (1:1) en disolventes tales como tolueno o dioxano a temperaturas que varían de 80°C -120°C da lugar a intermedios del tipo (XVIII) que se pueden halogenar usando reactivos tales como Br_2 o *N*-halosuccinimida en disolventes apróticos polares tales como DMF y a temperaturas que varían de 0°C a 100°C, proporcionando compuestos (XIX). Una segunda reacción de acoplamiento cruzado catalizada con paladio da lugar a los intermedios (XX) que se pueden desproteger con, por ejemplo, ácido trifluoroacético en diclorometano, dando lugar a los intermedios (V) deseados.

Los compuestos de fórmula general (Ib) que corresponden a compuestos de fórmula (I) en la que L es un enlace directo, G es un grupo hidroxi y A y B son como se definen en la reivindicación 1, se pueden preparar siguiendo el esquema de síntesis representado en el Esquema 3.

Esquema 3



Etapa a

Los aldehidos de fórmula (XXIV) se hacen reaccionar con los derivados halometilo de fórmula (XXV) proporcionando las cetonas de fórmula (XXIII) bien sea a través de intermedios cianohidrina o en un proceso en dos etapas que requiere la adición de un derivado organometálico de (XXV), con preferencia derivado de magnesio o zinc, seguido por la reoxidación del alcohol resultante usando agentes oxidantes tales como óxido de manganeso (IV).

Etapa b

De forma alternativa, se pueden obtener las cetonas de fórmula (XXIII) por condensación de los ésteres etílicos de fórmula (XXI) con los compuestos de fórmula (XXII). Esta reacción se lleva a cabo convenientemente en presencia de una base orgánica tal como bis(trimetilsilil)amida de litio en un intervalo de temperaturas de aproximadamente -10°C a aproximadamente 50°C y en disolventes orgánicos apróticos, con preferencia tetrahidrofurano o éter dietílico.

Etapas c a e

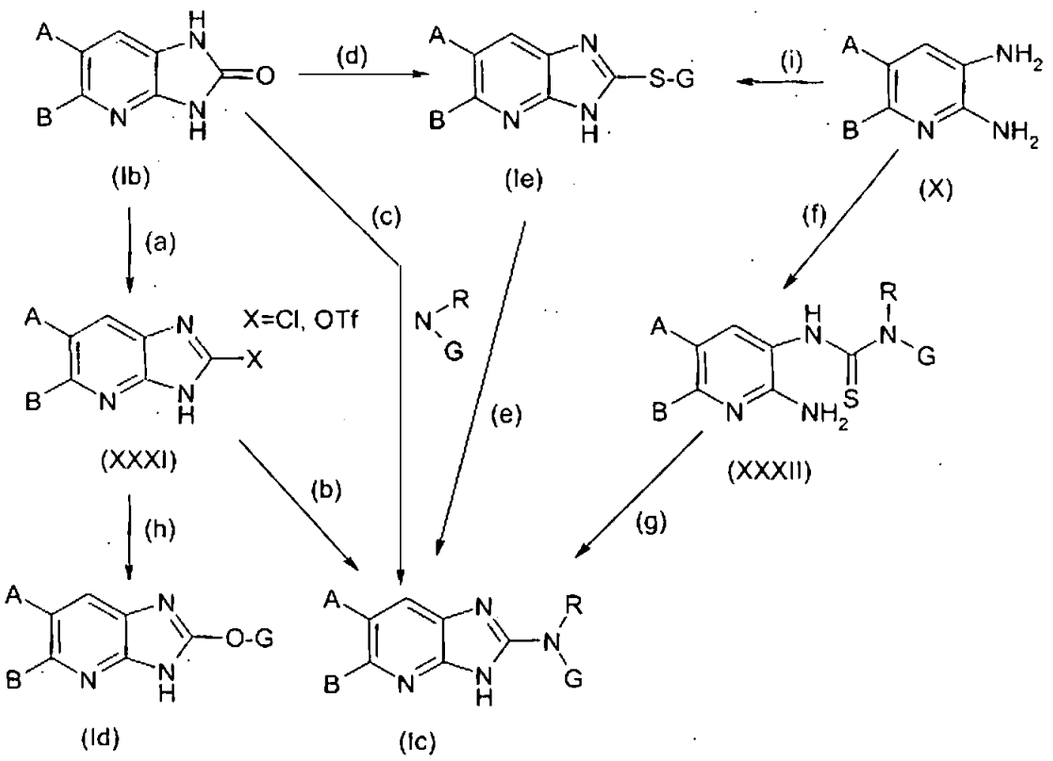
Se hacen reaccionar ahora las cetonas de fórmula (XXIII) en dialquilacetal de *N,N*-dimetilformamida puro, tal como dimetilacetal, a una temperatura que varia de temperatura ambiente a 150°C, proporcionando la dimetilaminocetona α,β insaturada de fórmula (XXVI) que se puede convertir en los 2-oxo-1,2-dihidropiridin-3-carbonitrilos de fórmula (XXVII) por ciclación en presencia de cianoacetamida usando alcóxidos tales como metóxido sódico en disolventes apróticos polares tales como dimetilformamida y a temperaturas que varían de 50°C a 150°C. Estos compuestos se pueden convertir en los 2-cloronicotinonitrilos de fórmula (XXVIII) por tratamiento de la piridona (XXVII) resultante con agentes de cloración tales como $POCl_3$, PCl_5 y $PhPOCl_2$ o usando una combinación de tales reaccionantes.

Etapas f a h

Se pueden hacer reaccionar 2-cloronicotinonitrilos de fórmula (XXVIII) con una solución saturada de amoníaco en un disolvente orgánico, preferiblemente etanol, a una temperatura que varía de 25°C a 150°C proporcionando los compuestos de fórmula (XXIX). La hidrólisis de compuestos (XXIX) al ácido carboxílico de fórmula (XXX) se puede conseguir con una base tal como hidróxido potásico en disolventes acuosos u orgánicos tales como etilenglicol y a una temperatura de 50°C a 200°C. Como alternativa, esta conversión se podría llevar a cabo en medios acuosos acídicos como ácido sulfúrico 6M. Estos compuestos se pueden someter a una transposición de Curtius mediante formación y reordenamiento del derivado acil azida que puede formarse haciendo reaccionar (XXX) con azida de difenilfosforilo (o azida de sodio con ácido activado) en un disolvente orgánico compatible con estas condiciones de reacción (por ejemplo, dioxano) y a un intervalo de temperatura de 0°C a 30°C seguido por calentar a una temperatura que varía de 50°C a 200°C, con formación *in situ* del anillo deseado de piridoimidazolona, proporcionando compuestos de fórmula (Ib).

Los compuestos de fórmula general (I) y, en particular, aquellos en los que A, B son como se definen en la reivindicación 1 y L representa un grupo de unión seleccionado del grupo consistente en -NR-, -S-, -O- y G representa un grupo seleccionado del grupo consistente en cicloalquilo C_{3-7}; alquilo C_{1-4}, arilo, heteroarilo y anillos heterocíclicos saturados que contienen nitrógeno se pueden preparar siguiendo el esquema de síntesis representado en el esquema 4.

Esquema 4



Etapas a a c

Los compuestos de fórmula general (XXXI) se pueden preparar a partir de imidazolonas (Ib) usando reactivos tales como cloruro de oxalilo, oxicloruro de fósforo, pentacloruro de fósforo o una combinación de los mismos a una temperatura que varía de 20º a 150°C en un disolvente como diclorometano o acetonitrilo. Como alternativa, los compuestos (XXXI) se pueden preparar tratando imidazolonas (Ib) con hidruro sódico y luego con cloruro de trifluorometanosulfonilo, anhídrido trifluorometanosulfónico o *N*-fenil-bis(trifluoroetanosulfonimida) en dimetilformamida en un intervalo de temperaturas que varía de 20°C a 150°C. Los compuestos de fórmula general (XXXI) se pueden tratar con aminas primarias o secundarias en un intervalo de temperaturas de 40º a 170°C dando los compuestos de fórmula general (Ic).

Como alternativa, los compuestos de fórmula general (Ic) se pueden obtener calentando imidazolonas (Ib) en presencia de una amina primaria o secundaria y un agente deshidratante como sulfato de magnesio o tamices moleculares.

Etapas (d), (e) e (i)

Por otro lado, se pueden preparar compuestos de fórmula general (Ie) a partir de imidazolonas (Ib) usando reaccionantes tales como cloruro de oxalilo o cloruro de fósforo a una temperatura que varía de 20° a 150°C y luego con un aril o alquil tiol a una temperatura de 60° a 150°C. Además, se pueden preparar compuestos de fórmula general (Ie) en la que G es un grupo alquilo o cicloalquilo por reacción de diaminas (X) con 1,1'-tiocarbonildiimidazol seguido por alquilación usando los haluros de alquilo correspondientes. Se pueden calentar a continuación compuestos (Ie) hasta una temperatura de 60°C a 150°C en presencia de la amina primaria o secundaria proporcionando compuestos de fórmula general (Ic). En algunos casos, puede ser necesaria la oxidación a la sulfona correspondiente o el uso de ácido de Lewis catalítico tal como cloruro de cinc.

Etapas f y g

Se pueden tratar diaminas (X) con isotiocianatos de alquilo o arilo dando las tioureas de fórmula general (XXXII). Las tioureas de fórmula (XXXII) se pueden tratar con alquilcarbodiimidas a temperatura ambiente o con ayuda de microondas dando compuestos de fórmula general (Ic). De forma alternativa, las tioureas de fórmula general (XXXII) se pueden tratar en condiciones reductoras tales como óxido de mercurio y azufre dando los compuestos de fórmula general (Ic).

Etapa h

Los compuestos de fórmula general (Id) se pueden preparar tratando compuestos de fórmula (XXXI) con nucleófilos ariloxi o alquiloxi tales como metóxido de sodio o fenil litio. De forma alternativa, los compuestos de fórmula general (Id) se pueden preparar a partir de imidazolonas (Ib) usando hidruro de sodio o potasio y haluros de alquilo o arilalquilo o triflatos en un disolvente tal como dimetilformamida o tetrahidrofurano en un intervalo de temperaturas de -78° a 100°C.

PARTE EXPERIMENTAL

ACTIVIDAD FARMACOLÓGICA

Ensayo de unión a radioligando por competencia con el subtipo de receptor de adenosina 2B

Se prepararon membranas A2B a partir de células HEK293 que expresan de forma estable el receptor A2B humano y que se adquirieron de Euroscreen (ES-013-C). Los ensayos de competencia se llevaron a cabo incubando en placas de 96 pocillos de polipropileno (nº 267245, NUNC) que contenían 2 µl de solución al 1% de DMSO de compuesto de ensayo o bien 5'NECA 100 µM (SIGMA E-2387) para la unión no específica, 100 µg de membranas A2B (preparadas en Tris-HCl 50 mM pH 6,5, $MgCl_2$ 10 mM, EDTA 1 mM, benzamidina 0,1 mM; tampón A) y [^{3}H]-DPCPX 35 nM (TRK1064, 128 Ci/mmol, Amersham), en un volumen total de 200 µl de tampón A + 2UI/ml de adenosina desaminasa, durante 60 minutos a temperatura ambiente. Al finalizar la incubación, se transfirieron las muestras a placas de filtro GF/C (Milipore MAFCN0B50) tratadas previamente durante 15 minutos con 250 µl de Tris-HCl 50 mM pH 6,5 (Tampón B). Las muestras se filtraron a continuación cuatro veces con 250 µl de tampón B. Se realizó el recuento de las muestras usando 30 µl de Hisafe II (Perkin Elmer) en un contador Trilux.

La Tabla 1 muestra las actividades de unión de algunos de los compuestos de la presente invención determinadas usando el ensayo de unión a radioligando por competencia con el subtipo de receptor 2B de adenosina descrito antes.

TABLA 1

Ejemplo	K_i
6	0,8
7	1,7
11	8
12	1,8
16	24
23	7
32	24
37	2,2
38	2,8
39	3,8
46	9,5

65	2.8
66	23
67	26

Los compuestos de fórmula (I) se han ensayado conforme al ensayo descrito antes y han mostrado ser potentes inhibidores del subtipo de receptor de adenosina A_{2B}. Los derivados de imidazopiridina preferidos de la invención poseen un valor de K_i para el efecto antagonista de A_{2B} (determinado como se ha definido antes) menor que 50 nM, con preferencia menor que 10 nM y, más preferiblemente menor que 5 nM.

Los derivados de imidazopiridina de la invención son útiles en el tratamiento o prevención de enfermedades conocidas por ser susceptibles de mejora por tratamiento con un antagonista del receptor A_{2B} de adenosina. Tales enfermedades incluyen, aunque sin quedar limitadas a las mismas, asma, enfermedad pulmonar obstructiva crónica, fibrosis pulmonar, enfisema, enfermedades alérgicas, inflamación, lesión por reperfusión, isquemia de miocardio, aterosclerosis, hipertensión, retinopatía, diabetes mellitus, trastornos inflamatorios del tracto gastrointestinal y/o enfermedades autoinmunes. Ejemplos de enfermedades autoinmunes que se pueden tratar o prevenir usando los compuestos de la invención son enfermedad de Addison, anemia hemolítica autoinmune, enfermedad de Crohn, síndrome de Goodpasture, enfermedad de Graves, tiroiditis de Hashimoto, púrpura trombocitopénica idiopática, diabetes mellitus dependiente de la insulina, esclerosis múltiple, miastenia grave, penfingo vulgar, anemia perniciosa, glomerulonefritis postestreptocócica, psoriasis, artritis reumatoide, esclerodermia, síndrome de Sjogren, infertilidad espontánea y lupus eritematoso sistémico.

Por consiguiente, los derivados imidazopiridina de la invención y las composiciones farmacéuticas que comprenden tales compuestos y/o sus sales, se pueden usar en un procedimiento de tratamiento de trastornos del cuerpo de un ser humano o animal que comprende administrar a un sujeto que requiere dicho tratamiento una cantidad eficaz de derivado imidazopiridina de la invención o una de sus sales farmacéuticamente aceptable.

Cuando los derivados de imidazopiridina de la invención se usan para el tratamiento de enfermedades respiratorias tales como asma, enfermedad pulmonar obstructiva crónica, fibrosis pulmonar o enfisema, puede ser ventajoso el uso de los mismos en combinación

con otros compuestos activos conocidos por ser útiles en el tratamiento de enfermedades respiratorias tales como (1) antagonistas de receptores muscarínicos M3, (2) agonistas β2, (3) inhibidores de PDE4, (4) corticosteroides, (5) antagonistas de leucotrieno D4, (6) inhibidores de egfr-quinasa, (7) inhibidores de quinasa p38, (8) agonistas del receptor NK1, (9) antagonistas de CRTh2, (10) inhibidores de quinasa syk, (11) antagonistas de CCR3 y (12) antagonistas de VLA-4.

Así, la presente invención también proporciona composiciones farmacéuticas que comprenden un derivado de imidazopiridina de la invención y otro compuestos activo seleccionado de los grupos consistentes en (1) antagonistas de los receptores muscarínicos M3, (2) agonistas β2, (3) inhibidores de PDE4, (4) corticosteroides, (5) antagonistas de leucotrieno D4, (6) inhibidores de egfr-quinasa, (7) inhibidores de quinasa p38, (8) agonistas del receptor NK1, (9) antagonistas de CRTh2, (10) inhibidores de quinasa syk, (11) antagonistas de CCR3 y (12) antagonistas de VLA-4

La presente invención también proporciona composiciones farmacéuticas que comprenden, como ingrediente activo, al menos un derivado imidazopiridina de fórmula (I) en asociación con un excipiente farmacéuticamente aceptable tal como un vehículo o diluyente. El ingrediente activo puede comprender de 0,001% a 99% en peso, preferiblemente de 0,01% a 90% en peso de la composición dependiendo de la naturaleza de la formulación y de si se realiza dilución adicional antes de la aplicación. Con preferencia, las composiciones se preparan en una forma adecuada para administración oral, tópica, nasal, rectal, percutánea inyectable o por inhalación.

Los excipientes farmacéuticamente aceptables que se mezclan con el compuesto activo o sales de dicho compuesto, formando las composiciones de esta invención son bien conocidos *per se* y los excipientes reales usados dependen *inter alia* del procedimiento deseado de administración de las composiciones.

Las composiciones de esta invención se adaptan preferiblemente a administración inhalada, inyectable u oral. Las composiciones para administración oral pueden adoptar la forma de comprimidos, comprimidos de liberación retardada, comprimidos sublinguales, cápsulas o preparaciones liquidas, tales como mezclas, elixires, jarabes o suspensiones. Las composiciones para inhalación pueden adoptar la forma de aerosoles para inhalación, soluciones para inhalación, inhalaciones de polvo seco, que contienen

todas el compuesto de la invención; tales preparaciones se pueden preparar por procedimientos bien conocidos en la técnica.

Los diluyentes que se pueden usar en la preparación de las composiciones incluyen los diluyentes líquidos y sólidos que son compatibles con el ingrediente activo, si se desea junto con agentes colorantes y aromatizantes. Los comprimidos y cápsulas pueden contener convenientemente de 2 a 500 mg de ingrediente activo o la cantidad equivalente de una de sus sales.

La composición líquida adaptada para uso oral puede estar en forma de soluciones o suspensiones. Las soluciones pueden ser soluciones acuosas de una sal soluble u otro derivado del compuesto activo asociado con, por ejemplo, sacarosa para formar un jarabe. Las suspensiones pueden comprender un compuesto activo insoluble de la invención o una de sus sales farmacéuticamente aceptable en asociación con agua, junto con un agente de suspensión o un agente aromatizante.

Las composiciones para inyección parenteral se pueden preparar a partir de sales solubles, que pueden estar o no liofilizadas y que se pueden disolver en medio acuoso exento de pirógenos u otro fluido para inyección parenteral apropiado.

Cuando se desean composiciones para inhalación, éstas pueden estar en forma de composiciones de pulverización para liberación tópica en el pulmón por inhalación o en forma de composiciones de polvo seco para liberación tópica en el pulmón por inhalación.

La composición de pulverización para inhalación se puede formular, por ejemplo, como soluciones o suspensiones acuosas o como aerosoles liberados desde envases a presión, tales como un inhalador de dosis medida, usando un propelente licuado adecuado.

Las composiciones de polvo seco para liberación tópica en el pulmón por inhalación se pueden presentar, por ejemplo, en diferentes sistemas de acondicionamiento (envase) primario (tales como cápsulas o cartuchos de, por ejemplo, gelatina o blisteres de, por ejemplo, lámina de aluminio estratificada) para usar en un inhalador o insuflador. El envasado de la formulación puede ser adecuado para la liberación de dosis unitarias o de varias dosis. En el caso de liberación de varias dosis, la formulación puede estar

dosificada previamente o dosificarse en uso. Los inhaladores de polvo seco se clasifican así en tres grupos: dispositivos de (a) dosis única, (b) varias dosis únicas y (c) dispositivos multidosis.

Las formulaciones de polvo seco contienen por lo general una mezcla de polvo para inhalación de los compuestos de la invención y una base de polvo adecuada (sustancia vehículo) tal como lactosa o almidón. Se prefiere el uso de lactosa. Cada cápsula o cartucho contiene por lo general de 20 µg a 400 µg de cada uno de los ingredientes terapéuticamente activos. Como alternativa, se pueden presentar los ingredientes sin excipientes.

Las dosis eficaces varían normalmente en el intervalo de 2 a 2000 mg de ingrediente activo por día. La dosificación diaria se puede administrar en uno o más tratamientos, por ejemplo, de 1 a 4 tratamientos por día.

Las síntesis de los compuestos de la invención y de los intermedios para usar en los mismos se ilustra por los siguientes Ejemplos (1 a 36) que incluyen Ejemplos de preparación (Intermedios 1 a 13) que no limitan el alcance de la invención en modo alguno.

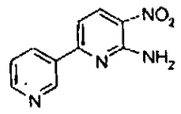
Los Espectros de Resonancia Magnética Nuclear de ^1H se registraron en un espectrómetro Varian Mercury que funcionaba a 200 MHz. Los puntos de fusión se registraron usando un aparato Büchi B-540. Las separaciones cromatográficas se obtuvieron usando un sistema Waters 2795 equipado con una columna Symmetry C18 (2,1 x 100 mm, 3,5 mm). Como detectores se usaron un espectrómetro de masas Micromass ZMD que usa ionización ES y un detector Waters 996 Diode Array. La fase móvil fue ácido fórmico (0,46 ml), amoniaco (0,115 ml) y agua (1000 ml) (A) y ácido fórmico (0,4 ml), amoniaco (0,1 ml), metanol (500 ml) y acetonitrilo (500 ml) (B): inicialmente desde 0% a 95% de B en 20 min, y luego 4 min. con 95% de B. El tiempo de reequilibrado entre dos inyecciones fue de 5 minutos. El caudal fue 0,4 l/min. El volumen de inyección fue 5 µl. Los cromatogramas de Diode Array se procesaron a 210 nm.

EJEMPLOS DE PREPARACIÓN

Intermedio 1:

3''-Fluoro-3,2':3',4''-terpiridin-5',6'-diamina

Etapa a:



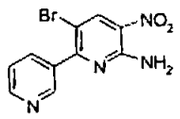
5-Nitro-2,3'-bipiridin-6-amina

Se cargó un tubo Schlenk resellable secado al horno con 6-cloro-3-nitropiridin-2-amina (5 g, 28,81 mmol), ácido 3-piridinbórico (5,31 g, 43,2 mmol), dioxano (250 ml) y una solución acuosa 2M de carbonato de cesio (43 ml, 86,4 mmol). Se sometió el tubo Schlenk a tres ciclos de evacuación-rellenado con argon, y se añadió complejo de dicloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio(II) - diclorometano (2,3 g, 2,81 mmol). Después de tres nuevos ciclos de evacuación-rellenado con argon, se tapón el tubo Schlenk y se colocó en un baño de aceite a 100°C. Después de 3 horas, la mezcla se enfrió, se repartió entre agua y acetato de etilo, la fase acuosa se extrajo dos veces con acetato de etilo, se lavaron las fases orgánicas con salmuera, se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 95:5) dando el compuesto del epígrafe (4,8 g, 77%) como un sólido.

δ RMN de ^1H ($CDCl_3$): 1,64 (s, 2H), 7,20-7,25 (d, 1H), 7,44-7,46 (m, 1H), 8,32-8,36 (d, 1H), 8,52-8,56 (d, 1H), 8,70-8,74 (m, 1H), 9,22-9,26 (m, 1H).

ESI/MS m/e: 217 ($[M+H]^+$, $C_{10}H_8N_4O_2$)

Etapa b:



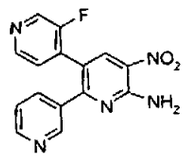
3-Bromo-5-nitro-2,3'-bipiridin-6-amina

Se añadió en porciones *N*-bromosuccinimida (4,75 g, 26,7 mmol) a una solución agitada enfriada a 0°C de 5-nitro-2,3'-bipiridin-6-amina (4,8 g, 22,2 mmol) en DMF (50 ml). Después de agitar a temperatura ambiente durante 16 h, el disolvente se eliminó a presión reducida. El residuo bruto se disolvió con acetato de etilo y se lavó con solución acuosa saturada de carbonato potásico. La fase orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 95:5) dando el compuesto del epígrafe (6,6 g, 100%) como un sólido.

δ RMN de ^{1}H ($CDCl_3$): 1,60 (s, 2H), 7,40-7,46 (dd, 1H), 8,03-8,09 (m, 1H), 8,67-8,77 (m, 2H), 8,93-9,02 (m, 1H).

ESI/MS m/e: 295, 297 ([M]$^+$, [M+2]$^+$,$C_{10}H_7BrN_4O_2$)

Etapa c:



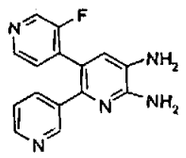
3''-Fluoro-5'-nitro-3,2':3',4''-terpirldin-6'-amina

Se cargó un tubo Schlenk resellable secado al horno con 3-bromo-5-nitro-2,3'-bipiridin-6-amina (4,51 g, 15,3 mmol), 3-fluoro-4-(tributilestannil)piridina (11,8 g, 30,6 mmol) y dimetilformamida (150 ml). Se sometió el tubo Schlenk a tres ciclos de evacuación-rellenado con argon y se añadieron cloruro de bis(trifenilfosfino)-paladio (II) (1,1 g, 1,53 mmol) y yoduro de cobre (I) (291 mg, 1,53 mmol). Después de tres nuevos ciclos de evacuación-rellenado con argon, se tapón el tubo Schlenk y se colocó en un baño de aceite a 160°C. Después de 3 horas se evaporó el disolvente y el residuo bruto se trató con solución acuosa 2N de cloruro de hidrógeno (130 ml) durante 45 minutos. La solución acuosa se lavó con acetato de etilo y luego se neutralizó con solución acuosa 6N de hidróxido sódico. La solución se extrajo con acetato de etilo, se secó ($MgSO_4$) y se evaporó. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 95:5) dando el compuesto del epígrafe (2,39 g, 51%) como un sólido.

δ RMN de ^{1}H ($CDCl_3$): 7,32-7,39 (m, 1H), 7,47-7,53 (dd, 1H), 7,66-7,72 (m, 1H), 8,43-8,45 (m, 2H), 8,48-8,50 (dd, 1H), 8,52-8,57 (m, 2H).

ESI/MS m/e: 312 ([M+H]$^+$, $C_{15}H_{10}FN_5O_2$)

Etapa d:



3''-Fluoro-3,2':3',4''-terpiridin-5',6'-diamina

Se agitó en atmósfera de hidrógeno una suspensión de 3''-fluoro-5'-nitro-3,2':3',4''-terpiridin-6'-amina (2,25 g, 7,23 mmol) y paladio al 10% sobre carbón (0,4 g) en una mezcla de THF/ etanol 40:60 (100 ml). Después de 3 h, la mezcla se filtró a través de

Celite® y la torta del filtro se lavó con etanol. El filtrado y las aguas de lavado combinados se evaporaron dando el compuesto del epígrafe como un sólido (2,01 g, 99%).

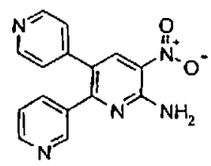
δ RMN de ^{1}H ($CDCl_3$): 5,10 (s, 2H), 5,95 (s, 2H), 6,75 (s, 1H), 7,18-7,30 (m, 2H), 7,49-7,55 (m, 1H), 8,29-8,31 (m, 1H), 8,32-8,34 (m, 1H), 8,35-8,38 (m, 1H), 8,40 (m, 1H).

ESI/MS m/e: 281 ([M+H]$^+$, $C_{15}H_{12}FN_5$)

Intermedio 2:

3,2':3',4"-Terpiridin-5',6'-diamina

Etapa a:



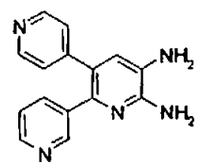
5'-Nitro-3,2':3',4"-terpiridin-6'-amina

Se obtuvo (220 mg, 22%) a partir de 3-bromo-5-nitro-2,3'-bipiridin-6-amina (**Intermedio 1-Etapa b**, 1,0 g, 3,4 mmol) y 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina (764 mg, 3,73 mmol) siguiendo el mismo procedimiento descrito en el Intermedio 1, etapa a.

δ RMN de ^{1}H (DMSO-d_6): 7,17 (d, 1H), 7,35 (dd, 1H), 7,68-7,40 (m, 3H), 7,82 (d, 1H), 8,22 (s ancho, 1H), 8,50-8,40 (m, 2H), 8,53 (d ancho, 1H), 8,69 (s ancho, 1H).

ESI/MS m/e: 294 ([M+H]$^+$, $C_{15}H_{11}N_5O_2$).

Etapa b:



3,2':3',4"-Terpiridin-5',6'-diamina

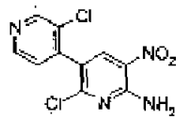
Se obtuvo (148 mg, 75%) a partir de 5'-nitro-3,2':3',4"-terpiridin-6'-amina (220 mg, 0,75 mmol) siguiendo el mismo protocolo descrito en el Intermedio 1, etapa d.

ESI/MS m/e: 264 ([M+H]$^+$, $C_{15}H_{13}N_5$).

Intermedio 3:

3"-Cloro-3,2':3',4"-terpiridin-5',6'-diamina

Etapa a:



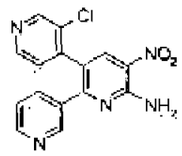
2,3'-Dicloro-5-nitro-3,4'-bipiridin-6-amina

Siguiendo el mismo procedimiento que para el Intermedio 1 (etapa a), pero usando 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-3-cloropiridina, se transformó 6-cloro-5-yodo-3-nitropiridin-2-amina (**Intermedio 5 - etapa a**) en el compuesto del epígrafe como un sólido blanco (205 mg, 22%).

δ RMN de ^{1}H ($CDCl_3$): 7,28 (d, 1H), 8,39 (s, 1H), 8,61 (d, 1H), 8,75 (s, 1H).

ESI/MS m/e: 286 ($[M+H]^+$, $C_{10}H_6Cl_2N_4O_2$).

Etapa b:

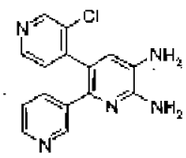


3''-Cloro-5'-nitro-3,2':3',4''-terpiridin-6'-amina

Siguiendo el mismo procedimiento que en el Intermedio 1 (etapa a), 2,3'-dicloro-5-nitro-3,4'-bipiridin-6-amina proporcionó el compuesto del epígrafe como un sólido color pardusco (127 mg, 54%).

ESI/MS m/e: 328 ($[M+H]^+$, $C_{15}H_{10}ClN_5O_2$).

Etapa c:



3''-Cloro-3,2':3',4''-terpiridin-5',6'-diamina

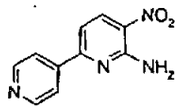
Se disolvió 3''-cloro-5'-nitro-3,2':3',4''-terpiridin-6'-amina (127 mg, 0,39 mmol) en EtOH (4,0 ml) y HCl concentrado HCl (245 µl). Se añadió hierro metálico (109 mg, 1,09 mmol) a la suspensión y se calentó la mezcla hasta 70 °C durante 1 h. La suspensión se filtró entonces a través de Celite® y el disolvente se eliminó a vacío. Se añadió $NaHCO_3$ (20 ml de una solución acuosa al 4% p/p) al residuo y la fase acuosa se extrajo con AcOEt (3 x 20 ml). La fase orgánica se secó, se filtró y se concentró hasta sequedad proporcionando el compuesto del epígrafe (52 mg, 45%), que se usó sin purificación adicional.

ESI/MS m/e: 298 ($[M+H]^+$, $C_{15}H_{12}ClN_5$).

Intermedio 4:

4,2':3',4''-Terpiridin-5',6'-diamina

Etapa a:



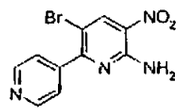
5-Nitro-2,4'-bipiridin-6-amina

Se obtuvo (0,240 g, 96% de rendimiento) a partir de 6-cloro-3-nitropiridin-2-amina (0,2 g, 1,15 mmol) y 4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-piridina (0,308 g, 1,50 mmol) siguiendo el procedimiento descrito en el Intermedio 1, etapa a.

δ RMN de ^{1}H ($CDCl_3$): 7,23-7,27 (d, 1H), 7,87-7,90 (m, 2H), 8,54-8,58 (d, 1H), 8,76-8,79 (m, 2H).

ESI/MS m/e: 217 ($[M+H]^+$, $C_{10}H_8N_4O_2$)

Etapa b:

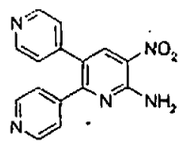


3-Bromo-5-nitro-2,4'-bipiridin-6-amina

Se obtuvo (0,246 g, 76% de rendimiento) a partir de 5-nitro-2,4'-bipiridin-6-amina (0,240 g, 1,11 mmol) siguiendo el procedimiento descrito en el Intermedio 1, etapa b.

ESI/MS m/e: 295, 297 ($[M]^+$, $[M+2]^+$, $C_{10}H_7BrN_4O_2$)

Etapa c:

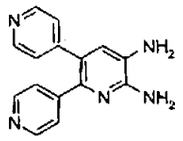


5'-Nitro-4,2':3',4''-terpiridin-6'-amina

Se obtuvo (0,144 g, 60% de rendimiento) a partir de 3-bromo-5-nitro-2,4'-bipiridin-6-amina (0,240 g, 0,813 mmol) y 4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-piridina (0,250 g, 1,220 mmol) siguiendo el procedimiento descrito en el Intermedio 1, etapa c.

ESI/MS m/e: 294 ($[M+H]^+$, $C_{15}H_{11}N_5O_2$)

Etapa d:



4,2':3',4"-Terpiridin-5',6'-diamina

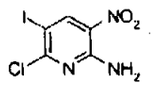
Se añadieron a una solución de 5'-nitro-4,2':3',4"-terpiridin-6'-amina (0,144 g, 0,490 mmol) en etanol (5 ml), 0,300 ml de cloruro de hidrógeno y 0,140 g (2,45 mmol) de hierro. La mezcla se calentó a 90°C durante 2 horas y se evaporó el disolvente. La mezcla bruta se extrajo entre acetato de etilo y agua. La fase orgánica se secó ($MgSO_4$) y el disolvente se evaporó dando el compuesto del epígrafe (0,120 g, 93% de rendimiento).

ESI/MS m/e: 264 ($[M+H]^+$, $C_{15}H_{13}N_5$)

Intermedio 5:

3-Fluoro-4,2':3',4"-terpiridin-5',6'-diamina

Etapa a:



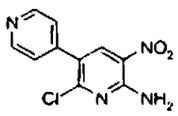
6-Cloro-5-yodo-3-nitropiridin-2-amina

Se añadieron a una suspensión de 6-cloro-3-nitropiridin-2-amina (6,3 g, 36,3 mmol) en etanol (110 ml), 9,2 g (36,3 mmol) de yodo y 11,32 g (36,3 mmol) de sulfato de plata. La mezcla bruta se agitó a temperatura ambiente durante la noche y se separó por filtración del precipitado formado. El sólido aislado se purificó por cromatografía ultrarrápida (1:1 hexano/ acetato de etilo) dando el compuesto del epígrafe (9,74 g, 88% de rendimiento).

δ RMN de ^1H ($CDCl_3$): 1,56 (s, 2H), 8,76 (s, 1H).

ESI/MS m/e: 300 ($[M+H]^+$, $C_5H_3ClIN_3O_2$)

Etapa b:

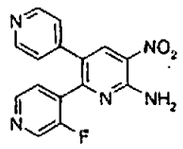


2-Cloro-5-nitro-3,4'-bipiridin-6-amina

Se obtuvo (0,666 g, 80% de rendimiento) a partir de 6-cloro-5-yodo-3-nitropiridin-2-amina (1 g, 3,34 mmol) y 4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-piridina (0,754 g, 3,67 mmol) siguiendo el procedimiento descrito en el Intermedio 1, etapa a.

ESI/MS m/e: 251 ($[M+H]^+$, $C_{10}H_7ClN_4O_2$)

Etapa c:



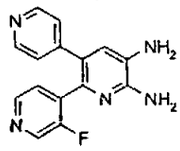
3-Fluoro-5'-nitro-4,2':3',4"-terpiridin-6'-amina

Se obtuvo (0,214 g, 69% de rendimiento) a partir de 2-cloro-5-nitro-3,4'-bipiridin-6-amina (0,250 g, 1 mmol) y 3-fluoro-4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-piridina (0,445 g, 2 mmol) siguiendo el procedimiento descrito en el Intermedio 1, etapa a.

δ RMN de ^{1}H ($CDCl_3$): 1,24 (s, 2H), 7,04-7,07 (m, 2H), 7,39-7,45 (m, 2H), 8,37 (s, 1H), 8,51-8,57 (m, 3H).

ESI/MS m/e: 312 ($[M+H]^+$, $C_{15}H_{10}FN_5O_2$)

Etapa d:



3-Fluoro-4,2':3',4"-terpiridin-5',6'-diamina

Se obtuvo (0,183 g, 94% de rendimiento) a partir de 3-fluoro-5'-nitro-4,2':3',4"-terpiridin-6'-amina (0,215 g, 0,69 mmol) siguiendo el procedimiento descrito en el Intermedio 1, etapa d.

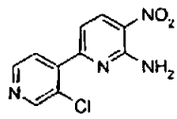
δ RMN de ^{1}H ($CDCl_3$): 1,26 (s, 4H), 7,00-7,05 (m, 3H), 7,37-7,43 (m, 1H), 8,27 (s, 1H), 8,40-8,48 (m, 3H).

ESI/MS m/e: 282 ($[M+H]^+$, $C_{15}H_{12}FN_5$)

Intermedio 6:

3-Cloro-4,2':3',4"-terpiridin-5',6'-diamina

Etapa a:



3'-Cloro-5-nitro-2,4'-bipiridin-6-amina

Siguiendo el mismo procedimiento que en el Intermedio 1 (etapa a), pero usando 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-3-cloropiridina, se transformó 6-cloro-3-nitropiridin-2-amina en el compuesto del epígrafe como un sólido blanco (2,14 g, 99%).

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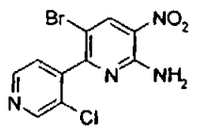
δ RMN de ^1H ($CDCl_3$): 7,15 (d, 1H), 7,52 (d, 1H), 8,55 (d, 1H), 8,62 (d, 1H), 8,73 (s, 1H).

ESI/MS m/e: 251 ($[M+H]^+$, $C_{10}H_7ClN_4O_2$).

Etapa b:



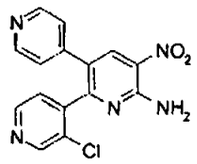
3-Bromo-3'-cloro-5-nitro-2,4'-bipiridin-6-amina

Siguiendo el mismo procedimiento que en el Intermedio 1 (etapa b) 3'-cloro-5-nitro-2,4'-bipiridin-6-amina proporcionó el compuesto del epígrafe como un sólido color pardusco (2,04 g, 93%).

δ RMN de ^1H ($CDCl_3$): 7,25 (d, 1H), 8,64 (d, 1H), 8,73 (s, 1H), 8,74 (d, 1H).

ESI/MS m/e: 328,330 ($[M]^+$, $[M+2]^+$, $C_{10}H_6BrClN_4O_2$).

Etapa c:



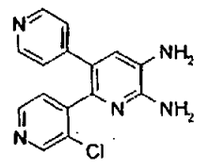
3-Cloro-5'-nitro-4,2':3',4''-terpiridin-6'-amina

Siguiendo el mismo procedimiento que en el Intermedio 1 (etapa a), pero usando 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina, se convirtió 3-bromo-3'-cloro-5-nitro-2,4'-bipiridin-6-amina en el compuesto del epígrafe como un sólido amarillento (0,84 g, 85%).

δ RMN de ^1H ($CDCl_3$): 7,03 (d ancho, 2H), 7,25 (d, 1H), 8,51 (d ancho, 2H), 8,55 (d, 1H), 8,57 (s, 1H), 8,59 (s, 1H).

ESI/MS m/e: 328 ($[M+H]^+$, $C_{15}H_{10}ClN_6O_2$).

Etapa d:



3-Cloro-4,2':3',4''-terpiridin-5',6'-diamina

Siguiendo el mismo procedimiento que en el Intermedio 1 (etapa d), 3-cloro-5'-nitro-4,2':3',4''-terpiridin-6'-amina proporcionó el compuesto del epígrafe como un sólido blanco (0,78 g, >99%).

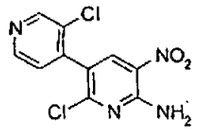
δ RMN de ^{1}H (DMSO): 5,14 (s ancho, 2H), 5,94 (s ancho, 2H), 6,83 (s, 1H), 6,95 (d ancho, 2H), 7,32 (d, 1H), 8,33 (d ancho, 2H), 8,42 (d, 1H), 8,46 (s, 1H).

ESI/MS m/e: 298 ([M+H]$^+$, $C_{15}H_{12}ClN_5$).

Intermedio 7:

3''-Cloro-4,2':3',4''-terpiridin-5',6'-diamina

Etapa a:

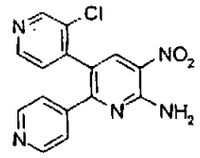


2,3'-Dicloro-5-nitro-3,4'-bipiridin-6-amina

Se obtuvo (0,118 g, 41% de rendimiento) a partir de 6-cloro-5-yodo-3-nitropiridin-2-amina (0,3 g, 1 mmol) y 3-cloro-4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-piridina (0,311 g, 1,3 mmol) siguiendo el procedimiento descrito en el Intermedio 3, etapa a.

ESI/MS m/e: 285 ([M+H]$^+$, $C_{10}H_6Cl_2N_4O_2$)

Etapa b:



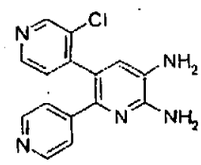
3''-Cloro-5'-nitro-4,2':3',4''-terpiridin-6'-amina

Se obtuvo (0,130 g, 99% de rendimiento) a partir de 2,3'-dicloro-5-nitro-3,4'-bipiridin-6-amina (0,120 g, 0,42 mmol) y 4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-piridina (0,130 g, 0,63 mmol) siguiendo el procedimiento descrito en el Intermedio 1, etapa a.

δ RMN de ^{1}H ($CDCl_3$): 1,24 (s, 2H), 7,12-7,23 (m, 3H), 7,40-7,64 (m, 1H), 8,48-8,57 (m, 2H), 8,61 (s, 1H).

ESI/MS m/e: 328 ([M+H]$^+$, $C_{15}H_{10}ClN_5O_2$)

Etapa c:

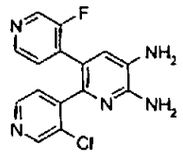


3''-Cloro-4,2':3',4''-terpiridin-5',6'-diamina

Se obtuvo (0,082 g, 62% de rendimiento) a partir de 3''-cloro-5'-nitro-4,2':3',4''-terpiridin-6'-amina (0,145 g, 0,443 mmol) siguiendo el procedimiento descrito en el Intermedio 4, etapa d.

ESI/MS m/e: 298 ([M+H]$^+$, $C_{15}H_{12}ClN_5$)

Intermedio 8



3-Cloro-3''-fluoro-4,2':3',4''-terpiridin-5',6'-diamina

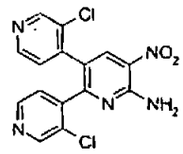
Se obtuvo como un sólido blanco (24%) a partir de 3-bromo-3'-cloro-5-nitro-2,4'-bipiridin-6-amina (**Intermedio 6-etapa b**) y 3-fluoro-4-(tributilestannil)piridina, siguiendo el mismo procedimiento que en el Intermedio1 (etapa c).

ESI/MS m/e: 316 ([M+H]$^+$, $C_{15}H_{11}ClFN_5$).

Intermedio 9:

3,3''-Dicloro-4,2':3',4''-terpiridin-5',6'-diamina

Etapa a:

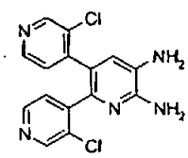


3,3''-Dicloro-5'-nitro-4,2':3',4''-terpiridin-6'-amina

Se obtuvo (0,034 g, 10% de rendimiento) a partir de 6-cloro-5-yodo-3-nitropiridin-2-amina (0,3 g, 1 mmol) y 3-cloro-4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-piridina (0,311 g, 1,3 mmol) siguiendo el procedimiento descrito en el Intermedio 1, etapa a.

ESI/MS m/e: 362 ([M+H]$^+$, $C_{15}H_9Cl_2N_5O_2$)

Etapa b:



3,3''-Dicloro-4,2':3',4''-terpiridin-5',6'-diamina

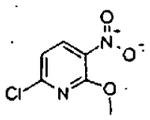
Se obtuvo (0,029 g, 72% de rendimiento) a partir de 3,3''-dicloro-5'-nitro-4,2':3',4''-terpiridin-6'-amina (0,045 g, 0,123 mmol) siguiendo el procedimiento descrito en el Intermedio 4, etapa d.

ESI/MS m/e: 332 ([M+H]$^+$, $C_{15}H_{11}Cl_2N_5$)

Intermedio 10:

2-(1,3-Oxazol-2-il)-3,4'-bipiridin-5,6-diamina

Etapa a:

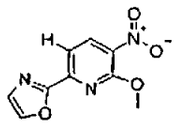


6-Cloro-2-metoxi-3-nitropiridina

Se añadió gota a gota metanol (3,3 g, 103 mmol) en xileno (100 ml) a una suspensión agitada de hidruro sódico (60% en aceite mineral, 2,72 g, 113 mmol) en xileno (300 ml) a 0°C en atmósfera de argon. Después 20 minutos, se añadió 2,6-dicloro-3-nitropiridina (20,0 g, 103 mmol) en xileno (300 ml), gota a gota y luego se calentó la reacción hasta temperatura ambiente y se agitó durante la noche. Se añadió seguidamente agua (200 ml) y se separaron las dos fases. La fase orgánica se lavó con agua y salmuera, se secó ($MgSO_4$) y se evaporó. El residuo se purificó por cromatografía ultrarrápida (10:1 hexanos/acetato de etilo) dando el compuesto del epígrafe (15,3 g, 78%) como un sólido blanco.

δ RMN de ^1H ($CDCl_3$): 4,10 (s, 3H), 7,05 (d, 1H), 8,28 (d, 1H).

Etapa b:



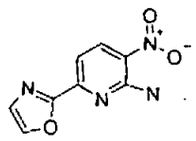
2-Metoxi-3-nitro-6-(1,3-oxazol-2-il)piridina

Se cargó un tubo Schlenk resellable secado al horno con 6-cloro-2-metoxi-3-nitropiridina (0,50 g, 2,6 mmol), 2-tributilestannaniloxazol (1,20 g, 3,4 mmol) y 1,4-dioxano (10 ml) y se sometió a varios ciclos de evacuación-rellenado con argon. Se añadió entonces tetrakis(trifenilfosfina)paladio (0,18 g, 0,16 mmol) y, después de tres nuevos ciclos de evacuación-rellenado con argon, se selló el tubo Schlenk y se agitó la mezcla y calentó en un baño de aceite hasta 110 °C. Después de agitar durante toda la noche, se añadieron agua y acetato de etilo y se lavó la fase orgánica con agua, se secó ($MgSO_4$) y se evaporó. El residuo se purificó por cromatografía ultrarrápida (2:1 hexanos/acetato de etilo) dando el compuesto del epígrafe (0,38 g, 67%) como un sólido amarillo.

δ RMN de ^{1}H ($CDCl_3$): 4,24 (s, 3H), 7,38 (s, 1H), 7,84 (d, 1H), 7,87 (s, 1H), 8,40 (d, 1H).

ESI/MS m/e: 222 ([M+H]+, $C_8H_7N_3O_4$)

Etapa c:



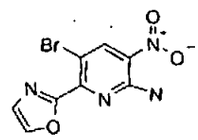
3-Nitro-6-(1,3-oxazol-2-il)piridin-2-amina

Se calentó una suspensión de 2-metoxi-3-nitro-6-(1,3-oxazol-2-il)piridina (0,187 g, 0,85 mmol) en amoníaco acuoso (32%, 5 ml) en un tubo sellado hasta 100ºC con agitación. Después de 2,5 horas la mezcla se enfrió y el precipitado se filtró y lavó con agua y luego se secó a vacío dando el compuesto del epígrafe (0,134 g, 77%) como un sólido amarillo.

δ RMN de ^{1}H (DMSO-d_6): 7,41 (d, 1H), 7,53 (s, 1H), 8,14 (s, 2H), 8,38 (s, 1H), 8,53 (d, 1H).

ESI/MS m/e: 207 ([M+H]+, $C_8H_6N_4O_3$)

Etapa d:



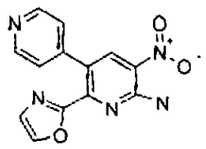
5-Bromo-3-nitro-6-(1,3-oxazol-2-il)piridin-2-amina

Se añadió *N*-bromosuccinimida (0,115 g, 0,65 mmol) a una solución agitada de 3-nitro-6-(1,3-oxazol-2-il)piridin-2-amina (0,127 g, 0,62 mmol) en dimetilformamida (3 ml) a 0ºC y la mezcla se calentó hasta temperatura ambiente. Después de 3 días, se añadió más *N*-bromosuccinimida (0,058 g, 0,33 mmol) y se prolongó la agitación durante 3 horas. La solución se vertió en agua y el precipitado se filtró, se lavó con agua y se secó dando el compuesto del epígrafe (0,18 g, 70%) como un sólido amarillo.

δ RMN de ^{1}H (DMSO-d_6): 7,56 (s, 1H), 8,19 (s, 2H), 8,41 (s, 1H), 8,68 (s, 1H).

ESI/MS m/e: 285/287 ([M+H]+, $C_8H_5BrN_4O_3$)

Etapa e:



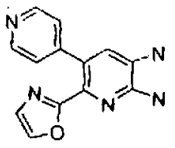
5-Nitro-2-(1,3-oxazol-2-il)-3,4'-bipiridin-6-amina

Se cargó un tubo Schlenk resellable secado al horno con 5-bromo-3-nitro-6-(1,3-oxazol-2-il)piridin-2-amina (0,141 g, 0,49 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina (0,203 g, 0,99 mmol), dioxano (5 ml) y una solución acuosa 2M de carbonato de cesio (0,74 ml, 1,48 mmol). Se sometió el tubo Schlenk a tres ciclos de evacuación-rellenado con argon y se añadió complejo de dicloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio(II) - diclorometano [$PdCl_2$dppf.DCM] (0,024 g, 0,03 mmol). Después de tres nuevos ciclos de evacuación-rellenado con argon, se selló el tubo Schlenk y la mezcla se agitó y calentó en un baño de aceite hasta 95°C. Después de 20 horas, la mezcla se enfrió y se repartió entre ácido clorhídrico acuoso 2M y acetato de etilo. La fase acuosa se filtró a través de Celite® y se ajustó el pH a 5-6 con hidróxido sódico sólido. La suspensión se enfrió en un baño de hielo y el precipitado se filtró, se lavó con agua y se secó dando el compuesto del epígrafe (0,090 g, 65%) como un sólido amarillo.

δ RMN de ^{1}H (DMSO-d_6): 7,24 (d, 2H), 7,33 (s, 1H), 8,24 (s, 1H), 8,29 (s, 2H), 8,43 (s, 1H), 8,52 (d, 2H).

ESI/MS m/e: 284 ([M+H]+, $C_{13}H_9N_5O_3$)

Etapa f:



2-(1,3-Oxazol-2-il)-3,4'-bipiridin-5,6-diamina

Se colocó en una atmósfera de hidrógeno (balón) y se agitó a temperatura ambiente una suspensión de 5-nitro-2-(1,3-oxazol-2-il)-3,4'-bipiridin-6-amina (0,089 g, 0,31 mmol) y paladio sobre carbón (10%, 20 mg) en etanol (15 ml). Después de 3 horas, la mezcla se filtró a través de Celite® y se evaporó el filtrado. La trituración con éter dietílico proporcionó el compuesto del epígrafe (0,077 g, 97%) como un sólido naranja pálido.

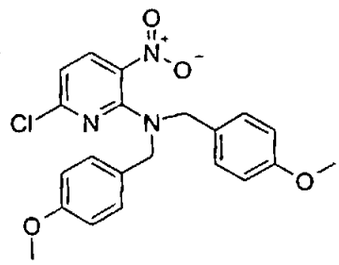
δ RMN de ^{1}H ($CDCl_3$): 6,87 (s, 1H), 7,13 (m, 3H), 7,49 (s, 1H), 8,56 (d, 2H).

ESI/MS m/e: 254 ([M+H]+, $C_{13}H_{11}N_5O$)

Intermedio 11

3'-Fluoro-2-(1,3-oxazol-2-il)-3,4'-bipiridin-5,6-diamina

Etapa a:



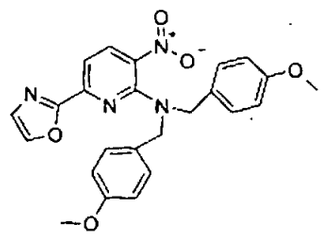
6-Cloro-*N*,*N*-bis(4-metoxibencil)-3-nitropiridin-2-amina

Se añadió una solución de N,N-bis(4-metoxibencil)amina (7,79 g, 30,3 mmol) y trietilamina (2,89 g, 28,6 mmol) en cloroformo (20 ml) durante 20 minutos a una solución agitada fría (baño de hielo) de 2,6-dicloro-3-nitropiridina (5,0 g, 26,0 mmol) en cloroformo (25 ml). La mezcla se calentó hasta temperatura ambiente y se agitó durante la noche. El disolvente se evaporó y la mezcla se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó dando un aceite. La mezcla se suspendió en diclorometano (120 ml) y se añadió resina de isocianato soportada en polímero (1,6 mmol/g, 8,0 g) y se removió la mezcla a temperatura ambiente durante 2 días. La mezcla se filtró y el filtrado se evaporó dando el compuesto del epígrafe (10,7 g, 100%) como un aceite amarillo brillante.

δ RMN de ^1H ($CDCl_3$): 3,78 (s, 6H), 4,51 (s, 4H), 6,68 (d, 2H), 6,80 (d, 4H), 8,23 (d, 4H), 8,02 (d, 1H).

ESI/MS m/e: 414 ([M+H]+, $C_{21}H_{20}ClN_3O_4$)

Etapa b:



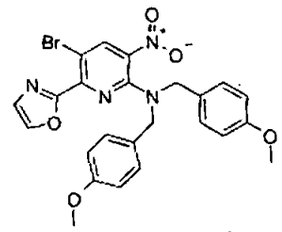
2-*N*,*N*-bis(4-metoxibencil)-3-nitro-6-(1,3-oxazol-2-il)piridina

Se obtuvo (79%) a partir de 6-cloro-N,N-bis(4-metoxibencil)-3-nitropiridin-2-amina y 2-tributilestannaniloxazol, siguiendo el procedimiento descrito en la Preparación 10, etapa b.

δ RMN de ^{1}H ($CDCl_3$): 3,79 (s, 6H), 4,60 (s, 4H), 6,80 (d, 4H), 7,10 (d, 4H), 7,34 (d, 1H), 7,55 (d, 1H), 7,82 (s, 1H), 8,20 (d, 1H).

ESI/MS m/e: 447 ([M+H]+, $C_{24}H_{22}N_4O_5$)

Etapa c:



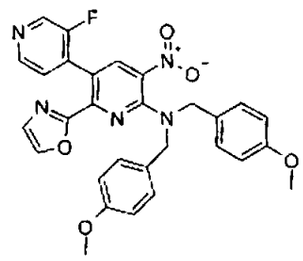
4-Bromo-2-*N*,*N*-bis(4-metoxibencil)-3-nitro-6-(1,3-oxazol-2-il)piridina

Se obtuvo (52%) a partir de 2-N,N-bis(4-metoxibencil)-3-nitro-6-(1,3-oxazol-2-il)piridina y *N*-bromosuccinimida, siguiendo el procedimiento descrito en la Preparación 10, etapa d.

δ RMN de ^{1}H (DMSO-d_6): 3,69 (s, 6H), 4,59 (s, 4H), 6,83 (d, 4H), 7,12 (d, 4H), 7,58 (s, 1H), 8,42 (s, 1H), 8,51 (s, 1H).

ESI/MS m/e: 525/527 ([M+H]+, $C_{24}H_{21}BrN_4O_5$)

Etapa d:



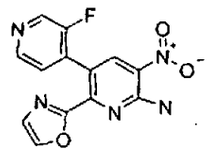
2-*N*,*N*-bis(4-metoxibencil)-4-(3-fluoropiridin-4-il)-3-nitro-6-(1,3-oxazol-2-il)piridina

Se cargó un tubo Schlenk resellable secado al horno con 4-bromo-2-N,N-bis(4-metoxibencil)-3-nitro-6-(1,3-oxazol-2-il)piridina (5,47 g, 10,4 mmol), 3-fluoro-4-(tributilestannil)piridina (5,22 g, 13,5 mmol) y dimetilformamida (82 ml). Se sometió el tubo Schlenk a tres ciclos de evacuación-rellenado con argon, y se añadieron cloruro de bis(trifenilfosfino)-paladio (II) (0,365 g, 0,52 mmol) y yoduro de cobre (I) (0,198 g, 1,04 mmol). Después de tres nuevos ciclos de evacuación-rellenado con argon, se selló el tubo Schlenk y la mezcla se agitó y calentó hasta 160 °C en un baño de aceite. Después de 20 horas, la mezcla se enfrió y el disolvente se evaporó. El residuo se suspendió en una mezcla de metanol y acetato de etilo, se filtró a través de un lecho corto de Celite® y se evaporó. La purificación por cromatografía ultrarrápida (hexanos/acetato de etilo 6:1

hasta hexanos/acetato de etilo) proporcionó el compuesto del epígrafe (4,07 g, 72%) como un sólido.

ESI/MS m/e: 542 ([M+H]+, $C_{29}H_{24}FN_5O_5$)

Etapa e:



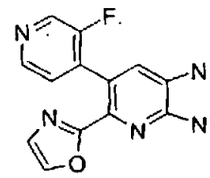
3'-Fluoro-5-nitro-2-(1,3-oxazol-2-il)-3,4'-bipiridin-6-amina

Se agitó a temperatura ambiente durante la noche una solución de 2-N,N-bis(4-metoxibencil)-4-(3-fluoropiridin-4-il)-3-nitro-6-(1,3-oxazol-2-il)piridina (0,15 g, 0,37 mmol) en diclorometano (2 ml) y ácido trifluoroacético (2 ml). El disolvente se evaporó y luego se neutralizó la mezcla con solución acuosa al 4% de bicarbonato sódico. El sólido que se formó se extrajo con acetato de etilo y la fase orgánica se lavó con agua, salmuera, se secó ($MgSO_4$) y se evaporó dando el compuesto del epígrafe (0,11 g, 67%) como un sólido amarillo.

δ RMN de ^1H ($CDCl_3$): 7,21 (s, 1H), 7,30 (m, 1H), 7,71 (s, 1H), 8,51 (m, 3H).

ESI/MS m/e: 302 ([M+H]+, $C_{13}H_8FN_5O_3$)

Etapa f:



3'-Fluoro-2-(1,3-oxazol-2-il)-3,4'-bipiridin-5,6-diamina

Se obtuvo (93%) a partir de 3'-fluoro-5-nitro-2-(1,3-oxazol-2-il)-3,4'-bipiridin-6-amina por hidrogenación con paladio sobre carbón siguiendo el procedimiento descrito en la Preparación 10, etapa f.

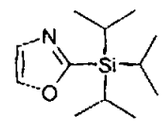
δ RMN de ^1H (DMSO-d_6): 5,42 (s, 2H), 6,07 (s, 2H), 6,65 (s, 1H), 7,05 (s, 2H), 7,30 (m, 1H), 7,96 (s, 1H), 8,39 (m, 2H).

ESI/MS m/e: 272 ([M+H]+, $C_{13}H_{10}FN_5O$)

Intermedio 12

2-(1,3-Oxazol-5-il)-3,4'-bipiridin-5,6-diamina

Etapa a:



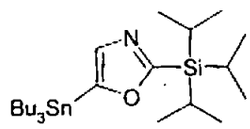
2-Triisopropilsililoxazol

Se añadió gota a gota durante 30 minutos n-BuLi (1,6M en hexanos, 76 ml, 190 mmol) a una solución agitada de oxazol (12,0 g, 174 mmol) en éter dietílico (400 ml) a –78 °C en argon. La solución se dejó agitando durante 60 minutos a –78 °C y luego se añadió gota a gota durante 30 minutos triflato de triisopropilsililo (46,3 ml, 172 mmol). La mezcla de reacción se calentó lentamente hasta temperatura ambiente y se agitó durante la noche. La mezcla se concentró a vacío y el residuo se suspendió en hexanos y se filtró a través de un lecho de gel de sílice eluyendo con hexanos/acetato de etilo 8:1. La concentración dio el compuesto del epígrafe (36,0 g, 93%) como un aceite incoloro.

δ RMN de ^{1}H ($CDCl_3$): 1,12 (d, 18H), 1,37 (m, 3H), 7,20 (m, 1H), 7,81 (d, 1H).

Etapa b:

5-Tributilstannanil-2-triisopropilsilanil-oxazol

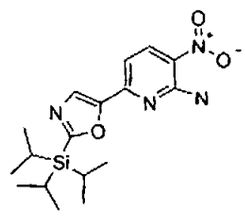


Se añadió gota a gota durante (aproximadamente) 30 minutos *terc*-BuLi (1,7M en *n*-pentano, 8,4 ml, 14,3 mmol) a una solución agitada de 2-triisopropilsililoxazol (3 g, 13 mmol) en tetrahidrofurano (75 ml) a –78°C en argon. La solución se dejó agitando durante 20 minutos a -78°C y se añadió entonces durante 20 minutos cloruro de tributilestaño (5,2 ml, 19,5 mmol). La mezcla de reacción se calentó hasta temperatura ambiente y se agitó durante otras 16 horas. La reacción se diluyó con acetato de etilo, se lavó con agua y la fase orgánica se secó ($MgSO_4$) y se concentró a presión reducida. El producto bruto se disolvió en n-pentano, se filtró a través de Celite® y se evaporó el disolvente dando el

compuesto del epígrafe con un rendimiento cuantitativo como un residuo oleoso color amarillo pálido que se usó sin purificación adicional en la siguiente etapa.

δ RMN de ^1H ($CDCl_3$): 1,12 (d, 18H), 1,38 (m, 3H), 1,42 (d, 9H), 1,52-1,95 (m, 18H) 7,22 (s, 1H).

Etapa c:



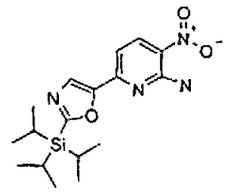
3-Nitro-6-(2-triisopropilsilanil-1,3-oxazol-5-il)piridin-2-amina

Se obtuvo (80%) a partir de 6-bromo-3-nitropiridin-2-amina y 5-tributilestannanil-2-triisopropilsilaniloxazol, siguiendo el procedimiento descrito en la Preparación 10, etapa b.

δ RMN de ^1H ($CDCl_3$): 1,17 (d, 18H), 1,43 (m, 3H), 7,11 (d, 1H), 7,85 (s, 1H), 8,48 (d, 1H).

ESI/MS m/e: 363 ([M+H]+, $C_{17}H_{26}N_4O_3Si$)

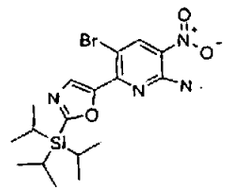
Etapa c: (procedimiento alternativo)



3-Nitro-6-(2-triisopropilsilanil-1,3-oxazol-5-il)piridin-2-amina

Se obtuvo (67%) a partir de 6-cloro-3-nitropiridin-2-amina y 5-tributilestannanil-2-triisopropilsilaniloxazol, siguiendo el procedimiento descrito en la Preparación 10, etapa b.

Etapa d:



134

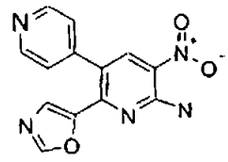
5-Bromo-3-nitro-6-(2-triisopropilsilanil-1,3-oxazol-5-il)piridin-2-amina

Se obtuvo (88%) a partir de 3-nitro-6-(2-triisopropilsilanil-1,3-oxazol-5-il)piridin-2-amina y *N*-bromosuccinimida, siguiendo el procedimiento descrito en la Preparación 10, etapa d.

δ RMN de ^{1}H ($CDCl_3$): 1,17 (d, 18H), 1,45 (m, 3H), 8,15 (s, 1H), 8,68 (s, 1H).

ESI/MS m/e: 441/443 ([M+H]+, $C_{17}H_{26}BrN_4O_3Si$)

Etapa e:



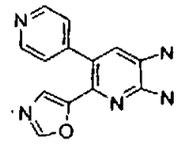
5-Nitro-2-(1,3-oxazol-5-il)-3,4'-bipiridin-6-amina

Se obtuvo (74%) a partir de 5-bromo-3-nitro-6-(2-triisopropilsilanil-1,3-oxazol-5-il)piridin-2-amina y 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina siguiendo el procedimiento descrito en la Preparación 10, etapa e.

δ RMN de ^{1}H ($CDCl_3$): 7,15 (s, 1H), 7,38 (d, 2H), 8,20 (s, 1H), 8,32 (s, 1H), 8,45 (s, 1H), 8,62 (d, 2H).

ESI/MS m/e: 284 ([M+H]+, $C_{13}H_9N_5O_3$)

Etapa f:



2-(1,3-Oxazol-5-*il*)-3,4'-bipiridin-5,6-diamina

Se obtuvo (82%) a partir de 5-nitro-2-(1,3-oxazol-5-il)-3,4'-bipiridin-6-amina por hidrogenación con paladio sobre carbón siguiendo el procedimiento descrito en la Preparación 10, etapa f.

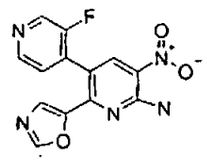
δ RMN de ^{1}H (DMSO-d_6): 5,26 (s, 2H), 5,94 (s, 2H), 6,67 (s, 1H), 6,79 (s, 1H), 7,16 (d, 2H), 8,12 (s, 1H), 8,52 (m, 2H).

ESI/MS m/e: 254 ([M+H]+, $C_{13}H_{11}N_5O$)

Intermedio 13

3'-Fluoro-2-(1,3-oxazol-5-il)-3,4'-bipiridin-5,6-diamina

Etapa a:



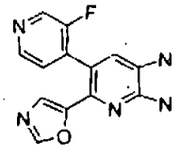
3'-Fluoro-5-nitro-2-(1,3-oxazol-5-il)-3,4'-bipiridin-6-amina

Se obtuvo (18%) a partir de 5-bromo-3-nitro-6-(2-triisopropilsilanil-1,3-oxazol-5-il)piridin-2-amina y 3-fluoro-4-(tributilestannil)piridina siguiendo el procedimiento descrito en la Preparación 11, etapa d.

δ RMN de ^{1}H ($CDCl_3$): 7,30 (m, 1H), 7,38 (s, 1H), 7,81 (s, 1H), 8,40 (s, 1H), 8,52 (m, 2H).

ESI/MS m/e: 302 ([M+H]+, $C_{13}H_8FN_5O_3$)

Etapa b:



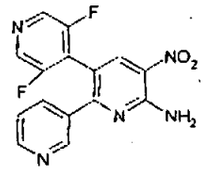
3'-Fluoro-2-(1,3-oxazol-5-il)-3,4'-bipiridin-5,6-diamina

Se obtuvo (89%) a partir de 3'-fluoro-5-nitro-2-(1,3-oxazol-5-il)-3,4'-bipiridin-6-amina por hidrogenación con paladio sobre carbón siguiendo el procedimiento descrito en la Preparación 10, etapa f.

ESI/MS m/e: 272 ([M+H]+, $C_{13}H_{10}FN_5O$)

Intermedio 14

Etapa a:



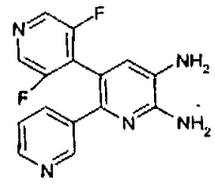
3'',5''-difluoro-5'-nitro-3,2':3',4''-terpiridin-6'-amina

Se calentó a 150ºC durante 6 horas en un sintetizador de microondas Biotage Initiator Microwave Synthesizer una mezcla de 3-bromo-5-nitro-2,3'-bipiridin-6-amina (**Intermedio 1, etapa b**, 1 g, 3,39 mmol), 3,5-difluoro-4-tributilestannanilpiridina (1,5 g, 3,71 mmol),

cloruro de bis(trifenilfosfino) paladio (II) (0,24 g, 0,34 mmol) y yoduro de cobre (I) (0,13 g, 0,68 mmol) en dioxano (15 ml). La mezcla se filtró a través de Celite® y la torta del filtro se lavó con dioxano. El disolvente se evaporó y el residuo bruto se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 95:5) proporcionando el compuesto del epígrafe (1,07 g, 95%) como un sólido amarillo.

ESI/MS m/e: 330 ($[M+H]^+$, $C_{15}H_9F_2N_5O_2$).

Etapa b:



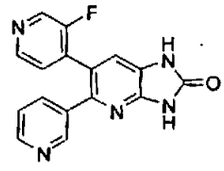
3'',5''-difluoro-3,2':3',4''-terpiridin-5',6'-diamina

Se agitó en atmósfera de hidrógeno a 2,76 bar una suspensión de 3'',5''-difluoro-5'-nitro-3,2':3',4''-terpiridin-6'-amina (0,2 g, 0,608 mmol) y paladio al 10% sobre carbón (0,04 g) en una mezcla de THF/ etanol 40:60 (8 ml). Después de 12 horas, la mezcla se filtró a través de Celite® y la torta del filtro se lavó con etanol y THF. El filtrado reunido y las aguas de lavado se evaporaron proporcionando el compuesto del epígrafe como un sólido (0,180 g, 99%).

ESI/MS m/e: 300 ($[M+H]^+$, $C_{15}H_{11}F_2N_5$).

EJEMPLOS

Ejemplo 1



6-(3-Fluoropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

Se añadieron secuencialmente Et_3N (156 µl, 1,12 mmol) y carbonildiimidazol (182 mg, 1,12 mmol) a una solución de 3''-fluoro-3,2':3',4''-terpiridin-5',6'-diamina (**Intermedio 1**, 158 mg, 0,56 mmol) en THF (5 ml). La mezcla de reacción se calentó hasta reflujo durante 4 horas y luego se eliminó el disolvente a presión reducida. La cromatografía ultrarrápida del aceite bruto resultante (CH_2Cl_2/EtOH/NH_3 ac. 60:8:1 hasta 40:8:1) seguida

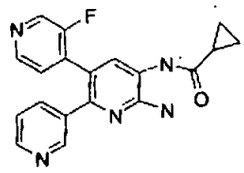
por cromatografía de fase inversa (CH_3CN al 0% en H_2O hasta CH_3CN al 25% en H_2O) proporcionó el compuesto del epígrafe como un sólido blanco (29 mg, 17%).

δ RMN de ^1H (DMSO-d_6): 7,27 (dd, 1H), 7,33 (s, 1H), 7,44 (dd, 1H), 7,59 (dt, 1H), 8,37 (d, 1H), 8,42 (m, 3H), 11,18 (s, 1H), 11,70 (s, 1H),

ESI/MS m/e: 308 ($[M+H]^+$, $C_{16}H_{10}FN_5O$).

Ejemplo 2

Etapa a:

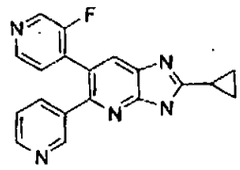


***N*-(6'-amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)ciclopropanocarboxamida**

Se añadieron 0,071 ml (0,78 mmol) de ciclopropanoilcarbonilo a una solución de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,2 g, 0,71 mmol) en piridina (2 ml). La mezcla se calentó a 80°C durante 4h y se evaporó el disolvente. La mezcla bruta se extrajo entre acetato de etilo y agua, la fase orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 90:10) dando el compuesto del epígrafe (0,202 g, 82% de rendimiento).

ESI/MS m/e: 350 ($[M+H]^+$, $C_{19}H_{16}FN_5O$)

Etapa b:

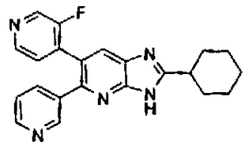


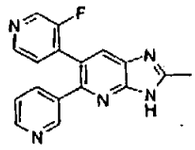
2-Ciclopropil-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se calentó en un tubo sellado a 130°C durante 16 horas una solución de *N*-(6'-amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)ciclopropanocarboxamida (0,2 g, 0,58 mmol) en ácido acético (2,5 ml). El disolvente se evaporó y se añadió agua (1 ml) y la solución se neutralizó con solución acuosa al 4% de bicarbonato sódico y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol/NH_3 100:8:1) dando el compuesto del epígrafe (0,024 g, 12% de rendimiento).

ESI/MS m/e: 332 ($[M+H]^+$, $C_{19}H_{14}FN_5$)

Ejemplo 3 y **Ejemplo 4**

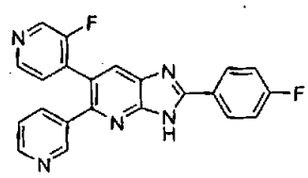




2-Ciclohexil-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina y **6-(3-fluoropiridin-4-il)-2-metil-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina**

Se siguió el mismo procedimiento que en el Ejemplo 2, pero usando cloruro de ciclohexanocarbonilo. La purificación final del residuo por cromatografía ultrarrápida (CH_2Cl_2/^{i}PrOH 98:2 hasta 65:35) proporcionó 2-ciclohexil-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3H-imidazo[4,5-b]piridina (**Ejemplo 3**) como un sólido amarillento (134 mg, 51%): δ RMN de ^{1}H ($CDCl_3$): 1,28-1,66 (m, 4H), 1,71-1,98 (m, 4H), 2,15 (d ancho, 2H), 7,36 (ddd, 1H), 7,52 (dd, 1H), 7,82 (dt, 1H), 8,01 (s, 1H), 8,36 (d, 1H), 8,42 (dd, 1H), 8,46 (dd, 1H), 8,51 (d ancho, 1H); ESI/MS m/e: 374 ($[M+H]^+$, $C_{22}H_{20}FN_5$), y 6-(3-fluoropiridin-4-il)-2-metil-5-piridin-3-il-3H-imidazo[4,5-b]piridina (**Ejemplo 4**) como un sólido blanco (90 mg, 42%) δ RMN de ^{1}H ($CDCl_3$): 2,69 (s, 3H), 7,36 (ddd, 1H), 7,52 (dd, 1H), 7,82 (dt, 1H), 8,02 (s, 1H), 8,36 (d, 1H), 8,41 (dd, 1H), 8,46 (dd, 1H), 8,50 (d ancho, 1H). ESI/MS m/e: 306 ($[M+H]^+$, $C_{17}H_{12}FN_5$).

Ejemplo 5



2-(4-Fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

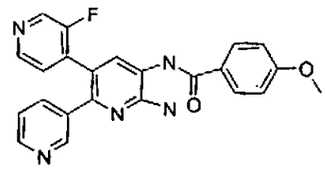
Se colocaron en un tubo sellado 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 158 mg, 0,56 mmol), cloruro de 4-fluorobenzoilo (73,0 µl, 0,62 mmol) y piridina (aproximadamente 4 ml). La solución se calentó inicialmente a 140ºC durante 48 h y luego a 160ºC durante otras 48 horas. A continuación, se enfrió la mezcla de reacción hasta temperatura ambiente, se eliminó la piridina a vacío y se purificó el aceite bruto por cromatografía en columna ultrarrápida (CH_2Cl_2/EtOH, 95:5) proporcionando el compuesto del epígrafe como un sólido blanco (141 mg, 65%).

δ RMN de ^{1}H (DMSO-d_6): 6,89 (t, 1H), 7,06 (t, 2H), 7,26 (dd, 1H), 7,56 (dt, 1H), 7,77 (dd, 1H), 7,82 (s, 1H), 7,96 (dd, 2H), 8,14 (dd, 1H), 8,18 (d ancho, 1H), 8,25 (s ancho, 1H).

ESI/MS m/e: 386 ([M+H]$^+$, $C_{22}H_{13}F_2N_5$).

Ejemplo 6

Etapa a:

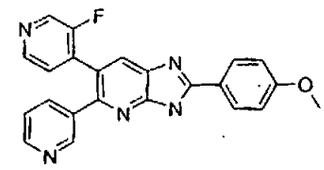


***N*-(6'-Amino-3''-fluoro-3,2':3',4''-terpiridin-5'-il)-4-metoxibenzamida**

Se añadió cloruro de 4-metoxibenzoilo (0,066 g, 0,39 mmol) a una solución de 3''-fluoro-3,2':3',4''-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,36 mmol) en piridina (2 ml). La mezcla se agitó a temperatura ambiente durante la noche y se evaporó el disolvente. Se añadieron diclorometano (1,6 ml) y tris-(2-aminoetil)amina poliestireno (0,180 g, 0,72 mmol) y la mezcla se agitó a temperatura ambiente durante 1 hora. La resina se filtró y se lavó dos veces con diclorometano. Los filtrados se reunieron y el disolvente se evaporó dando el compuesto del epígrafe (0,172 g) que se usó en la siguiente etapa sin purificación adicional.

ESI/MS m/e: 416 ([M+H]$^+$, $C_{23}H_{18}FN_5O_2$)

Etapa b:



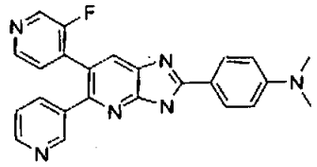
6-(3-Fluoropiridin-4-il)-2-(4-metoxifenil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,039 g, 28% de rendimiento) a partir de *N*-(6'-amino-3''-fluoro-3,2':3',4''-terpiridin-5'-il)-4-metoxibenzamida siguiendo el procedimiento descrito en el Ejemplo 2, etapa b.

δ RMN de ^{1}H ($CDCl_3$): 3,93 (s, 3H), 7,09-7,14 (d, 2H), 7,08-7,36 (m, 4H), 7,48-7,52 (s, 1H), 8,09 (s, 1H), 8,21-8,25 (d, 2H), 8,42-8,48 (m, 1H), 8,54-8,62 (m, 1H), 9,42-9,46 (m, 1H).

ESI/MS m/e: 398 ([M+H]$^+$, $C_{23}H_{16}FN_5O$)

Ejemplo 7



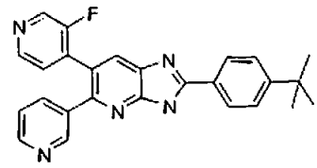
***N*-{4-[6-(3-Fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]fenil}-*N*,*N*-dimetilamina**

Se obtuvo (0,020 g, 14% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y cloruro de 4-(dimetilamino)benzoilo (0,072 g, 0,391 mmol) siguiendo el procedimiento descrito en el Ejemplo 6.

δ RMN de ^{1}H ($CDCl_3$): 3,10 (s, 6H), 6,81-6,85 (d, 2H), 7,21-7,30 (m, 4H), 7,62-7,66 (m, 1H), 7,99 (s, 1H), 8,04-8,09 (d, 2H), 8,37-8,42 (m, 1H), 8,53-8,55 (m, 1H), 8,65-8,70 (m, 1H).

ESI/MS m/e: 411 ($[M+H]^+$, $C_{24}H_{19}FN_6$)

Ejemplo 8



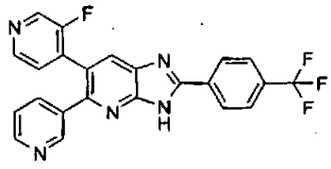
6-(3-Fluoropiridin-4-il)-2-(4-*terc*-butilfenil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,050 g, 33% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y cloruro de 4-terc-butilbenzoilo (0,072 ml, 0,391 mmol) siguiendo el procedimiento descrito en el Ejemplo 6.

δ RMN de ^{1}H ($CDCl_3$): 1,41 (s, 9H), 7,16-7,37 (m, 2H), 7,46-7,50 (m, 2H), 7,61-7,65 (d, 2H), 8,15 (s, 1H), 8,24-8,28 (d, 2H), 8,43-8,49 (m, 2H), 8,66-8,68 (m, 1H), 9,54 (s ancho, 1H).

ESI/MS m/e: 424 ($[M+H]^+$, $C_{26}H_{22}FN_5$)

Ejemplo 9



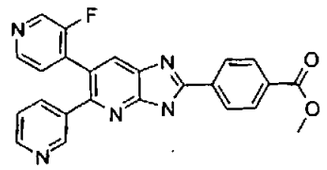
6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-[4-(trifluorometil)fenil]-3*H*-imidazo[4,5-*b*]piridina

Siguiendo el mismo procedimiento que en el **Ejemplo 2**, pero usando cloruro de 4-(trifluorometil)benzoilo, se obtuvo el compuesto del epígrafe como un sólido blanco (172 mg, 57%).

δ RMN de ^{1}H ($CDCl_3$): 7,21 (dd, 1H), 7,39 (t, 1H), 7,46 (d ancho, 1H), 7,89 (d, 2H), 8,19 (s, 1H), 8,47 (d, 2H), 8,52 (s ancho, 2H), 8,67 (d ancho, 1H), 8,68 (s, 1H), 9,80 (s ancho, 1H).

ESI/MS m/e: 436 ([M+H]$^+$, $C_{23}H_{13}F_4N_5$).

Ejemplo 10



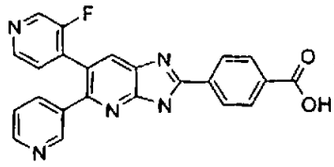
4-[6-(3-Fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoato de metilo

Se obtuvo (0,047 g, 31% de rendimiento) a partir de 3''-fluoro-3,2':3',4''-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y 4-(clorocarbonil)benzoato de metilo (0,078 g, 0,391 mmol) siguiendo el procedimiento descrito en el Ejemplo 6.

δ RMN de ^{1}H (DMSO-d_6): 3,90 (s, 3H), 7,30-7,37 (m, 2H), 7,55-7,60 (m, 2H), 7,68-7,74 (m, 2H), 8,14-8,24 (m, 3H), 8,40-8,51 (m, 4H).

ESI/MS m/e: 426 ([M+H]$^+$, $C_{24}H_{16}FN_5O_2$)

Ejemplo 11



Ácido 4-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoico

Se añadió solución acuosa 2N de hidróxido sódico (0,1 ml) a una solución de 4-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3H-imidazo[4,5-b]piridin-2-il]benzoato de metilo (**Ejemplo 10**, 0,041 g, 0,097 mmol) en una mezcla de THF/etanol 1:1 (1,2 ml). La mezcla se calentó a 60ºC durante 3h y luego se neutralizó con solución acuosa 2N de cloruro de hidrógeno. El disolvente se evaporó y la mezcla bruta se purificó por cromatografía ultrarrápida sobre

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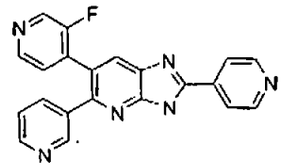
gel de silice (diclorometano/etanol/acetato de etilo/ácido acético 78:10:10:2) dando el compuesto del epígrafe (0,013 g, 31% de rendimiento).

δ RMN de ^{1}H (DMSO-d_6): 7,31-7,37 (m, 2H), 7,55-7,60 (m, 2H), 7,68-7,74 (m, 2H), 8,09-8,13 (m, 1H), 8,21 (s, 1H), 8,30-8,35 (d, 2H), 8,47-8,51 (m, 3H).

ESI/MS m/e: 412 ([M+H]$^+$, $C_{23}H_{14}FN_5O_2$)

Ejemplo 12



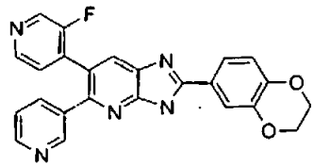
6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,070 g, 53% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y cloruro de isonicotinoilo (0,070 g, 0,391 mmol) siguiendo el procedimiento descrito en el Ejemplo 6.

δ RMN de ^{1}H ($CDCl_3$): 7,24-7,34 (m, 3H), 7,65-7,69 (m, 1H), 8,12-8,20 (m, 3H), 8,38-8,44 (m, 2H), 8,53-8,55 (m, 1H), 8,68-8,70 (m, 1H), 8,79-8,82 (m, 2H)

ESI/MS m/e: 369 ([M+H]$^+$, $C_{21}H_{13}FN_6$)

Ejemplo 13



2-(2,3-Dihidro-1,4-benzodioxin-6-il)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

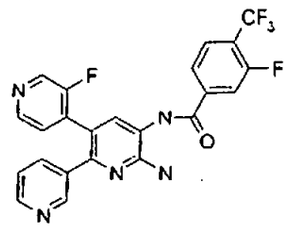
Se obtuvo (0,027 g, 18% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y cloruro de 2,3-dihidro-1,4-benzodioxina-6-carbonilo (0,078 g, 0,391 mmol) siguiendo el procedimiento descrito en el Ejemplo 6.

δ RMN de ^{1}H ($CDCl_3$): 4,37 (s, 4H), 7,05-7,34 (m, 4H), 7,36-7,43 (d, 1H), 7,82-7,87 (m, 2H), 8,10 (s, 1H), 8,42-8,49 (m, 2H), 8,66-8,69 (m, 1H), 9,64 (s, 1H).

ESI/MS m/e: 426 ([M+H]$^+$, $C_{24}H_{16}FN_5O_2$)

Ejemplo 14

Etapa a:

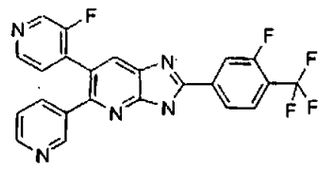


***N*-(6'-Amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)-3-fluoro-4-metilbenzamida**

Se añadieron 0,071 ml (0,78 mmol) de cloruro de 3-fluoro-4-metilbenzoilo a una solución de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,2 g, 0,71 mmol) en piridina (2 ml). La mezcla se calentó a 40ºC durante 4h y se evaporó el disolvente. La mezcla bruta se extrajo entre acetato de etilo y agua, se secó la fase orgánica ($MgSO_4$) y se evaporó dando el compuesto del epígrafe (0,295 g, 88% de rendimiento) que se usó en la siguiente etapa sin purificación adicional.

ESI/MS m/e: 418 ($[M+H]^+$, $C_{23}H_{17}F_2N_5O$)

Etapa b:



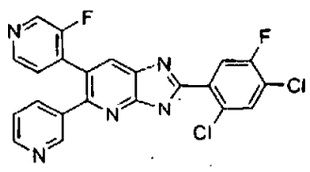
6-(3-Fluoropiridin-4-il)-2-[3-fluoro-4-(trifluorometil)fenil]-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,043 g, 15% de rendimiento) a partir de *N*-(6'-amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)-3-fluoro-4-metilbenzamida siguiendo el procedimiento descrito en el Ejemplo 2, etapa b.

δ RMN de ^1H ($CDCl_3$): 7,19-7,24 (m, 2H); 7,38-7,46 (m, 2H), 7,83-7,91 (t, 1H), 8,21 (s, 1H), 8,22-8,29 (m, 2H), 8,45 (s, 1H), 8,52-8,55 (d, 1H), 8,69-8,71 (d, 1H), 9,89 (s, 1H).

ESI/MS m/e: 454 ($[M+H]^+$, $C_{23}H_{12}F_5N_5$)

Ejemplo 15

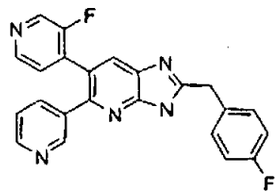


2-(2,4-Dicloro-5-fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,075 g, 47% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y cloruro de 2,4-dicloro-5-fluorobenzoilo (0,070 g, 0,391 mmol) siguiendo el procedimiento descrito en el Ejemplo 6.

ESI/MS m/e: 454 ([M+H]$^+$, $C_{22}H_{11}Cl_2F_2N_5$)

Ejemplo 16



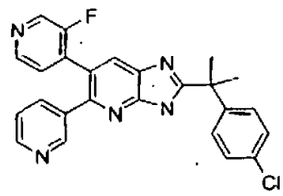
2-(4-Fluorobencil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,035 g, 25% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y cloruro de (4-fluorofenil)acetilo (0,054 ml, 0,391 mmol) siguiendo el procedimiento descrito en el Ejemplo 6.

δ RMN de ^{1}H ($CDCl_3$): 4,33 (s, 2H), 7,01-7,09 (m, 2H), 7,25-7,38 (m, 4H), 7,55-7,59 (d, 1H), 8,02 (s, 1H), 8,36-8,42 (m, 3H), 8,46-8,49 (d, 1H), 8,70 (s, 1H).

ESI/MS m/e: 400 ([M+H]$^+$, $C_{23}H_{15}F_2N_5$)

Ejemplo 17



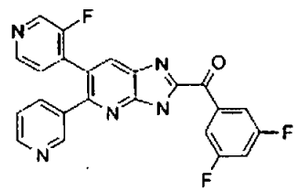
2-[1-(4-Clorofenil)-1-metiletil]-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,040 g, 49% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y cloruro de 2-(4-clorofenil)-2-metilpropanoilo (0,14 g, 0,651 mmol) siguiendo el procedimiento descrito en el Ejemplo 6.

δ RMN de ^{1}H ($CDCl_3$): 1,61 (s, 6H), 7,00-7,06 (m, 2H), 7,26-7,38 (m, 4H), 8,08-8,14 (m, 3H), 8,42-8,44 (m, 1H), 8,46-8,48 (d, 2H), 9,30 (s, 1H).

ESI/MS m/e: 444 ([M+H]$^+$, $C_{25}H_{19}ClFN_5$)

Ejemplo 18



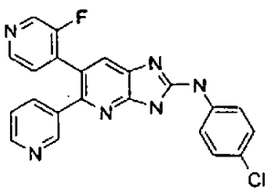
(3,5-Difluorofenil)[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]metanona

Se añadieron 0,071 ml (0,78 mmol) de cloruro de 3,5-difluorobenzoilo a una solución de 3''-fluoro-3,2':3',4''-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,79 mmol) en piridina (2 ml). La mezcla se agitó a temperatura ambiente durante 16 h y se evaporó el disolvente. La mezcla bruta se purificó por cromatografía ultrarrápida (diclorometano/metanol 95:5) dando el compuesto del epígrafe (0,015 g, 10% de rendimiento).

δ RMN de ^{1}H ($CDCl_3$): 6,96-7,08 (m, 1H), 7,22-7,35 (m, 3H), 7,75 (s, 1H), 7,82-7,87 (m, 1H), 8,18-8,24 (m, 2H), 8,45-8,47 (m, 2H), 8,56-8,58 (m, 2H).

ESI/MS m/e: 432 ([M+H]$^+$, $C_{23}H_{12}F_3N_5O$)

Ejemplo 19



***N*-(4-Clorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina**

Se añadió 1,3-diisopropilcarbodiimida (0,042 ml, 0,267 mmol) a una solución de 3''-fluoro-3,2':3',4''-terpiridin-5',6'-diamina (**Intermedio 1**, 0,050 g, 0,179 mmol) y 1-cloro-4-isotiocianatobenceno (0,045 g, 0,267 mmol) en etanol (1 ml). La mezcla se calentó a 50ºC durante 2h. Después de enfriar a temperatura ambiente, el sólido precipitado se separó por filtración dando el compuesto del epígrafe (0,035 g, 47% de rendimiento).

δ RMN de ^{1}H (MeOD): 7,34-7,38 (m, 3H), 7,44-7,49 (dd, 1H), 7,67-7,70 (m, 2H), 7,73 (s, 1H), 7,77-7,84 (m, 1H), 8,34-8,48 (m, 5H).

ESI/MS m/e: 417 ([M+H]$^+$, $C_{22}H_{14}ClFN_6$)

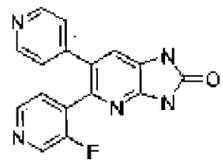
Ejemplo 20

5,6-Dipiridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

Se obtuvo (0,012 g, 23% de rendimiento) a partir de 4,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 4**, 0,048 g, 0,18 mmol) siguiendo el procedimiento descrito en el **Ejemplo 1**.

ESI/MS m/e: 290 ($[M+H]^+$, $C_{16}H_{11}N_5O$)

Ejemplo 23

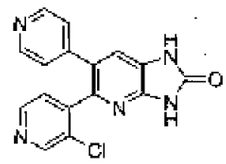


5-(3-Fluoropiridin-4-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

Se obtuvo (0,024 g, 15% de rendimiento) a partir de 3-fluoro-4,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 5**, 0,173 g, 1,06 mmol) siguiendo el procedimiento descrito en el **Ejemplo 1**.

ESI/MS m/e: 308 ($[M+H]^+$, $C_{16}H_{10}FN_5O$)

Ejemplo 24



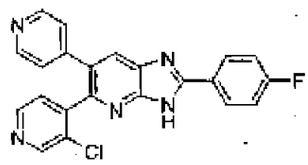
5-(3-Cloropiridin-4-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

Siguiendo el mismo protocolo que en el Ejemplo 1, pero usando 3-cloro-4,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 6**), se obtuvo el compuesto del epígrafe como un sólido blanco (74 mg, 65%).

δ RMN de ^1H (DMSO-d_6): 7,11 (d ancho, 2H), 7,35 (s, 1H), 7,41 (d, 1H), 8,41 (d ancho, 2H), 8,47 (d, 1H), 8,54 (s, 1H), 11,24 (s ancho, 1H), 11,69 (s ancho, 1H).

ESI/MS m/e: 324 ($[M+H]^+$, $C_{16}H_{10}ClN_5O$).

Ejemplo 25



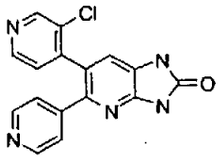
5-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

Siguiendo el mismo protocolo que en el Ejemplo 5, pero usando 3-cloro-4,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 6**), se obtuvo el compuesto del epígrafe como un sólido blanco (68 mg, 34%).

δ RMN de ^{1}H ($CDCl_3$): 7,15 (d, 2H), 7,23-7,32 (m, 3H), 8,14-8,25 (m, 2H), 8,21 (dd, 1H), 8,49 (m, 1H), 8,51 (d, 2H), 8,58 (s, 1H).

ESI/MS m/e: 402 ($[M+H]^+$, $C_{22}H_{13}ClFN_5$).

Ejemplo 26



6-(3-Cloropiridin-4-il)-5-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

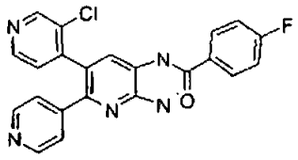
Se obtuvo (0,021 g, 23% de rendimiento) a partir de 3"-cloro-4,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 7**, 0,082 g, 0,275 mmol) siguiendo el procedimiento descrito en el Ejemplo 1.

δ RMN de ^{1}H (DMSO-d_6): 7,13-7,16 (m, 2H), 7,26 (s, 1H), 7,41-7,43 (m, 1H), 8,41-8,43 (m, 2H), 8,48-8,51 (m, 1H), 8,62 (s, 1H).

ESI/MS m/e: 324 ($[M+H]^+$, $C_{16}H_{10}ClN_5O$)

Ejemplo 27

Etapa a:

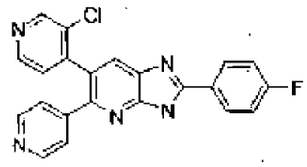


***N*-(6'-Amino-3"-cloro-4,2':3',4"-terpiridin-5'-il)-4-fluorobenzamida**

Se obtuvo (0,335 g, 95% de rendimiento) a partir de 3"-cloro-4,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 7**, 0,250 g, 0,84 mmol) y cloruro de 4-fluorobenzoilo (0,120 ml, 1,01 mmol) siguiendo el procedimiento descrito en el Ejemplo 2, etapa a. La mezcla bruta se usó en la siguiente etapa sin purificación adicional.

ESI/MS m/e: 420 ($[M+H]^+$, $C_{22}H_{15}ClFN_5O$)

Etapa b:



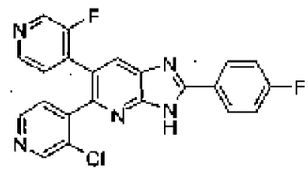
6-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-5-piridin-4-il-3H-imidazo[4,5-b]piridina

Se obtuvo (0,099 g, 31% de rendimiento) a partir de *N*-(6'-amino-3"-cloro-4,2':3',4"-terpiridin-5'-il)-4-fluorobenzamida (0,005 g, 0,8 mmol) siguiendo el procedimiento descrito en el Ejemplo 2, etapa b.

δ RMN de ^{1}H (DMSO-d_6): 7,25-7,28 (m, 2H), 7,41-7-54 (m, 3H), 8,08 (s, 1H), 8,30-8,37 (m, 2H), 8,46-8,49 (m, 2H), 8,54-8,56 (d, 1H), 8,64 (s, 1H).

ESI/MS m/e: 402 ([M+H]$^+$, $C_{22}H_{13}ClFN_5$)

Ejemplo 28

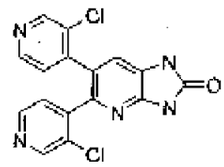


5-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-6-(3-fluoropiridin-4-il)-3*H*-imidazo[4,5-*b*]piridina

Siguiendo el mismo protocolo que en el Ejemplo 2, pero usando cloruro de 4-fluorobenzoilo y 3-cloro-3"-fluoro-4,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 8**), se obtuvo el compuesto del epígrafe como un sólido blanco (13 mg, 12%).

ESI/MS m/e: 420 ([M+H]$^+$, $C_{22}H_{12}ClF_2N_5$).

Ejemplo 29

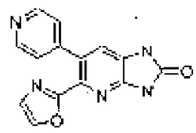


5,6-Bis(3-cloropiridin-4-il)-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

Se obtuvo (0,026 g, 84% de rendimiento) a partir de 3,3"-dicloro-4,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 9**, 0,029 g, 0,09 mmol) siguiendo el procedimiento descrito en el Ejemplo 1.

ESI/MS m/e: 358 ([M+H]$^+$, $C_{16}H_9Cl_2N_5O$)

Ejemplo 30



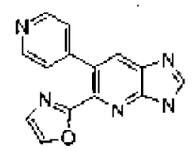
5-(1,3-Oxazol-2-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

Se calentó hasta 100°C en un tubo sellado una solución de 2-(1,3-oxazol-2-il)-3,4'-bipiridin-5,6-diamina (**Intermedio 10**, 0,077 g, 0,3 mmol), *N,N'*-carbonildiimidazol (0,146 g, 0,9 mmol) y trietilamina (91 mg, 0,9 mmol) en *N,N*-dimetilformamida (1 ml). Después de 4 horas, la mezcla se enfrió y se concentró a vacío. Se añadió agua al residuo y el sólido que se separó se lavó con agua y se secó dando el compuesto del epígrafe (0,038 g, 45%) como un sólido blanco.

δ RMN de ^{1}H (DMSO-d_6): 7,21 (d, 2H), 7,29 (s, 1H), 8,08 (s, 1H), 8,51 (d, 2H), 11,39 (s, 1H), 11,78 (s, 1H).

ESI/MS m/e: 280 ([M+H]+, $C_{14}H_9N_5O_2$)

Ejemplo 31



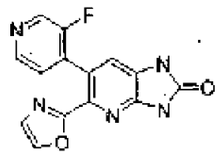
5-(1,3-Oxazol-2-il)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

Se calentó en un tubo sellado hasta 140°C una mezcla de 2-(1,3-oxazol-2-il)-3,4'-bipiridin-5,6-diamina (Intermedio 10, 0,100 g, 0,39 mmol) y ortoformiato de trietilo (0,117 g, 0,79 mmol) en ácido acético glacial (2 ml). Después de agitar durante 2 horas, la mezcla se enfrió y se llevó hasta pH 7 con solución acuosa 6N de hidróxido sódico. Se añadió acetato de etilo a la mezcla y, después de agitar durante 30 minutos, se filtró el sólido separado, se lavó con éter dietílico y se secó a vacío dando el compuesto del epígrafe (0,047 g, 49%) como un sólido blanquecino.

δ RMN de ^{1}H (DMSO-d_6): 7,20 (m, 3H), 8,06 (m, 2H), 8,50 (d, 2H), 8,60 (s, 1H).

ESI/MS m/e: 264 ([M+H]+, $C_{14}H_9N_5O$)

Ejemplo 32



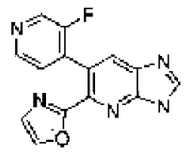
6-(3-Fluoropiridin-4-il)-5-(1,3-oxazol-2-il)-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

Se obtuvo (37%) a partir de 3'-fluoro-2-(1,3-oxazol-2-il)-3,4'-bipiridin-5,6-diamina (**Intermedio 11**) y *N,N'*-carbonildiimidazol siguiendo el procedimiento descrito para la preparación del ejemplo 30.

δ RMN de ^{1}H (DMSO-d_6): 7,18 (s, 1H), 7,31 (s, 1H), 7,47 (dd, 1H), 8,12 (s, 1H), 8,49 (m, 2H), 11,36 (s, 1H), 11,85 (s, 1H).

ESI/MS m/e: 298 ([M+H]+, $C_{14}H_8FN_5O_2$)

Ejemplo 33



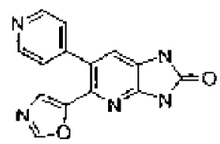
6-(3-Fluoropiridin-4-il)-5-(1,3-oxazol-2-il)-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (26%) a partir de 3'-fluoro-2-(1,3-oxazol-2-il)-3,4'-bipiridin-5,6-diamina (**Intermedio 11**) y ortoformiato de trietilo siguiendo el procedimiento descrito para la preparación del ejemplo 31.

δ RMN de ^{1}H (DMSO-d_6): 7,21 (s, 1H), 7,53 (dd, 1H), 8,18 (m, 2H), 8,50 (m, 2H), 8,71 (s, 1H).

ESI/MS m/e: 282 ([M+H]+, $C_{14}H_8FN_5O$)

Ejemplo 34



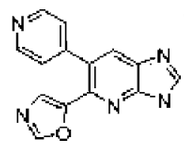
5-(1,3-Oxazol-5-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

Se obtuvo (58%) a partir de 2-(1,3-oxazol-5-il)-3,4'-bipiridin-5,6-diamina (**Intermedio 12**) y N,N'-carbonildiimidazol siguiendo el procedimiento descrito para la preparación del ejemplo 30.

δ RMN de ^{1}H (DMSO-d_6): 6,92 (s, 1H), 7,20 (s, 1H), 7,30 (d, 2H), 8,24 (s, 1H), 8,58 (d, 2H), 11,21 (s, 1H), 11,69 (s, 1H).

ESI/MS m/e: 278 ([M-H]+, $C_{14}H_9N_5O_2$)

Ejemplo 35



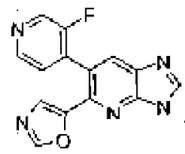
5-(1,3-oxazol-5-il)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (66%) a partir de 2-(1,3-oxazol-5-il)-3,4'-bipiridin-5,6-diamina (**Intermedio 12**) y ortoformiato de trietilo siguiendo el procedimiento descrito para la preparación del ejemplo 31.

δ RMN de ^{1}H (DMSO-d_6): 7,00 (m, 1H), 7,36 (m, 2H), 8,00 (m, 1H), 8,31 (s, 1H), 8,62 (m ,3H), 13,0 (s, 1H).

ESI/MS m/e: 264 ([M+H]+, $C_{14}H_9N_5O$)

Ejemplo 36



6-(3-Fluoropiridin-4-il)-5-(1,3-oxazol-5-il)-3*H*-imidazo[4,5-*b*]piridina

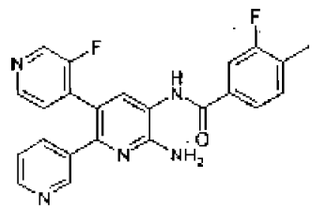
Se obtuvo (25%) a partir de 3'-fluoro-2-(1,3-oxazol-5-il)-3,4'-bipiridin-5,6-diamina (**Intermedio 13**) y ortoformiato de trietilo siguiendo el procedimiento descrito para la preparación del ejemplo 31.

δ RMN de ^{1}H (DMSO-d_6): 7,17 (s, 1H), 7,58 (dd, 1H), 8,15 (s, 1H), 8,32 (s, 1H), 8,55 (dd, 1H), 8,65 (m, 2H).

ESI/MS m/e: 282 ([M+H]+, $C_{14}H_8FN_5O$)

Ejemplo 37

Etapa a:

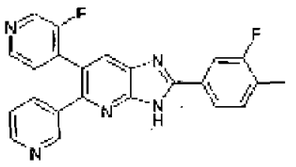


***N*-(6'-Amino-3''-fluoro-3,2':3',4''-terpiridin-5'-il)-3-fluoro-4-metilbenzamida**

Se añadieron 0,15 g (0,89 mmol) de cloruro de 3-fluoro-4-metilbenzoilo a una solución de 3''-fluoro-3,2':3',4''-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) en piridina (2 ml). La mezcla se agitó a temperatura ambiente durante la noche y se evaporó el disolvente. La mezcla bruta (0,33 g) se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 95:5) proporcionando el compuesto del epígrafe (0,12 g, 81% de rendimiento).

ESI/MS m/e: 418 ([M+H]$^+$, $C_{23}H_{17}F_2N_5O$)

Etapa b:



2-(3-Fluoro-4-metilfenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

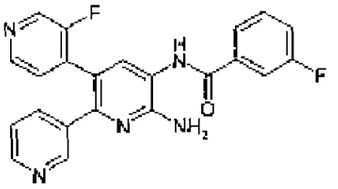
Se calentó en un tubo herméticamente cerrado a 118°C durante 16 horas una solución de *N*-(6'-amino-3''-fluoro-3,2':3',4''-terpiridin-5'-il)-3-fluoro-4-metilbenzamida (0,12 g, 0,288 mmol) en ácido acético (2 ml). El disolvente se evaporó y se añadió solución acuosa al 4% de bicarbonato sódico y se extrajo con acetato de etilo. La fase orgánica se secó y se evaporó. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 95:5) proporcionando el compuesto del epígrafe (0,03 g, 26% de rendimiento).

δ RMN de ^{1}H ($CDCl_3$): 2,41 (s, 3H), 7,17-7,50 (m, 4H), 7,96 (m, 1H), 8,01 (s, 1H), 8,14 (s, 1H), 8,43 (d, 1H), 8,49 (dd, 1H), 8,65 (dd, 1H), 9,57 (m, 1H).

ESI/MS m/e: 400 ([M+H]$^+$, $C_{23}H_{15}F_2N_5$).

Ejemplo 38

Etapa a:

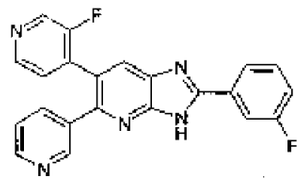


***N*-(6'-Amino-3''-fluoro-3,2':3',4''-terpiridin-5'-il)-3-fluorobenzamida**

Se obtuvo (0,180 g) a partir de 3''-fluoro-3,2':3',4''-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y cloruro de 3-fluorobenzoilo (0,048 ml, 0,392 mmol) siguiendo el procedimiento descrito en el Ejemplo 6, etapa a.

ESI/MS m/e: 404 ([M+H]$^+$, $C_{22}H_{15}F_2N_5O$)

Etapa b:



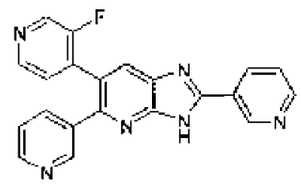
2-(3-Fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,035 g, 26% de rendimiento) a partir de *N*-(6'-amino-3''-fluoro-3,2':3',4''-terpiridin-5'-il)-3-fluorobenzamida siguiendo el procedimiento descrito en el Ejemplo 37, etapa b.

δ RMN de ^{1}H ($CDCl_3$): 7,20 (m, 1H), 7,39 (m, 3H), 7,60 (td, 1H), 8,09 (m, 2H), 8,16 (s, 1H), 8,44 (s, 1H), 8,50 (d, 1H), 8,68 (dd, 1H), 9,73 (s, 1H).

ESI/MS m/e: 386 ([M+H]$^+$, $C_{22}H_{13}F_2N_5$).

Ejemplo 39



6-(3-Fluoropiridin-4-il)-2,5-dipiridin-3-il-3*H*-imidazo[4,5-*b*]piridina

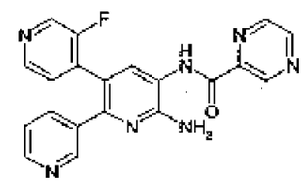
Se obtuvo (0,025 g, 24% de rendimiento) a partir de 3''-fluoro-3,2':3',4''-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) e hidrocloruro de cloruro de nicotinoilo (0,070 g, 0,392 mmol) siguiendo el procedimiento descrito en el Ejemplo 38.

δ RMN de ^{1}H ($CDCl_3$): 7,21 (m, 1H), 7,41 (m, 2H), 7,59 (m, 1H), 8,20 (s, 1H), 8,45 (s, 1H), 8,52 (m, 1H), 8,69 (s, 1H), 8,72 (s, 1H), 8,82 (m, 1H), 9,61 (m, 1H), 9,82 (m, 1H).

ESI/MS m/e: 369 ([M+H]$^+$, $C_{21}H_{13}FN_6$).

Ejemplo 40

Etapa a:

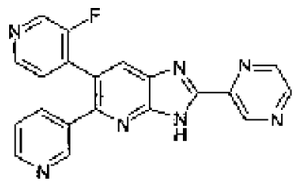


_N_-(6'-Amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)pirazin-2-carboxamida

Se calentó a 40°C durante 15 minutos una solución de ácido pirazin-2-carboxílico (0,114 g, 0,924 mmol), hidrocloruro de _N_-[3-(dimetilamino)propil]-_N'_-etilcarbodiimida (0,178 g, 0,924 mmol) y 1_H_-1,2,3-benzotriazol-1-ol (0,096 g, 0,712 mmol) en DMF (6 ml). Finalmente, se añadió 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) en DMF (1 ml) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla bruta se extrajo entre acetato de etilo y agua. La fase orgánica se lavó con solución acuosa al 4% de bicarbonato sódico y agua, se secó ($MgSO_4$) y se evaporó. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 90:10) proporcionando el compuesto del epígrafe (0,057 g, 41% de rendimiento).

ESI/MS m/e: 388 ([M+H]$^+$, $C_{20}H_{14}FN_7O$).

Etapa b:



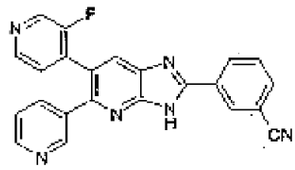
6-(3-Fluoropiridin-4-il)-2-pirazin-2-il-5-piridin-3-il-3_H_-imidazo[4,5-_b_]piridina

Se obtuvo (0,016 g, 28% de rendimiento) a partir de _N_-(6'-amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)pirazin-2-carboxamida siguiendo el procedimiento descrito en el Ejemplo 37, etapa b.

δ RMN de ^{1}H ($CDCl_3$): 7,20-7,35 (m, 3H), 7,57 (m, 1H), 8,22 (s, 1H), 8,43 (m, 1H), 8,48 (d, 1H), 8,72-8,77 (m, 3H), 9,24 (m, 1H), 9,75 (d, 1H).

ESI/MS m/e: 370 ([M+H]$^+$, $C_{20}H_{12}FN_7$).

Ejemplo 41



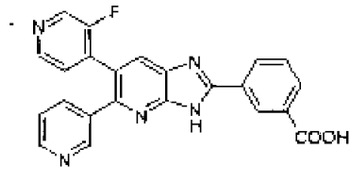
3-[6-(3-Fluoropiridin-4-il)-5-piridin-3-il-3_H_-imidazo[4,5-_b_]piridin-2-il]benzonitrilo

Se obtuvo (0,11 g, 53% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,15 g, 0,534 mmol) y cloruro de 3-cianobenzoilo (0,133 g, 0,803 mmol) siguiendo el procedimiento descrito en el Ejemplo 38.

δ RMN de ^{1}H ($CDCl_3$): 7,22 (m, 1H), 7,37-7,45 (m, 2H), 7,72-7,88 (m, 2H), 8,19 (s, 1H), 8,46 (d, 1H), 8,54 (d, 1H), 8,64 (d, 1H), 8,71 (m, 1H), 8,73 (m, 1H), 9,92 (m, 1H).

ESI/MS m/e: 393 ([M+H]$^+$, $C_{23}H_{13}FN_6$).

Ejemplo 42



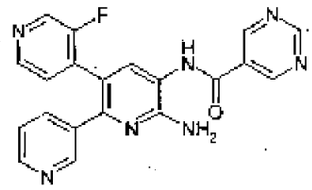
Ácido 3-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoico

Se añadió solución acuosa al 37% (1,07 ml) de cloruro de hidrógeno a una solución de 3-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzonitrilo (**Ejemplo 41**, 0,1 g, 0,255 mmol) en una mezcla de THF/agua 1:2,5 (0,83 ml). La mezcla se calentó a 70°C durante 4 días. Después de enfriar a temperatura ambiente, se separó el sólido precipitado por filtración proporcionando el compuesto del epígrafe (0,070 g, 67% de rendimiento).

ESI/MS m/e: 412 ([M+H]$^+$, $C_{23}H_{14}FN_5O_2$).

Ejemplo 43

Etapa a:

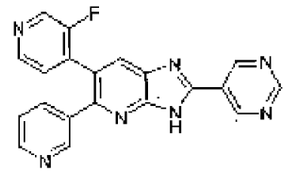


***N*-(6'-Amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)pirimidin-5-carboxamida**

Se calentó a 40°C durante 15 minutos una solución de ácido pirimidin-5-carboxílico (0,088 g, 0,709 mmol), hidrocloruro de *N*-[3-(dimetilamino)propil]-*N'*-etilcarbodiimida (0,136 g, 0,709 mmol) y 1H-1,2,3-benzotriazol-1-ol (0,072 g, 0,534 mmol) en DMF (4 ml). Finalmente, se añadió 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,15 g, 0,534 mmol) en DMF (4 ml) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla bruta se extrajo entre acetato de etilo y agua. La fase orgánica se lavó con solución acuosa al 4% de bicarbonato sódico y agua, se secó ($MgSO_4$) y se evaporó. El residuo (0,2 g) se usó en la siguiente etapa sin purificación adicional.

ESI/MS m/e: 388 ([M+H]$^+$, $C_{20}H_{14}FN_7O$).

Etapa b:

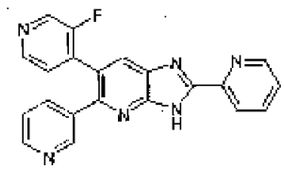


6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-pirimidin-5-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,024 g, 12% de rendimiento) a partir de *N*-(6'-amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)pirimidin-5-carboxamida siguiendo el procedimiento descrito en el Ejemplo 37, etapa b.

ESI/MS m/e: 370 ([M+H]$^+$, $C_{20}H_{12}FN_7$).

Ejemplo 44



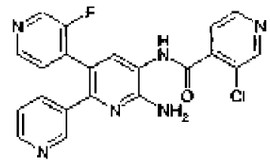
6-(3-Fluoropiridin-4-il)-2-piridin-2-il-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,006 g, 18% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y cloruro de piridin-2-carbonilo (0,131 g, 0,926 mmol) siguiendo el procedimiento descrito en el Ejemplo 37.

ESI/MS m/e: 369 ([M+H]$^+$, $C_{21}H_{13}FN_6$).

Ejemplo 45

Etapa a:



***N*-(6'-Amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)-3-cloroisonicotinamida**

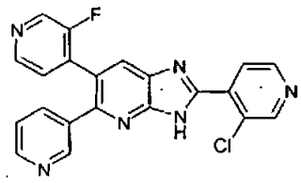
Se agitó durante 15 minutos una solución de ácido 3-cloroisonicotínico (0,075 g, 0,48 mmol), hexafluorofosfato de *N*-[(dimetilamino)(3*H*-[1,2,3]triazolo[4,5-*b*]piridin-3-iloxi)metilen]-*N*-metilmetanaminio (0,178 g, 0,47 mmol) y *N*-etil-*N*-isopropilpropan-2-amina (0,15 ml, 0,86 mmol) en DMF (1 ml). Finalmente, se añadió 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,11 g, 0,39 mmol) en DMF (2,9 ml) y la mezcla se agitó a temperatura ambiente durante 3,5 horas. La mezcla bruta se extrajo entre acetato de etilo

(58

y agua. La fase orgánica se lavó con agua y salmuera, se secó ($MgSO_4$) y se evaporó. El residuo (0,195 g) se usó en la siguiente etapa sin purificación adicional.

ESI/MS m/e: 421 ([M+H]$^+$, $C_{21}H_{14}ClFN_6O$).

Etapa b:



2-(3-Cloropiridin-4-il)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

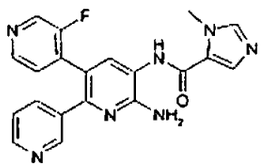
Se obtuvo (0,030 g, 16% de rendimiento) a partir de *N*-(6'-amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)-3-cloroisonicotinamida siguiendo el procedimiento descrito en el Ejemplo 37, etapa b.

δ RMN de ^{1}H ($CDCl_3$): 7,19 (dd, 1H), 7,31 (t, 1H), 7,57 (d, 1H), 8,25 (m, 2H), 8,42 (s, 1H), 8,47 (d, 1H), 8,57 (dt, 1H), 8,73 (d, 1H), 8,82 (s, 1H), 9,11 (s, 1H).

ESI/MS m/e: 403 ([M+H]$^+$, $C_{21}H_{12}ClFN_6$).

Ejemplo 46

Etapa a:

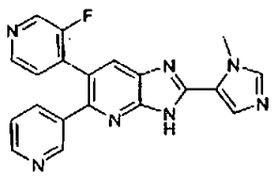


***N*-(6'-amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)-1-metil-1*H*-imidazol-5-carboxamida**

Se obtuvo (0,040 g, 19% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,15 g, 0,534 mmol) y ácido 1-metil-1*H*-imidazol-5-carboxílico (0,088 g, 0,694 mmol) siguiendo el procedimiento descrito en el Ejemplo 41, etapa a.

ESI/MS m/e: 390 ([M+H]$^+$, $C_{20}H_{16}FN_7O$).

Etapa b:



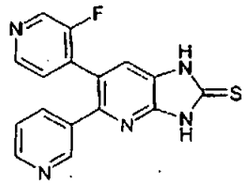
6-(3-Fluoropiridin-4-il)-2-(1-metil-1*H*-imidazol-5-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se calentó en un tubo herméticamente cerrado a 118°C durante 16 horas una solución de *N*-(6'-amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)-1-metil-1*H*-imidazol-5-carboxamida (0,040 g, 0,103 mmol) en ácido acético (1 ml). El disolvente se evaporó y se añadió solución acuosa al 4% de bicarbonato sódico y se extrajo con acetato de etilo. La fase orgánica se secó y se evaporó proporcionando el compuesto del epígrafe (0,022 g, 58% de rendimiento).

ESI/MS m/e: 372 ([M+H]$^+$, $C_{20}H_{14}FN_7$).

Ejemplo 47

Etapa a:



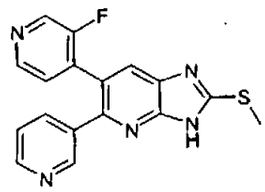
6-(3-Fluoropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-tiona

Se calentó a 80°C en un tubo herméticamente cerrado una solución de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 2 g, 7,11 mmol), 1,1'-tiocarbonildiimidazol (2,54 g, 14,22 mmol) y trietilamina (2 ml, 14,22 mmol) en THF (30 ml). Después de 6 horas, la mezcla se enfrió y el sólido se filtró, se lavó con NH_4Cl acuoso y agua y se secó proporcionando el compuesto del epígrafe (2,03 g, 88%) como un sólido blanco.

δ RMN de ^{1}H (DMSO-d_6): 7,31 (dd, 1H), 7,49 (dd, 1H), 7,58 (s, 1H), 7,64 (dt, 1H), 8,39-8,48 (m, 4H).

ESI/MS m/e: 324 ([M+H]+, $C_{18}H_{10}FN_5S$).

Etapa b:



6-(3-Fluoropiridin-4-il)-2-(metiltio)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se añadió gota a gota a 0°C en argon una suspensión de 6-(3-fluoropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-tiona (0,6 g, 1,86 mmol) en DMF (15 ml) a una suspensión de hidruro sódico al 60% (0,098 g, 2,45 mmol) en DMF (5 ml). La solución se dejó agitando durante 30 minutos a 0°C y luego se añadió gota a gota yodometano (0,116 ml, 1,86 mmol) en DMF (1 ml). La mezcla de reacción se calentó hasta temperatura

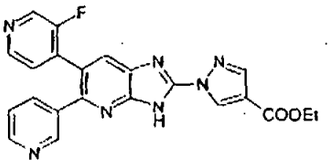
ambiente y se agitó durante 2,5 horas. La mezcla se concentró y se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol/amoniaco 150:40:5) proporcionando el compuesto del epígrafe (0,34 g, 54% de rendimiento).

δ RMN de ^{1}H (DMSO-d_6): 2,74 (s, 3H), 7,309 (dd, 1H), 7,51 (t, 1H), 7,66 (dt, 2H), 7,98 (s, 1H), 8,43-8,47 (m, 4H).

ESI/MS m/e: 338 ([M+H]+, $C_{17}H_{12}FN_5S$).

Ejemplo 48

Etapa a:

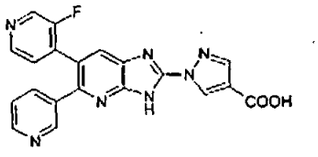


1-[6-(3-Fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]-1*H*-pirazol-4-carboxilato de etilo

Se calentó a 120°C en un tubo herméticamente cerrado una solución de 6-(3-fluoropiridin-4-il)-2-(metiltio)-5-piridin-3-il-3H-imidazo[4,5-b]piridina (**Ejemplo 47**, 0,1 g, 0,3 mmol), 1*H*-pirazol-4-carboxilato de etilo (0,125 g, 0,88 mmol) y carbonato potásico (0,164 mg, 1,18 mmol) en DMF (2 ml). Después de 2 días, el disolvente se evaporó y la mezcla bruta se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol/amoniaco 100:8:1) proporcionando el compuesto del epígrafe (0,034 g, 27% de rendimiento).

ESI/MS m/e: 430 ([M+H]+, $C_{22}H_{16}FN_7O_2$).

Etapa b:



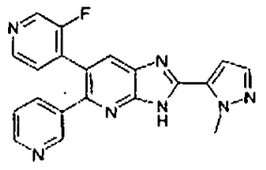
Ácido 1-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]-1*H*-pirazol-4-carboxílico

Se añadió solución acuosa de hidróxido sódico 2N (0,05 ml) a una solución de 1-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]-1*H*-pirazol-4-carboxilato de etilo (0,022 g, 0,05 mmol) en una mezcla de THF/etanol 1:1 (1 ml). La mezcla se calentó a 60°C durante 2 horas y luego se neutralizó con solución acuosa 2N de cloruro de

hidrógeno. El disolvente se evaporó y la mezcla bruta se purificó por extracción en fase sólida, SCX, se lavó con agua y eluyó con metanol/amoníaco (9:1) proporcionando el compuesto del epígrafe (0,007 g, 29% de rendimiento).

ESI/MS m/e: 402 ([M+H]$^+$, $C_{20}H_{12}FN_7O_2$).

Ejemplo 49

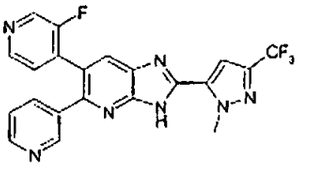


6-(3-Fluoropiridin-4-il)-2-(1-metil-1*H*-pirazol-5-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,012 g, 24% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,2 g, 0,71 mmol), *N*,*N*'-diciclohexilcarbodiimida (0,19 g, 0,92 mmol), 1*H*-1,2,3-benzotriazol-1-ol (0,099 g, 0,73 mmol) y ácido 1-metil-1H-pirazol-5-carboxílico (0,116 g, 0,92 mmol) siguiendo el procedimiento descrito en el Ejemplo 41.

ESI/MS m/e: 372 ([M+H]$^+$, $C_{20}H_{14}FN_7$).

Ejemplo 50



6-(3-Fluoropiridin-4-il)-2-[1-metil-3-(trifluorometil)-1*H*-pirazol-5-il]-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

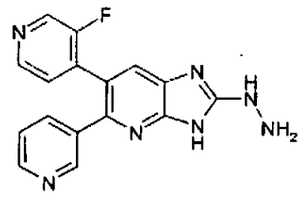
Se obtuvo (0,017 g, 24% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,085 g, 0,30 mmol), *N*,*N*'-diciclohexilcarbodiimida (0,074 g, 0,36 mmol), 1*H*-1,2,3-benzotriazol-1-ol (0,042 g, 0,31 mmol) y ácido 1-metil-3-(trifluorometil)-1H-pirazol-5-carboxílico (0,071 g, 0,36 mmol) siguiendo el procedimiento descrito en el Ejemplo 41.

δ RMN de ^{1}H (DMSO-d_6): 4,45 (s, 3H), 7,33 (dd, 1H), 7,55-7,59 (m, 2H), 7,71 (dt, 1H), 8,31 (s, 1H), 8,48-8,50 (m, 4H).

ESI/MS m/e: 440 ([M+H]$^+$, $C_{21}H_{13}F_4N_7$).

Ejemplo 51

Etapa a:

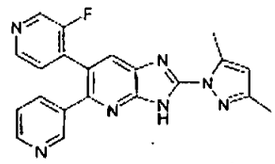


6-(3-Fluoropiridin-4-il)-2-hidrazino-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se calentó en un tubo herméticamente cerrado a 100°C durante 30 horas una solución de 6-(3-fluoropiridin-4-il)-2-(metiltio)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina (**Ejemplo 47**, 0,05 g, 0,15 mmol) en hidrazina (0,5 ml). El disolvente se evaporó y el residuo (0,05 g) se usó en la siguiente etapa sin purificación adicional.

ESI/MS m/e: 322 ([M+H]+, $C_{16}H_{12}FN_7$).

Etapa b:



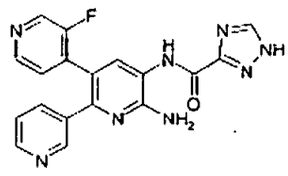
2-(3,5-Dimetil-1*H*-pirazol-1-il)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se calentó en un tubo herméticamente cerrado a 80°C durante 16 horas una solución de 6-(3-fluoropiridin-4-il)-2-hidrazino-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina (0,05 g, 0,15 mmol), pentan-2,4-diona (0,016 ml, 0,16 mmol) y solución acuosa de cloruro de hidrógeno en etanol (1 ml). El pH ácido se neutralizó y luego se evaporó el disolvente y la mezcla bruta se purificó por cromatografía de fase inversa (agua/acetonitrilo) proporcionando el compuesto del epígrafe (0,015 g, 25% de rendimiento).

ESI/MS m/e: 386 ($[M+H]^+$, $C_{21}H_{16}FN_7$).

Ejemplo 52

Etapa a:

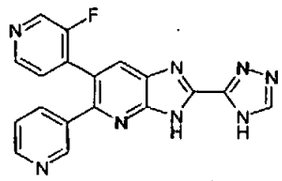


N-(6'-Amino-3''-fluoro-3,2':3',4''-terpiridin-5'-il)-1*H*-1,2,4-triazol-3-carboxamida

Se agitó durante 15 minutos en argon una solución de ácido 1*H*-1,2,4-triazol-3-carboxílico (0,072 g, 0,64 mmol), hexafluorofosfato de *N*-[(dimetilamino)(3*H*-[1,2,3]triazolo[4,5-*b*]piridin-3-iloxi)metilen]-*N*-metilmetanaminio (0,243 g, 0,64 mmol) y *N*-etil-*N*-isopropilpropan-2-amina (0,205 ml, 1,17 mmol) en DMF (1,5 ml). Finalmente, se añadió 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,15 g, 0,53 mmol) en DMF (3 ml) y la mezcla se agitó a temperatura ambiente durante 20 horas. El disolvente se evaporó y la mezcla bruta se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 90:10) proporcionando el compuesto del epígrafe (0,070 g, 35% de rendimiento).

ESI/MS m/e: 377 ([M+H]+, $C_{18}H_{13}FN_8O$).

Etapa b:



6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-(4H-1,2,4-triazol-3-il)-3*H*-imidazo[4,5-*b*]piridina

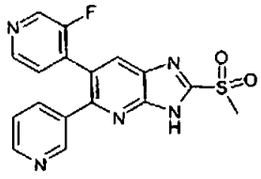
Se calentó en un tubo herméticamente cerrado a 120°C durante 18 horas una solución de *N*-(6'-amino-3"-fluoro-3,2':3',4"-terpiridin-5'-il)-1*H*-1,2,4-triazol-3-carboxamida (0,070 g, 0,19 mmol) en ácido acético (2,5 ml). El disolvente se evaporó y el residuo se suspendió en acetato de etilo y solución acuosa al 4% de bicarbonato sódico. El sólido formado se filtró y se secó al vacío proporcionando el compuesto del epígrafe (0,039 g, 59% de rendimiento).

δ RMN de ^{1}H (DMSO-d_6): 7,33 (m, 1H), 7,56 (m, 1H), 7,69 (m, 1H), 8,13 (m, 1H), 8,47 (m, 4H), 8,69 (m, 1H).

ESI/MS m/e: 359 ([M+H]$^+$, $C_{18}H_{11}FN_8$).

Ejemplo 53

Etapa a:



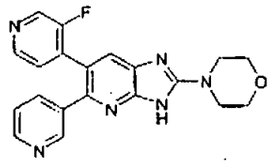
6-(3-Fluoropiridin-4-il)-2-(metilsulfonil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se añadió ácido 3-clorobencenocarboperoxoico (0,128 g, 77% de pureza, 0,570 mmol) a 0°C a una solución de 6-(3-fluoropiridin-4-il)-2-(metiltio)-5-piridin-3-il-3*H*-imidazo[4,5-

b]piridina (**Ejemplo 47**, 0,096 g, 0,285 mmol) en DCM (6 ml). La mezcla de reacción se calentó hasta temperatura ambiente y se agitó durante 16 horas. La mezcla se concentró y se purificó por cromatografía de fase inversa (agua/acetonitrilo) proporcionando el compuesto del epígrafe (0,040 g, 38% de rendimiento).

ESI/MS m/e: 370 ([M+H]+, $C_{17}H_{12}FN_5O_2S$).

Etapa b:

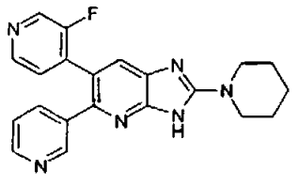


6-(3-Fluoropiridin-4-il)-2-morfolin-4-il-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se calentó en un tubo herméticamente cerrado a 120°C durante la noche una solución de 6-(3-fluoropiridin-4-il)-2-(metilsulfonil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina (0,025 g, 0,068 mmol), morfolina (0,024 ml, 0,268 mmol) en dioxano (0,5 ml). El disolvente se evaporó y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 95:5) proporcionando el compuesto del epígrafe (0,011 g, 44% de rendimiento).

ESI/MS m/e: 377 ($[M+H]^+$, $C_{20}H_{17}FN_6O$).

Ejemplo 54

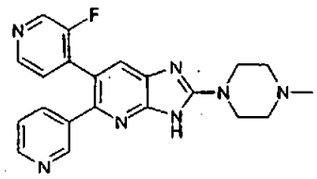


6-(3-Fluoropiridin-4-il)-2-piperidin-1-il-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se calentó a 120°C en un tubo herméticamente cerrado una solución de 6-(3-fluoropiridin-4-il)-2-(metiltio)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina (**Ejemplo 47**, 0,05 g, 0,15 mmol), piperidina (0,052 ml, 0,45 mmol) y ácido acético en xileno (1 ml). Después de 2 días, el disolvente se evaporó y la mezcla bruta se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 95:5) proporcionando el compuesto del epígrafe (0,03 g, 54% de rendimiento).

ESI/MS m/e: 430 ([M+H]+, $C_{21}H_{19}FN_6$).

Ejemplo 55



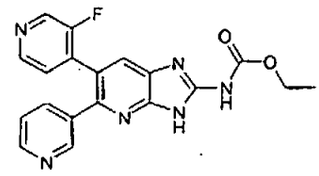
6-(3-Fluoropiridin-4-il)-2-(4-metilpiperazin-1-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,045 g, 55% de rendimiento) a partir de 6-(3-fluoropiridin-4-il)-2-(metiltio)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina (**Ejemplo 47**, 0,1 g, 0,3 mmol) y 1-metilpiperazina (0,117 ml, 1,05 mmol) siguiendo el procedimiento descrito en el Ejemplo 57.

ESI/MS m/e: 390 ($[M+H]^+$, $C_{21}H_{20}FN_7$).

Ejemplo 56

Etapa a:



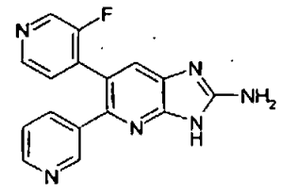
[6-(3-Fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]carbamato de etilo

Se obtuvo (0,175 g, 87% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,15 g, 0,53 mmol) e isotiocianatodicarbonato de etilo (0,094 ml, 0,8 mmol) siguiendo el procedimiento descrito en el Ejemplo 19 (tiempo de reacción: 20 h).

δ RMN de ^1H ($CDCl_3$): 1,37 (t, 3H), 4,37 (c, 2H), 7,23 (m, 2H), 7,70 (d, 1H), 7,81 (s, 1H), 8,39 (m, 2H), 8,51 (d, 1H), 8,57 (m, 1H).

ESI/MS m/e: 379 ($[M+H]^+$, $C_{19}H_{15}FN_6O_2$).

Etapa b:



6-(3-Fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina

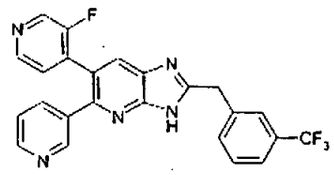
Se calentó a 110°C durante 24 horas una solución de [6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]carbamato de etilo (0,175 g, 0,46 mmol), hidróxido potásico (0,17 g, 3,01 mmol) en propan-2-ol (2 ml). El disolvente se evaporó y la mezcla bruta

(0,38 g) se purificó por cromatografía de fase inversa (agua/acetonitrilo) proporcionando el compuesto del epígrafe (0,08 g, 57% de rendimiento).

δ RMN de ^{1}H (DMSO-d_6): 6,98 (s, 1H), 7,26 (dd, 1H), 7,42 (m, 2H), 7,62 (dt, 1H), 8,36-8,41 (m, 3H).

ESI/MS m/e: 307 ($[M+H]^+$, $C_{16}H_{11}FN_6$).

Ejemplo 57



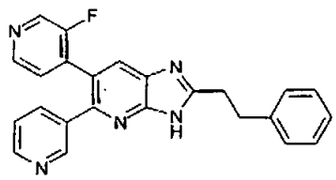
6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-[3-(trifluorometil)bencil]-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,026 g, 42% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y cloruro de [3-(trifluorometil)fenil]acetilo (0,075 g, 0,337 mmol) siguiendo el procedimiento descrito en el Ejemplo 37.

δ RMN de ^{1}H ($CDCl_3$): 4,47 (s, 2H), 7,04-7,11 (m, 1H), 7,25-7,60 (m, 6H), 7,66 (s, 1H), 8,04 (s, 1H), 8,26 (d, 1H), 8,40 (m, 1H), 8,46 (d, 1H), 9,31 (s, 1H).

ESI/MS m/e: 450 ($[M+H]^+$, $C_{24}H_{15}F_4N_5$).

Ejemplo 58



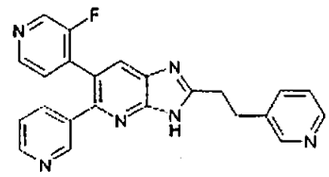
6-(3-Fluoropiridin-4-il)-2-(2-feniletil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,060 g, 49% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y cloruro de 3-fenilpropanoilo (0,080 ml, 0,534 mmol) siguiendo el procedimiento descrito en el Ejemplo 37.

δ RMN de ^{1}H ($CDCl_3$): 3,24 (m, 4H), 7,11 (dd, 1H), 7,20-7,33 (m, 6H), 7,46 (d, 1H), 8,04 (s, 1H), 8,40 (d, 1H), 8,45 (d, 1H), 8,49 (dd, 1H), 9,23 (s, 1H), 12,76 (s, 1H).

ESI/MS m/e: 396 ($[M+H]^+$, $C_{24}H_{18}FN_5$).

Ejemplo 59



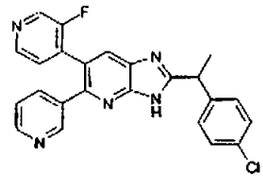
6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-(2-piridin-3-iletil)-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,02 g, 59% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y ácido 3-piridin-3-ilpropanoico (0,070 g, 0,463 mmol) siguiendo el procedimiento descrito en el Ejemplo 41.

δ RMN de ^{1}H ($CDCl_3$): 3,29 (s, 4H), 7,23 (m, 3H), 7,61 (d, 2H), 8,00 (s, 1H), 8,37 (d, 1H), 8,40 (d, 1H), 8,45 (m, 1H), 8,52 (d, 1H), 8,54 (d, 1H), 8,65 (d, 1H).

ESI/MS m/e: 397 ($[M+H]^+$, $C_{23}H_{17}FN_6$).

Ejemplo 60



2-[1-(4-Clorofenil)etil]-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

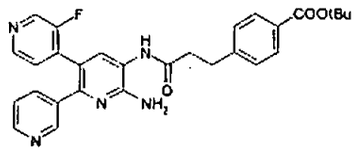
Se obtuvo (0,035 g, 52% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,15 g, 0,534 mmol) y ácido 2-(4-clorofenil)propanoico (0,128 g, 0,694 mmol) siguiendo el procedimiento descrito en el Ejemplo 41.

δ RMN de ^{1}H ($CDCl_3$): 1,91 (d, 3H), 4,51 (c, 1H), 7,08 (m, 1H), 7,30 (m, 5H), 7,39 (m, 1H), 8,07 (s, 1H), 8,28 (dd, 1H), 8,41 (d, 1H), 8,47 (d, 1H), 9,24 (d, 1H), 12,58 (s, 1H).

ESI/MS m/e: 430 ($[M+H]^+$, $C_{24}H_{17}ClFN_5$).

Ejemplo 61

Etapa a:

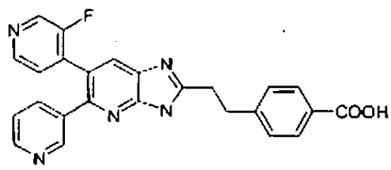


Éster *terc*-butílico del ácido 4-[2-(6'-amino-3"-fluoro-[3,2';3',4"]terpiridin-5'-ilcarbamoil)-etil]-benzoico

Se obtuvo (0,135 g, 49% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,15 g, 0,534 mmol) y ácido 3-[4-(terc-butoxicarbonil)fenil]propanoico (0,174 g, 0,694 mmol) siguiendo el procedimiento descrito en el Ejemplo 41, etapa a.

ESI/MS m/e: 514 ($[M+H]^+$, $C_{29}H_{28}FN_5O_3$).

Etapa b:

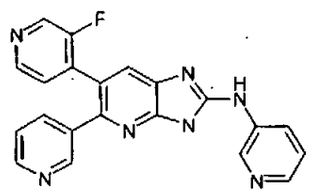


Ácido 4-{2-[6-(3-fluoro-piridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]-etil}-benzoico

Se calentó en un tubo herméticamente cerrado a 118°C durante 16 horas una solución de éster *terc*-butílico del ácido 4-[2-(6'-amino-3"-fluoro-[3,2';3',4"]terpiridin-5'-ilcarbamoil)-etil]-benzoico (0,135 g, 0,263 mmol) en ácido acético (2 ml). El disolvente se evaporó y se añadió acetato de etilo. El sólido formado se filtró y se lavó con solución acuosa al 4% de bicarbonato sódico, agua y se secó proporcionando el compuesto del epígrafe (0,08 g, 69% de rendimiento).

ESI/MS m/e: 440 ($[M+H]^+$, $C_{25}H_{18}FN_5O_2$).

Ejemplo 62



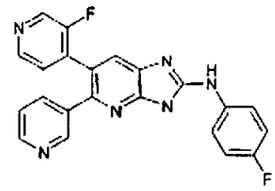
6-(3-Fluoropiridin-4-il)-*N*,5-dipiridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina

Se añadió 1,3-diisopropilcarbodiimida (0,083 ml, 0,534 mmol) a una solución de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,1 g, 0,356 mmol) y 3-isotiocianatopiridina (0,06 ml, 0,534 mmol) en etanol (2 ml). La mezcla se calentó a 50°C durante 2h. Después de enfriar a temperatura ambiente, el disolvente se evaporó. La mezcla bruta se purificó por cromatografía ultrarrápida sobre gel de sílice (diclorometano/metanol 95:5) proporcionando el compuesto del epígrafe (0,045 g, 33% de rendimiento).

ESI/MS m/e: 384 ($[M+H]^+$, $C_{21}H_{14}FN_7$).

169

Ejemplo 63



***N*-(4-Fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina**

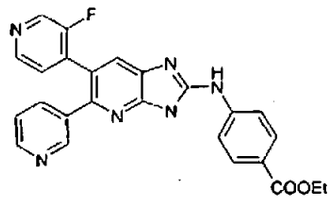
Se obtuvo (0,048 g, 49% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,15 g, 0,534 mmol) y 1-fluoro-4-isotiocianato benceno (0,082 g, 0,534 mmol) siguiendo el procedimiento descrito en el Ejemplo 62.

δ RMN de ^{1}H (DMSO-d_6): 7,19 (t, 2H), 7,30 (dd, 1H), 7,47 (dd, 1H), 7,63-7,69 (m, 2H), 7,80-7,87 (m, 2H), 8,43 (m, 4H).

ESI/MS m/e: 401 ([M+H]$^+$, $C_{22}H_{14}F_2N_6$).

Ejemplo 64

Etapa a:

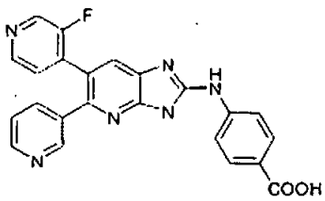


Éster etílico del ácido 4-[6-(3-fluoro-piridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-ilamino]-benzoico

Se obtuvo (0,120 g, 74% de rendimiento) a partir de 3"-fluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 1**, 0,10 g, 0,356 mmol) y 4-isotiocianatobenzoato de etilo (0,111 g, 0,534 mmol) siguiendo el procedimiento descrito en el Ejemplo 62.

ESI/MS m/e: 455 ([M+H]$^+$, $C_{25}H_{19}FN_6O_2$).

Etapa b:



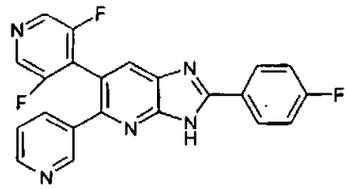
Ácido 4-{[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]amino}benzoico

(70

Se añadió solución acuosa 2N de hidróxido sódico (0,53 ml) a una solución de éster etílico del ácido 4-[6-(3-fluoro-piridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-ilamino]-benzoico (0,120 g, 0,264 mmol) en etanol (3,5 ml). La mezcla se agitó a temperatura ambiente durante la noche y luego se neutralizó con solución acuosa 2N de cloruro de hidrógeno. El disolvente se evaporó y la mezcla bruta (0,18 g) se purificó por cromatografía de fase inversa (agua/acetonitrilo) proporcionando el compuesto del epígrafe (0,02 g, 18% de rendimiento).

ESI/MS m/e: 427 ([M+H]$^+$, $C_{23}H_{15}FN_6O_2$).

Ejemplo 65



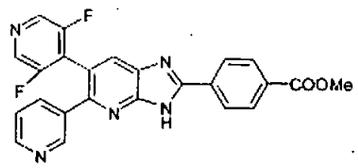
6-(3,5-Difluoropiridin-4-il)-2-(4-fluorofenil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Se obtuvo (0,037 g, 20% de rendimiento) a partir de 3",5"-difluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 14**, 0,10 g, 0,33 mmol) y cloruro de 4-fluorobenzoilo (0,059 ml, 0,5 mmol) siguiendo el procedimiento descrito en el Ejemplo 37.

ESI/MS m/e: 404 ([M+H]$^+$, $C_{22}H_{12}F_3N_5$).

Ejemplo 66

Etapa a:

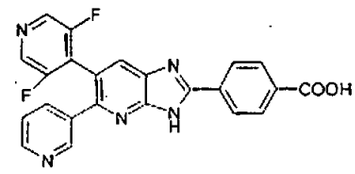


4-[6-(3,5-Difluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoato de metilo

Se obtuvo (0,050 g, 70% de rendimiento) a partir de 3",5"-difluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 14**, 0,10 g, 0,33 mmol) y ácido 4-(metoxicarbonil)benzoico (0,078 g, 0,43 mmol) siguiendo el procedimiento descrito en el Ejemplo 41.

ESI/MS m/e: 404 ([M+H]$^+$, $C_{22}H_{12}F_3N_5$).

Etapa b:



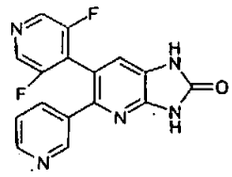
Ácido 4-[6-(3,5-difluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoico

Se añadió solución acuosa 2N de hidróxido sódico (0,11 ml) a una solución de 4-[6-(3,5-difluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoato de metilo (0,05 g, 0,11 mmol) en etanol (1,1 ml). La mezcla se calentó a 60°C durante 5,5 h y luego se neutralizó con solución acuosa 2N de cloruro de hidrógeno. El disolvente se evaporó y la mezcla bruta se suspendió en agua, el sólido formado se filtró y se secó proporcionando el compuesto del epígrafe (0,04 g, 76% de rendimiento).

δ RMN de ^{1}H (MeOD): 7,41 (m, 1H), 7,86 (m, 1H), 8,22-8,33 (m, 5H), 8,42 (s, 2H), 8,50 (s, 1H), 8,57 (s, 1H).

ESI/MS m/e: 430 ([M+H]$^+$, $C_{23}H_{13}F_2N_5O_2$).

Ejemplo 67



6-(3,5-Difluoropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

Se calentó a 80°C en un tubo herméticamente cerrado una solución de 3",5"-difluoro-3,2':3',4"-terpiridin-5',6'-diamina (**Intermedio 14**, 0,045 g, 0,15 mmol), *N,N'*-carbonildiimidazol (0,1 g, 0,6 mmol) y trietilamina (0,084 ml, 0,6 mmol) en THF (1,5 ml). Después de 72 horas, la mezcla se enfrió y el sólido se separó, se lavó con THF y se secó proporcionando el compuesto del epígrafe (0,029 g, 59% de rendimiento).

δ RMN de ^{1}H (DMSO-d_6): 7,30 (dd, 1H), 7,44 (s, 1H), 7,61 (d, 1H), 8,38 (d, 1H), 8,46 (dd, 1H), 8,50 (s, 2H).

ESI/MS m/e: 326 ([M+H]+, $C_{16}H_9F_2N_5O$).

EJEMPLO DE COMPOSICIÓN 1

Se prepararon de acuerdo con la siguiente formulación 50.000 cápsulas que contenían cada una 100 mg de 5-(3-fluoropiridin-4-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona (ingrediente activo):

Ingrediente activo	5 Kg
Lactosa monohidratada	10 Kg
Dióxido de silicio coloidal	0,1 Kg
Almidón de maíz	1 Kg
Estearato de magnesio	0,2 Kg

Procedimiento

Se tamizaron los ingredientes anteriores a través de un tamiz de malla 60 y se cargaron en un mezclador adecuado y llenaron en 50.000 cápsulas de gelatina.

EJEMPLO DE COMPOSICIÓN 2

Se prepararon a partir de la siguiente formulación 50.000 comprimidos que contenían cada uno 50 mg de 5-(3-fluoropiridin-4-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona (ingrediente activo):

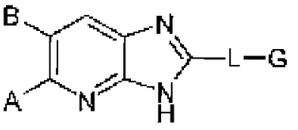
Ingrediente activo	2,5 Kg
Celulosa microcristalina	1,95 Kg
Lactosa secada por aspersión	9,95 Kg
Carboximetilalmidón	0,4 Kg
Estearil fumarato sódico	0,1 Kg
Dióxido de silicio coloidal	0,1 Kg

Procedimiento

Se hicieron pasar todos los polvos a través de una malla con una apertura de 0,6 mm, luego se mezclaron en un mezclador adecuado durante 20 minutos y se compactaron en forma de comprimidos de 300 mg usando un disco de 9 mm y punzones biselados planos. El tiempo de disgregación de los comprimidos fue de aproximadamente 3 minutos.

REIVINDICACIONES

1. Un compuesto de fórmula (I)



en la que:

A representa un grupo heteroarilo monocíclico que contiene nitrógeno opcionalmente sustituido con uno o más sustituyentes seleccionados de forma independiente del grupo consistente en átomos de halógeno, grupos alquilo C_{1-4}, cicloalquilo C_{3-7}, cicloalquil C_{3-7}-alquilo C_{1-4}, alcoxi C_{1-4}, aril-alcoxi C_{1-4}, alquil C_{1-4}tio, mono o di-alquil C_{1-4}amino, trifluorometilo, hidroxi y ciano;

B representa un grupo heteroarilo monocíclico que contiene nitrógeno opcionalmente sustituido con uno o más sustituyentes seleccionados de forma independiente del grupo que comprende átomos de halógeno, grupos alquilo C_{1-4}, cicloalquilo C_{3-7}, cicloalquil C_{3-7}-alquilo C_{1-4}, alcoxi C_{1-4}, aril-alcoxi C_{1-4}, alquil C_{1-4}tio, mono o di-alquil C_{1-4}amino, trifluorometilo, hidroxi y ciano;

L representa un grupo de unión seleccionado del grupo que comprende, enlace directo, -$(CRR')_n$-, -NR-, -S-, -O- y -CO-; siendo n un número entero que varía de 0 a 2;

G representa un grupo seleccionado del grupo que comprende –H, -OH, cicloalquilo C_{3-7}; alquilo C_{1-6}, arilo, heteroarilo y anillos heterocíclicos saturados que contienen nitrógeno, estando los grupos arilo, heteroarilo y heterocíclicos saturados que contienen nitrógeno no sustituidos o sustituidos con uno o más grupos seleccionados de átomos de halógeno, grupos alquilo C_{1-4}, alquil C_{1-4}tio, alcoxi C_{1-4}, mono- o di-alquil C_{1-4}amino, ciano, trifluorometilo –COOH y -CO-O-alquilo C_{1-4};

R y R' se seleccionan independientemente de entre átomos de hidrógeno y grupos alquilo C_{1-4};

y sus y N-óxidos sales farmacéuticamente aceptables.

2. Un compuesto según la reivindicación 1, en el que A representa un grupo piridina opcionalmente sustituido o un grupo oxazol opcionalmente sustituido.

3. Un compuesto según cualquiera de las reivindicaciones anteriores, en el que el grupo A representa un anillo de piridina no sustituido o sustituido con un átomo de halógeno.

4. Un compuesto según cualquiera de las reivindicaciones anteriores, en el que B representa un grupo piridina o pirimidina que pueden estar opcionalmente sustituidos.

5. Un compuesto según la reivindicación 4, en el que B representa un grupo piridina que no está sustituido o está sustituido con uno o más átomos de halógeno.

6. Un compuesto según cualquiera de las reivindicaciones anteriores, en el que –L-G representa un resto seleccionado del grupo que comprende átomos de hidrógeno, grupos hidroxilo, grupos fenilo opcionalmente sustituido, piridilo opcionalmente sustituido, bencilo opcionalmente sustituido, benzoilo opcionalmente sustituido, cicloalquilo C_{3-7}; alquilo C_{1-6}, morfolino opcionalmente sustituido, piperidino opcionalmente sustituido y piperazina opcionalmente sustituido, pudiendo tener los grupos opcionalmente sustituidos de 0 a 2 sustituyentes seleccionados del grupo consistente en átomos de halógeno, alquilo C_{1-4}, alquil C_{1-4}tio, alcoxi C_{1-4}, mono o di-alquil C_{1-4}amino, ciano, -(CO)OH, -(CO)O-alquilo C_{1-4}, trifluorometilo, piperidinilmetilo, piridinilmetilo, fenilamino y piperidinilamino.

7. Un compuesto según la reivindicación 1 que es uno de:

6-(3-Fluoropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona
2-Ciclopropil-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
2-Ciclohexil-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
6-(3-Fluoropiridin-4-il)-2-metil-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
2-(4-Fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
6-(3-Fluoropiridin-4-il)-2-(4-metoxifenil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
N-{4-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3H-imidazo[4,5-b]piridin-2-il]fenil}-*N*,*N*-dimetilamina
6-(3-Fluoropiridin-4-il)-2-(4-*terc*-butilfenil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina
6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-[4-(trifluorometil)fenil]-3*H*-imidazo[4,5-*b*]piridina

4-[6-(3-Fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoato de metilo

Ácido 4-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoico

6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

2-(2,3-Dihidro-1,4-benzodioxin-6-il)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-[3-fluoro-4-(trifluorometil)fenil]-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-(2,4-Dicloro-5-fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-(4-Fluorobencil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-[1-(4-Clorofenil)-1-metiletil]-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

(3,5-Difluorofenil)[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]metanona

N-(4-clorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina

2-(4-Fluorofenil)-5-piridin-3-il-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Cloropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5,6-Dipiridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(3-Fluoropiridin-4-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(3-Cloropiridin-4-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Cloropiridin-4-il)-5-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

6-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-5-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

5-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-6-(3-fluoropiridin-4-il)-3*H*-imidazo[4,5-*b*]piridina

5,6-Bis(3-cloropiridin-4-il)-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(1,3-Oxazol-2-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(1,3-Oxazol-2-il)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-5-(1,3-oxazol-2-il)-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

6-(3-Fluoropiridin-4-il)-5-(1,3-oxazol-2-il)-3*H*-imidazo[4,5-*b*]piridina

5-(1,3-Oxazol-5-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(1,3-Oxazol-5-il)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

4-[6-(3-Fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoato de metilo

Ácido 4-[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoico

6-(3-Fluoropiridin-4-il)-5-piridin-3-il-2-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

2-(2,3-Dihidro-1,4-benzodioxin-6-il)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-2-[3-fluoro-4-(trifluorometil)fenil]-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-(2,4-Dicloro-5-fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-(4-Fluorobencil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

2-[1-(4-Clorofenil)-1-metiletil]-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

(3,5-Difluorofenil)[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]metanona

N-(4-clorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina

2-(4-Fluorofenil)-5-piridin-3-il-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Cloropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5,6-Dipiridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(3-Fluoropiridin-4-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(3-Cloropiridin-4-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Cloropiridin-4-il)-5-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

6-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-5-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

5-(3-Cloropiridin-4-il)-2-(4-fluorofenil)-6-(3-fluoropiridin-4-il)-3*H*-imidazo[4,5-*b*]piridina

5,6-Bis(3-cloropiridin-4-il)-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(1,3-Oxazol-2-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(1,3-Oxazol-2-il)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

6-(3-Fluoropiridin-4-il)-5-(1,3-oxazol-2-il)-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

6-(3-Fluoropiridin-4-il)-5-(1,3-oxazol-2-il)-3*H*-imidazo[4,5-*b*]piridina

5-(1,3-Oxazol-5-il)-6-piridin-4-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

5-(1,3-Oxazol-5-il)-6-piridin-4-il-3*H*-imidazo[4,5-*b*]piridina

(77)

Ácido 4-{2-[6-(3-fluoro-piridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]-etil}-benzoico

6-(3-Fluoropiridin-4-il)-*N*,5-dipiridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina

N-(4-Fluorofenil)-6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-amina

Ácido 4-{[6-(3-fluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]amino}benzoico

6-(3,5-Difluoropiridin-4-il)-2-(4-fluorofenil)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridina

Ácido 4-[6-(3,5-difluoropiridin-4-il)-5-piridin-3-il-3*H*-imidazo[4,5-*b*]piridin-2-il]benzoico

6-(3,5-Difluoropiridin-4-il)-5-piridin-3-il-1,3-dihidro-2*H*-imidazo[4,5-*b*]piridin-2-ona

8. Un compuesto según una cualquiera de las reivindicaciones 1 a 7 para uso en el tratamiento de un estado patológico o enfermedad susceptible de aliviar por efecto antagonista del receptor de adenosina A_{2B}.

9. Una composición farmacéutica que comprende un compuesto como el definido en una cualquiera de las reivindicaciones 1 a 7 en asociación con un diluyente o vehículo farmacéuticamente aceptable.

10. Uso de un compuesto como el definido en una cualquiera de las reivindicaciones 1 a 7 en la fabricación de un medicamento para el tratamiento de un estado patológico o enfermedad susceptible de mejora por efecto antagonista del receptor de adenosina A_{2B}.

11. Uso según la reivindicación 10, en el que el estado patológico o enfermedad es asma, broncoconstricción, enfermedades alérgicas, hipertensión, aterosclerosis, lesión por reperfusión, isquemia de miocardio, retinopatía, inflamación, trastornos del tracto gastrointestinal, trastornos de proliferación celular, diabetes mellitus y/o enfermedades autoinmunes.

12. Un procedimiento para tratar a un sujeto que sufre un estado patológico o enfermedad susceptible de alivio por efecto antagonista del receptor de adenosina A_{2B}, que comprende administrar a dicho sujeto una cantidad eficaz de un compuesto como el definido en una cualquiera de las reivindicaciones 1 a 7.

13. Un procedimiento según la reivindicación 12, en el que el estado patológico o enfermedad es asma, broncoconstricción, enfermedades alérgicas, hipertensión, aterosclerosis, lesión por reperfusión, isquemia de miocardio, retinopatía, inflamación, trastomos del tracto gastrointestinal, trastornos de proliferación celular, diabetes mellitus y/o enfermedades autoinmunes.

14. Un producto de combinación que comprende:

(i) Un compuesto según una cualquiera de las reivindicaciones 1 a 7; y

(ii) otro compuesto seleccionado de (1) antagonistas de los receptores muscarínicos M3, (2) agonistas β2, (3) inhibidores de PDE4, (4) corticosteroides, (5) antagonistas de leucotrieno D4, (6) inhibidores de egfr-quinasa, (7) inhibidores de quinasa p38, (8) agónistas del receptor NK1, (9) antagonistas de CRTh2, (10) inhibidores de quinasa syk, (11) antagonistas de CCR3 y (12) antagonistas de VLA-4

para el uso simultáneo, por separado o secuencial en el tratamiento del cuerpo humano o de un animal.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/009620

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P37/00 A61P9/00 A61P3/10
A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/002566 A (CV THERAPEUTICS, INC; PALLE, VENKATA; VARKHEDKAR, VAIBHAV; ZABLOCKI, J) 9 January 2003 (2003-01-09) cited in the application the whole document	1-14
A	WO 03/068773 A (GLAXO GROUP LIMITED; WITHERINGTON, JASON) 21 August 2003 (2003-08-21) claims; example 39	1-14
A	EP 1 221 444 A (EISAI CO., LTD) 10 July 2002 (2002-07-10) claims; examples 61-63	1-14
A	& WO 01/02400 A 11 January 2001 (2001-01-11) cited in the application	

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 January 2007	09/01/2007

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, Peter

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/009620

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2005/100353 A1 (ALMIRALL PRODESFARMA, SA, SPAIN; VIDAL JUAN, BERNAT) 27 October 2005 (2005-10-27) claims; examples	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/009620

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12 and 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/009620

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03002566 A	09-01-2003	AT 307132 T	15-11-2005
		CA 2451244 A1	09-01-2003
		DE 60206756 T2	13-07-2006
		DK 1401837 T3	07-11-2005
		EP 1401837 A1	31-03-2004
		ES 2247356 T3	01-03-2006
		HK 1064096 A1	16-12-2005
		JP 2004536102 T	02-12-2004
WO 03068773 A	21-08-2003	AU 2003245700 A1	04-09-2003
EP 1221444 A	10-07-2002	AT 303387 T	15-09-2005
		AU 778450 B2	09-12-2004
		AU 5571700 A	22-01-2001
		CA 2376835 A1	11-01-2001
		CN 1365361 A	21-08-2002
		DE 60022366 D1	06-10-2005
		DE 60022366 T2	14-06-2006
		DK 1221444 T3	14-11-2005
		WO 0102400 A1	11-01-2001
		NZ 516260 A	27-08-2004
		PT 1221444 T	30-11-2005
		US 6841549 B1	11-01-2005
WO 0102400 A	11-01-2001	AT 303387 T	15-09-2005
		AU 778450 B2	09-12-2004
		AU 5571700 A	22-01-2001
		CA 2376835 A1	11-01-2001
		CN 1365361 A	21-08-2002
		DE 60022366 D1	06-10-2005
		DE 60022366 T2	14-06-2006
		DK 1221444 T3	14-11-2005
		EP 1221444 A1	10-07-2002
		NZ 516260 A	27-08-2004
		PT 1221444 T	30-11-2005
		US 6841549 B1	11-01-2005
WO 2005100353 A1	27-10-2005	AR 049018 A1	21-06-2006
		AU 2005233279 A1	27-10-2005
		CA 2562369 A1	27-10-2005
		EP 1735310 A1	27-12-2006
		ES 2241496 A1	16-10-2005

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
A10618PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2006/009620	05.10.2006	06.10.2005

International Patent Classification (IPC) or national classification and IPC

INV. C07D471/04

Applicant

LABORATORIOS ALMIRALL, S.A.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2007-04-30	29.08.2007

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized officer

Bosma, Peter

Telephone No. +31 70 340-0

Form PCT/IPEA/409 (Cover Sheet) (April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2006/009620

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-79 as originally filed

   Claims, Numbers

   1-14 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12,13 with respect to Industrial Applicability

because:

☒ the said international application, or the said claims Nos. 12,13 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings: the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2006/009620

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11,14
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III.

Claims 12 and 13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present claims 12 and 13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V.

1 Reference is made to the following documents:

D1 : WO 03/002566 A (CV THERAPEUTICS, INC) 9 January 2003 cited in the application

D2 : EP 1 221 444 A (EISAI CO., LTD) 10 July 2002

2 Document D1, which could be considered to represent the most relevant state of the art, discloses **purine** derivatives useful as A_{2B} adenosine receptor antagonists. From this, the subject-matter of claims 1-14 mainly differs in the definition of the condensed heterocyclic ring system being an **imidazo[4,5-b]pyridine** system in the present application substituted by two nitrogen-containing heteroaryl groups (A and B), which compounds are also useful as A_{2B} adenosine receptor antagonists.

D2 discloses fused imidazol[4,5-b]pyridine derivatives, useful as A2 adenosine receptor antagonists, which are not substituted by two nitrogen-containing heteroaryl groups on the pyridine ring of the condensed ring system.
The subject-matter of claims 1-14 is therefore novel (Article 33(2) PCT).

3 The problem to be solved by the present invention may be regarded as the provision of further compounds useful as A_{2B} adenosine receptor antagonists.
The solution to this problem proposed in claims 1-14 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

No incentives can be found in any of the available prior art documents for the use of compounds, which are substituted by two nitrogen-containing heteroaryl groups on the pyridine ring of the condensed ring system, as A_{2B} adenosine receptor antagonists. The two nitrogen-containing heteroaryl groups (A and B) can be regarded as the special technical (structural) feature of the present application.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud: 08-34096

22) Fecha de solicitud: 04-04-2008

(30) Prioridad (31) *Prioridad* (32) *Fecha* (33) *País*
P200502433 06/10/2005 ES

(51) Int Cl: **C07D 471/004**

(71)Solicitante(s) **LABORATORIOS ALMIRALL S.A.**

(72) Inventor(es) **BERNAT VIDAL JUAN**
SILVIA FONQUERA POU Y OTROS

(74) Apoderado: **EMILIO FERRERO**

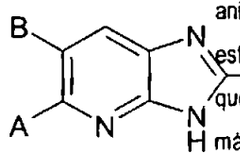
(85) Fecha límite inicio fase nacional: 06/04/2008
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 05/10/2006
No. de solicitud PCT/EP2006/009620

(87) Publicación internacional
Fecha: 12/04/2007
N° publicación: ***WO 2007/039297 A1***

(54) Título: **NUEVOS DERIVADOS IMIDAZOPIRIDINA**

Reivindicación(es):

1. Un compuesto de fórmula (I)



en la que:

A representa un grupo heteroarilo monocíclico que contiene nitrógeno opcionalmente sustituido con uno o más sustituyentes seleccionados de forma independiente del grupo consistente en átomos de halógeno, grupos alquilo C_{1-4}, cicloalquilo C_{3-7}, cicloalquil C_{3-7}- alquilo C_{1-4}, alcoxi C_{1-4}, aril-alcoxi C_{1-4}, alquil C_{1-4} tio, mono o di-alquil C_{1-4} amino, trifluorometilo, hidroxi y ciano;

B representa un grupo heteroarilo monocíclico que contiene nitrógeno opcionalmente sustituido con uno o más sustituyentes seleccionados de forma independiente del grupo que comprende átomos de halógeno, grupos alquilo C_{1-4}, cicloalquilo C_{3-7}, cicloalquil C_{3-7}- alquilo C_{1-4}, alcoxi C_{1-4}, aril-alcoxi C_{1-4}, alquil C_{1-4} tio, mono o di-alquil C_{1-4} amino, trifluorometilo, hidroxi y ciano;

L representa un grupo de unión seleccionado del grupo que comprende, enlace directo, $-(CRR')_n-$, -NR-, -S-, -O- y -CO-; siendo *n* un número entero que varía de 0 a 2;

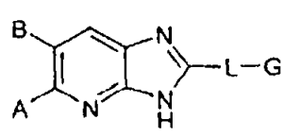
G representa un grupo seleccionado del grupo que comprende –H, -OH, cicloalquilo C_{3-7}; alquilo C_{1-6}, arilo, heteroarilo y anillos heterocíclicos saturados que contienen nitrógeno, estando los grupos arilo, heteroarilo y heterocíclicos saturados que contienen nitrógeno no sustituidos o sustituidos con uno o más grupos seleccionados de átomos de halógeno, grupos alquilo C_{1-4}, alquil C_{1-4}tio, alcoxi C_{1-4}, mono- o di-alquil C_{1-4}amino, ciano, trifluorometilo –COOH y -CO-O-alquilo C_{1-4};

R y R' se seleccionan independientemente de entre átomos de hidrógeno y grupos alquilo C_{1-4};

y sus y N-óxidos sales farmacéuticamente aceptables.

2. Un compuesto según la reivindicación 1, en el que A representa un grupo piridina opcionalmente sustituido o un grupo oxazol opcionalmente sustituido.

3. Un compuesto según cualquiera de las reivindicaciones anteriores, en el que el grupo A representa un anillo de piridina no sustituido o no sustituido con un átomo de halógeno.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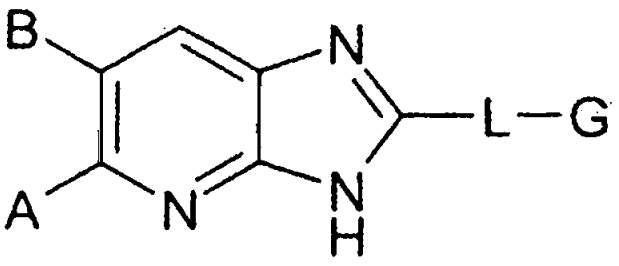

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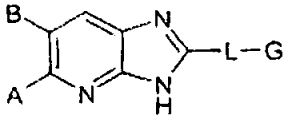

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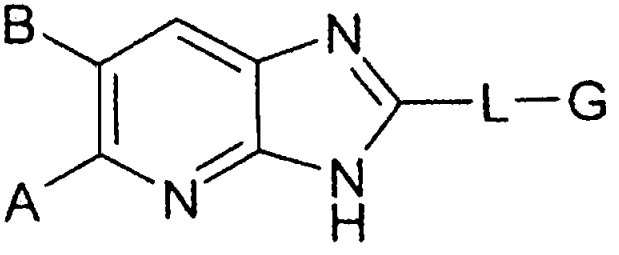

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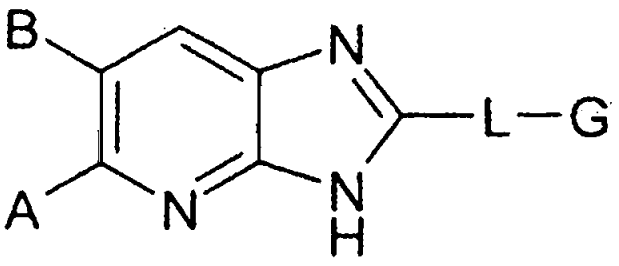

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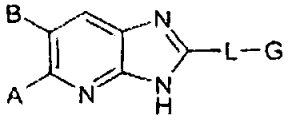

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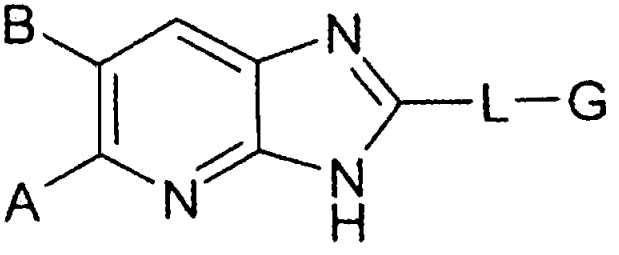

(I)

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-034096- -00000-0000

Fecha: 2008-04-04 16:45:07 Dep: 2020 NUECREACION
Tra: 11 PATENTEYM Eve: 379 PASENACIONALII
Act: 411 PRESENTACION Folios: 191

RECIBO OFICIAL DE CAJA : 08 - 23,420
FECHA : MARZO 17 DE 2008

***** 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	RECIBO DE CAJA			23181	17/03/2008	48,918,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
		TOTAL : $	501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo 00734 - 841 - 007 - 6

192

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-034096- -00000-0000

Fecha: 2003-04-04 16:45:07 Dep: 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 191

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

FDO B
Firma Responsable

Fecha 04-AB-Y.

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

193

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 197

2020
Bogotá D.C.,

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
LABORATORIOS ALMIRALL S.A.

REFERENCIA	Radicación No.	8 34096
	Solicitud internacional	PCT/EP2006/009620
	Fecha inicio fase nacional	06/05/2008
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	6089
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 15 MAYO 2008

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa11